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

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

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

Results: The baseline (BL) median (range) values for UACR, mg/g, were: PBO: 180 (30 to 926), DAPA 5 mg: 397 (31 to 4790) and DAPA 10 mg: 179 (32 to 4792). The corresponding mean (SD) values for eGFR, mL/min/1.73 m² were: 45.1 (9.37), 43.9 (8.96) and 44.1 (11.1), respectively. A reduction in UACR was already evident at Week 1. At 104 weeks the mean (95% CI) PBO-corrected reduction in UACR was −44% (−71.9, 0.9) and −57% (−77, −20) for DAPA 5 and 10 mg, respectively. After adjusting for changes in blood pressure, Hba1c and eGFR, the reductions were largely maintained. During the 104 week study period 7% of PBO patients regressed to normoalbuminuria, the corresponding numbers for DAPA 5 and 10 mg were 19 and 18%, respectively. After a transient decrease in eGFR in DAPA-treated patients, the DAPA 5 and 10 mg groups showed PBO-corrected 104 week changes of 2.1 (–1.3, 5.5) and –0.7 (–4.0, 2.6) mL/min/1.73 m².

Conclusions: Dapagliflozin reduces UACR for up to 2 years in subjects with CKD3, without increases in renal AEs. The UACR reduction remained present after adjustments for changes in blood pressure, Hba1c and eGFR, indicating a direct renal effect independent of changes in these variables. Funding: Pharmaceutical Company Support - AstraZeneca

Dapagliflozin Reduces Albuminuria Over 2 Years in Diabetic Patients with Renal Impairment

TH-OR002
Structural Predictors of Loss of Renal Function in Type 2 Diabetes
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Background: Diabetes is the leading cause of kidney failure in the US, but the early structural determinants of renal function loss are poorly understood. We examined the association between morphometrically-determined renal structural variables and renal function loss in 111 Pima Indians with type 2 diabetes who volunteered for a research kidney biopsy and for annual measurement of glomerular filtration rate (GFR, isohalateme).

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

Results: Of the 111 participants (82% women, baseline mean age 46 years, diabetes duration 16 years, Hba1c 9.4%, GFR 147 ml/min, and median albumin:creatinine ratio [ACR] 41 mg/g), 51 (46%) developed renal function loss during a median follow-up of 6.6 years (IQR=4.9–13.1). Higher mean glomerular fractional volume (HR=2.33, 95% CI 1.63–3.33), lower glomerular volume (HR=1.57, 95% CI 1.18-2.09), non-podocyte cell number per glomerulus (HR=1.49, 95% CI 1.08-2.05), GBM width (HR=1.45, 95% CI 1.04-2.04), lower glomerular filtration surface density (HR=0.61, 95% CI 0.41-0.93), and reduced endothelial fenestrations (HR=0.67, 95% CI 0.47-0.94) were each associated with loss of renal function after adjustment for baseline age, sex, duration of diabetes, Hba1c and GFR. Although power was reduced when 14 participants with baseline GFR <90 ml/min were excluded from the analysis, baseline structure still predicted renal function loss.

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

Dapagliflozin Reduces Albuminuria Over 2 Years in Diabetic Patients with Renal Impairment

TH-OR003
Mitic catastrophe in Diabetic Nephropathy
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Background: Podocyte injury is a prominent feature in the progression of diabetic nephropathy. Apoptosis is thought to be a major mechanism for loss of podocytes. However, apopptic podocytes (Podo) are not seen in renal biopsy specimens with diabetes. Instead mitotic catastrophe (MC) is a newly recognized form of podocyte death characterized by Podo multinucleation, aberrant mitotic spindles and micronucleoli. Because injured podocytes may die and released in the urine, in this study we sought to quantify MC in urine samples from diabetic patients.

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

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

Results: The PCX-podo showed various nuclear morphology such as 1) mononucleated, normal shape (8.7%), 2) mononucleated, large and abnormal shape (3.8 %), 3) multinucleated with or without micromucleoli (40.2%) 4) single nucleus and fragmented cytofilaments (23%) and 5) numerous mitotically abnormal nuclei (31.8%). We considered 2) and 3) as definitive MC, and 4) and 5) suspected MC. Apoptotic bodies were not found. 50% of PCX-podo were positive for GLEPP1, 11% of PCX-podo were positive for nephrin and podocin. None of PCX-podo were positive for leucocyte and parietal epithelial cell markers. Annexin V, cleaved caspase-3 and Tunel assay. 10 % of PCX-podo were positive for phosphorylated vimentin.

Conclusions: Urine from diabetic patients contains a significant number of urinary Podo with MC and no Podos with apoptotic bodies. Our results indicate that the majority of urine podocytes in diabetic patients may be due to MC and not to apoptosis. Funding: AHA/NIDDK, PCORI.
Conclusions: In DKD, higher serum SAA concentration is associated with increased risk of death and ESRD. SAA improves risk prediction when added to traditional risk factors. SAA is a candidate biomarker that may advance DKD risk assessment and is a potential therapeutic target.
Funding: Private Foundation Support

TH-OR006
Biomarkers of Early Decline in Renal Function: A Translational Study in Type 2 Diabetes Jennifer W. Xu,1 Carla Cavallini,1 Sonja Haku,1,2 Michael S. Simonson,1,2 Nephrology and Hypertension, Univ Hospitals Case Medical Center and CWRU School of Medicine, Cleveland, OH; Dept of Medical Science and Cardiovascular Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan.

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

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

Results: For classifying participants with baseline early renal function decline (eGFR 90 – 60 vs normal function (i.e., ≥90), the highest performing biomarkers were: transforming growth factor b (TGFb, AUC+SD, 0.827 ± 0.070), interleukin-6 (IL-6, 0.815 ± 0.065) and endothelin-1 (ET-1, 0.720 ± 0.082); all P < 0.01 compared to ACR. Testing was validated in the independent test group. AUCs were unchanged after multivariate adjustment for age, sex, race, duration of diabetes, angiotensinogen 0.465 ± 0.093 and angiotensinogen 0.465 ± 0.090). Performance was validated in the independent test group.

Conclusions: Urine levels of TGFb, IL-6 and ET-1 may identify patients with early renal function decline and aid development of novel therapeutics.
Funding: Other NIH Support - R01DK096549

TH-OR007
Primary Prevention of Albuminuria Using Renin-Angiotensin-System Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis Frederik I. Persson,1 Bianca Hemmingsen,2 Morten Lindhardt,1 Peter Rossing,1,3,4 Hans-Henrik Parving,1,2 1Steno Diabetes Center, Gentofte, Denmark; 2Copenhagen Trial Unit, Copenhagen Univ Hospital, Copenhagen, Denmark; 3HEALTH, Univ of Aarhus, Aarhus, Denmark; 4Novo Nordisk Foundation for Basic and Medical Research, Univ of Copenhagen, Copenhagen, Denmark; 5Dept of Medical Endocrinology, Rigshospitalet, Copenhagen Univ Hospital, Copenhagen, Denmark.

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

Methods: We searched MEDLINE, EMBASE and the Cochrane Library for double-masked randomised controlled trials, with a population of patients with type 2 diabetes and normoalbuminuria, comparing angiotensin enzyme inhibitors or receptor blockers. In patients with eGFR 90 – 60 at baseline, TGFb, IL-6 and ET-1 predicted a composite renal outcome at 5 years (eGFR < 60 or ESRD) better than ACR (0.769 ± 0.105, 0.690 ± 0.128, and 0.793 ± 0.091, all P < 0.05 versus ACR, 0.520 ± 0.119).

Conclusions: Urine levels of TGFb, IL-6 or ET-1 may identify patients with early renal function decline and aid development of novel therapeutics.
Funding: Other NIH Support - R01DK096549
Methods: 1,424 active HD patients with DM from 26 FMCNA facilities with glycemic marks from Jan-March 2013 were followed until April, 2015. Poor glyemic control was based on: HgbA1c >7% (sensitivity analysis=8%), AlBF > 974 µmol/L; G a ≥ 300 µmol/L. Standard and Time-dependent (TD) Cox models with adjustment for age, sex, race, ethnicity, vintage, BMI, HD catheter, and baseline comorbid illnesses were utilized to determine associations between each dichotomized glyemic index and hospitalization/death outcomes.

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

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

TH-OR10
Renal Biopsy for Diabetic Nephropathy: Is Useful for the Prediction of Cardiovascular Events – 10-Year Follow Up

Katsuhiko Morimori, Ken-ichi Samejima, Masaru Matsui, Yasuhiro Akai, Mito Tagawa, Yoshihiko Saito. First Dept of Internal Medicine, Nara Medical Univ, Kashihara, Japan.

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

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

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

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

TH-OR11
Racial Differences in Hospitalization Rates Among U.S. Veterans with and without Chronic Kidney Disease Jennifer L. Brag-Cresham,1 Hal Morgenstern,2 Neil R. Powe,2 Deidra C. Crews,2 Nilka Rios Burrows,3 Sharon Saydel,1 Kara Zivin,1 Rajiv Saran,1 KECC & SPH, Univ of Michigan, Ann Arbor, MI; 1Univ of California, San Francisco, CA; 2Johs Hopkins Univ, Baltimore, MD; 1Centers for Disease Control and Prevention, Atlanta, GA.

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

Methods: This cohort study included 2.6 million black and white veterans who attended 1 or more patient visit, had a serum creatinine value during the baseline period (10/1/09-03/10), and had no indication of ESRD on 9/31/10. Cox regression was used to estimate the combined effects of race and CKD status on first hospitalization during the next 2 years, adjusting for age, gender, comorbidities, and prior hospitalization during the baseline period. CKD was defined by clinical diagnosis or eGFR <60 ml/min/1.73m2. Results: Black patients with a higher prevalence of diabetes, but lower prevalence other comorbidities, including hypertension. Although the overall prevalence of CKD at baseline was higher in whites (21.0% vs. 15.8%), the prevalence of a definitive diagnosis was higher in blacks (11.8% vs. 9.4%). The rate of first hospitalization was greater for blacks in both groups with and without CKD (HR=1.30, 95% CI: 1.29-1.31 & HR=1.16, 95% CI: 1.15-1.17, respectively). The 2-year risk of hospitalization was greatest (27.9%) in black patients with CKD, compared with the other groups (figure; p for interaction <0.001).

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

Acknowledging the role of racial disparities in the end-stage renal disease (ESRD) in the setting of cardiovascular disease and diabetes (CV), it is important to study the impact of these disparities.

TH-OR12
Optimal Endpoint Definition for Transition in Albuminuria Stage in Clinical Trials Tobias Felix Kröpelin,1 Dick de Zeeuw,1 Rudolf W. Bilous,2 Giuseppe Remuzzi,1 Hans-Henrik Parving,3 Hiddo Jan Lambers Heerspink.1 Clinical Pharmacy and Pharmacology, UMCG, Groningen; 1Newcastle Univ, United Kingdom; 2IRCBS Mario Negri Inst for Pharmacological Research, Ospedale Papa Giovanni XXIII, Bergamo, Italy; 3Medical Endocrinology, Univ of Copenhagen, Denmark.

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

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

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

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

TH-OR13

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

Methods: We studied 11,143 participants in the ARIC Study, a bi-ethnic community-based cohort. Baseline CKD measures (eGFR and ACR) were assessed at visit 4 (1996-
Results: A total of 693 hospitalizations related to GI bleeding was observed during a median follow-up of 13.9 years (incident rate 4.9 per 1,000 person-years). After adjusting for potential confounders, both lower eGFR and higher ACR were independently associated with increased risk of GI bleeding (Table). Compared to eGFR <60 ml/min/1.73m², the association was particularly strong in eGFR <30 ml/min/1.73m² (HR 8.37 [5.04-13.88] in Model 2), but eGFR between 30-60 also reached significance (HR 1.55 [1.16-2.06]). Compared to ACR <10 mg/g, both microalbuminuria (10-299 mg/g) and macroalbuminuria (>300 mg/g) were associated with 2.2-5 greater hazard of GI bleeding (HR 2.14 [1.69-2.72] and 2.40 [1.59-3.62], respectively, in Model 2). Of note, high-normal albuminuria (10-29 mg/g) was also significantly associated with GI bleeding (HR 1.36 [1.09-1.70]). These results were highly consistent even after adjusting for each of kidney measures (Model 3) or accounting for cardiovascular events and incident dialysis during follow-up.

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

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

<table>
<thead>
<tr>
<th>Model</th>
<th>eGFR category (mL/min/1.73 m²)</th>
<th>Events</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;60</td>
<td>1267</td>
<td>2.00 (1.50-2.65)</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>44.8</td>
<td>1.97 (1.03-3.80)</td>
</tr>
<tr>
<td>3</td>
<td>90-109</td>
<td>11.4</td>
<td>1.76 (0.67-4.66)</td>
</tr>
<tr>
<td>4</td>
<td>110-129</td>
<td>2.5</td>
<td>1.56 (0.82-2.98)</td>
</tr>
<tr>
<td>5</td>
<td>130-149</td>
<td>0.5</td>
<td>1.00 (0.59-1.70)</td>
</tr>
</tbody>
</table>

ACR category (mg/g/Cr)

<table>
<thead>
<tr>
<th>Model</th>
<th>ACR category (mg/g/Cr)</th>
<th>Events</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;0.9</td>
<td>10.2</td>
<td>1.22 (0.69-2.20)</td>
</tr>
<tr>
<td>2</td>
<td>1.0-1.4</td>
<td>61.0</td>
<td>1.22 (0.78-1.93)</td>
</tr>
<tr>
<td>3</td>
<td>1.5-2.9</td>
<td>15.3</td>
<td>1.17 (0.64-2.17)</td>
</tr>
<tr>
<td>4</td>
<td>3.0-9.9</td>
<td>3.9</td>
<td>1.13 (0.66-1.91)</td>
</tr>
</tbody>
</table>

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

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

Funding: NIDDK Support

TH-OR015

Risk Factors for Cognitive Impairment in Chronic Kidney Disease – The Brain in Kidney Disease Study

Anne M. Murray,1 Elizabeth J. Bell,1 David S. Knopman,2 Yelena Slinin,2 Robert N. Foley,1 David Tupper,1 Minneapolis Medical Research Foundation;1 Dept of Neurology, Mayo Clinic;2 Nephrology Div, U of Minnesota;3 VA Medical Center;4 Neuropsychology Section, Hennepin County Medical Center (HCMC); 5 Geriatrics Div, HICMC.

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

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

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

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

Funding: Other NIH Support - National Institute on Aging, Pharmaceutical Company Support - Satellite Healthcare Research Foundation
TH-OR016
Increased Risk of Incidental Chronic Kidney Disease, Cardiovascular Disease and Mortality in Diabetic Patients with Comorbid Depression
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Background: Depressed patients with diabetes have worse diabetes self-care and worse clinical outcomes. Here we aimed to determine the association of depression and the risk of incident CKD, cardio-vascular (CV) outcomes and all-cause mortality in a population of US veterans with diabetes mellitus (DM).

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

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

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

Funding: Veterans Administration Support

TH-OR017
Cardiorespiratory Fitness and Neurocognitive Function in Older Adults with Chronic Kidney Disease
Daniel E. Weineg, 1 Lindsay J. Lajoie, 1,2 Eamon F. Fleming, 3 Dylan R. Kim, 2 Shari R. Waldstein, 1 Jason Kissier, 1 Kieran Reid, 1 Roger A. Fielding, 1,2 Stephen L. Seliger, 1 Friedman School of Nutrition, Tufts Univ; 2Human Nutrition Research Center on Aging, Tufts Univ; 3Tufts Medical Center; 4Univ of Maryland Baltimore County; 5Univ of Maryland School of Medicine.

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

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

Results: Among 71 participants, with mean age 68±7.74 years and mean eGFR=32±10.6 ml/min/1.73m2, higher VO2peak was associated with better performance on the MMSE (β=0.08, p=0.04), and DSST (β=-0.75, p=0.03). While not statistically significant, directionality was similar for other cognitive tests, including the MoCA (β=-0.12, p=0.20), TMT-Part A (β=-0.47, p=0.30) and TMT-Part B (β=-1.39, p=0.38).

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

Funding: NIDDK Support

TH-OR018
Low Birth Weight and Risk of Progression to End Stage Renal Disease in IgA Nephropathy
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Background: Low Birth Weight (LBW) is a surrogate for fetal undernutrition and is associated with impaired nephron development in utero. Low birth weight is associated with fewer and larger glomeruli and increased risk of hypertension and renal disease in later life. In this study, we investigate whether low birth weight (LBW) and low birth weight for gestational age (LBW-GA) predict progression to ESRD in IgAN patients.

Methods: The Medical Birth Registry has recorded medical data for all births in Norway since 1967 and the Norwegian Renal Registry has recorded all patients With ESRD since 1980. From the Norwegian Kidney Biopsy Registry we retrieved all patients who had been diagnosed with IgAN from 1988-2013. These registries were linked and we analysed risk of progression to ESRD associated with LBW (defined as less than the 10th percentile of gender-specific birth weight) and/or LBW-GA (defined as less than the 10th percentile of birth weight for gestational age) by regression statistics.

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

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

Funding: Veterans Administration Support

TH-OR019
Risks of End-Stage Renal Disease (ESRD) in the United States
Patrick J. Albertus, 1 Hal Morgenstern, 1 Bruce M. Robinson, 2 Rjiv Saran, 2
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Background: Although incidence rates of ESRD are reported routinely by the USRDS, these are not directly relevant for individuals or providers. The objective of this study was to utilize incidence rate information to estimate the short- and long-term risk of ESRD by age, sex and race/ethnicity.

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

Results: Among males, the lifetime risk of ESRD from birth using 2013 data was 3.08% for non-Hispanic (NH) whites, 8.06% for NH blacks, 3.80% for NH Native Americans, 5.05% for NH Asians/Pacific Islanders, and 6.23% for Hispanics. Among females, the lifetime risks were 2.03% for NH whites, 6.80% for NH blacks, 3.63% for NH Native Americans, 3.78% for NH Asian/Pacific Islanders, and 4.34% for Hispanics. The 10-year risk was highest at age 70 at 1.52% for males and 1.03% for females. Comparing risk estimates based on 2013 data to 2000 data, the lifetime risk of ESRD from birth increased compared to 2000 data, the lifetime risk of ESRD from birth increased from 3.5% to 3.96% in males and decreased from 2.96% to 2.85% in females, but these changes were not uniform across racial/ethnic groups.

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

Funding: NIDDK Support

TH-OR020
The Relevance of Systolic Blood Pressure to Renal Progression: Observations from the Study of Heart and Renal Protection (SHARP)

Background: Meta-analysis of intensive versus standard blood pressure (BP) lowering trials has demonstrated that lower BP reduces the risk of end-stage renal disease (ESRD), but there is uncertainty about optimal BP targets in chronic kidney disease (CKD), particularly in those with advanced albuminuria.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

5A
Results: Each 20 mmHg higher usual SBP was associated with an average increase of 71% in the risk of ESRD (adjusted hazard ratio [HR] 1.71, 95% CI 1.50-1.95). The risk of ESRD was substantially attenuated, but remained statistically significant, after adjustment for albuminuria (HR 1.18, 1.02-1.35). Among those with at least 3 creatinine measurements, each 20 mmHg higher usual SBP was associated with a 1.3 (95% CI 1.0-1.6) mL/min/1.73m²/year greater mean decline in eGFR, which reduced to 0.7 (0.4-1.0) after adjustment for albuminuria. Mean rate of reduction in eGFR was similar irrespective of baseline albuminuria (macroalbuminuria 0.7 [0.1-1.3]; microalbuminuria 0.6 [0.2-1.0]; normoalbuminuria 0.6 [0.1-1.1]).

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

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

TH-OR021

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

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

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

Results: Although the significant improvement of U-Prot was observed at 1 month after treatment, U-PCX and U-POD decreased more gradually (Fig). A weakly positive association of baseline albuminuria to urinary protein (sensitivity 80%, specificity 86%, PPV 80%, NPV 86%).

Conclusions: U-PCX and U-POD would be novel biomarkers of podocyte injury in LN.

Funding: Government Support - Non-U.S.

TH-OR022


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

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

Results: Fifty one patients with MLN were distributed by induction drug in 3 groups: MMF (mean 2.6±0.4g/day), IV cyclophosphamide (5.4g/m² BSA cumulative dose), azathioprine (mean 2.1±0.6 mg/kg/d). Median follow-up was 44 months (IQR 15-94). At presentation, patients in IVC group had a trend to worse urinary protein to creatinine ratio (uPCR) and a longer time from symptoms to start of treatment. Complete remission rates at 12, 12 and 24 months were 23.1, 61.5 and 61.5% for MMF, 62.4, 14.8 and 26.9% for IV and 27.3, 40.5 and 47.9 for AZA. MMF induction was superior to IVC on Kaplan-Meier analysis (HR 5.42, 95% CI 1.38-21.2, p=0.03), but after Cox multivariate analysis there was only a trend to a better complete remission with MMF (HR 3.65, 95% CI 0.94-14.2, p=0.061). There were no differences between groups in adverse effects and thrombotic events. Only two MLN patients developed ESRD on follow-up. When compared with an historical cohort, patients with proliferative (HR 8.83, 1.56-50.1, p=0.014) and mixed histological classes (HR 4.38, 1.89-10.2, p<0.001) were more likely to develop ESRD.

Conclusions: Mycophenolate mofetil, IVC and AZA are effective for induction treatment of MLN. At our center, there is a trend to treat severe nephrotic patients with IVC and less severe cases with MMF or AZA. MLN has a similar rate of response to treatment and better long-term outcome than proliferative and mixed classes.
Impact of Tabalumab on the Kidney in Lupus: Results from Two Phase 3 Clinical Trials
Brad H. Rovin,1 Mary Anne Dooley,2 Jai Radhakrishnan,3 Ellen M. Ginzel,4 Tammy Forrester,1 Pamela W. Anderson. 5
1Ohio State Univ, Columbus, OH; 2Univ of North Carolina, Chapel Hill, NC; 3Columbia Univ, New York, NY; 4SUNY Downstate, Brooklyn, NY; 5Eli Lilly & Company, Indianapolis, IN; 6Eli Lilly & Company, Indianapolis, IN.

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

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

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

ITT Tab Q2W N=597 Tab Q4W N=583 PBO N=575
ΔScr 0.54±10.7 0.11±9.8 0.31±11.4
p-value vs PBO .549 .897
ΔGFR -1.71±17.6 0.63±14.8 0.38±16.6
p-value vs PBO .622 .805
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p-value vs PBO .718 .517

ITT+uPCR
ΔScr 1.68±13.0 1.42±12.1 2.73±14.4
p-value vs PBO .471 .655
ΔGFR -0.87±18.9 0.29±16.0 -2.14±20.7
p-value vs PBO .604 .559
ΔuPCR -1.25±85.8 -0.08±111.8 -7.53±102.9
p-value vs PBO .383 .434

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

Funding: Pharmaceutical Company Support - Eli Lilly and Company

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

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

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

Results: Our review indicated increased expression of monocytic chemotactic protein (MCP)-1, sC5bC9, C3a and C5a in urine, whereas GM-CSF, sFlt1, CRP, IL-17A, C5a, hyaluronan, C3 and IL-18 bp were identified to be diversely regulated in active and inactive disease in blood samples. Our cross-sectional analysis revealed increased expression of CRP, C5a, C3a, IL-18 bp in blood and C5a and MCP-1 in urine samples during active AAV (all p<0.05).

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

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

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

Funding: Pharmaceutical Company Support - Eli Lilly and Company

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

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Conclusions: Prolonged remission maintenance therapy with AZA/PRED beyond 24 months after diagnosis reduced relapse rate. Continuation of immunosuppression was associated with better renal survival but not with improvement of overall patient survival.
TH-OR026

Pharmacogenetics of Rituximab in ANCA Associated Vasculitis

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

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

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

Results: 213 patients were enrolled in the primary and 109 in the replication cohorts. A SNP in the TF/FPI/H gene region(BAFF) was associated to TF in the primary (HR12.4,p=7x10^-04) and replication cohorts (HR5.2,p=0.0024). Meta-analyses showed an association with both end-points.

| Carriers of the risk genotype had higher rate of detectable B cells 6 months after RTX (50%vs14%,p=0.0146). The association was restricted to patients historically PR3-ANCA positive (TF risk-OR 9.9,p=0.0141;TTR HR 8.2,p=7.3x10^-04) while in the MPO-ANCA subgroup an association with a SNP in chromosome 4 was identified (TF risk-OR 9.0,p=0.0141;TTR HR 8.2,p=7.3x10^-04).

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<tr>
<th>Primary cohort</th>
<th>Replication cohort</th>
<th>Meta-analysis</th>
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<tr>
<td>TF at 6 months</td>
<td>8.07</td>
<td>9.8</td>
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<td>TTR</td>
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Conclusions: These results demonstrate that combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods, and should allow modification of treatment based on risk assessment using data readily available at the time of biopsy.

TH-OR027

The MEST Score in IgA Nephropathy: Implications for Clinical Management

Sean Barbour,1,2,3 Gabriel Espino-Hernandez,2,3 Heather N. Reich,1 Rosanna Coppo,1,4,5,6 Bob Isroel,7,8 John Fechohly,1,9 Daniel C. Cattran,1,10 1Univ of BC; 2BC Renal Agency; 3Univ of Toronto; 4Oxford Univ; 5Leicester General Hospital; 6For the Oxford Derivation, North American Validation and VALIGA Consortia.

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

Methods: We used a cohort of 213 patients with IgAN from the Oxford derivation, North American validation and VALIGA studies to analyze the risk of a 50% decrease in eGFR (mild proteinuria, 3.7% vs. 10.8% and 14.6%; moderate proteinuria, 7.6% vs. 6.5% and 14.6%; severe proteinuria, 12.4% vs. 8.2% and 16%, respectively). Cox proportional hazards models revealed that the combined therapy significantly prevented a 50% increase in serum creatinine compared with conventional therapy in the groups with moderate and severe proteinuria (hazards ratio, 3.04 and 1.09, respectively).

Results: The ratio of urinary remission at final observation was significantly higher in the three groups after receiving combined, steroid or conservative therapy during a mean follow-up of 6.2±3.4 years.

Conclusions: Using modern prediction tools, we examined whether combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods, and should allow modification of treatment based on risk assessment using data readily available at the time of biopsy.

TH-OR028

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

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

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

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

Results: The ratio of urinary remission at final observation was significantly higher in the groups given combined, than steroid or conservative therapy (mild proteinuria: 63% vs. 46% and 42%; moderate proteinuria, 52% vs. 44% and 23%; severe proteinuria, 43% vs. 33% and 16%, respectively). In contrast, the ratio of a 50% increase in serum creatinine decreased more groups given combined, than steroid or conservative therapy (mild proteinuria, 3.7% vs. 10.8% and 14.6%; moderate proteinuria, 7.6% vs. 6.5% and 19.8%; severe proteinuria, 16.7% vs. 25.0% and 36.8%, respectively). Cox proportional hazards models revealed that the combined therapy significantly prevented a 50% increase in serum creatinine compared with conventional therapy in the groups with moderate and severe proteinuria (hazards ratio, 3.04 and 1.09, respectively).

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

TH-OR029

Pregnancy and IgA Nephropathy: Renal, Maternal and Fetal Outcomes

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

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

Methods: This study included women with biopsy proven IgAN from 1979 to 2013 and all mothers with delivery record from 1999 to 2014 in Seoul National University Hospital.
A survey was done by medical chart review and telephone poll. Primary outcome for kidney was eGFR 20-75 mL/min/1.73 m². In a covariate analysis, CCX140-B was effective on UACR across patient groups. In a pre-specified subgroup with high baseline UACR (>800 mg/g creatinine), CCX140-B resulted in a placebo-corrected 28% improvement in albuminuria over 52 wks, and a slower rate of decline in eGFR. CCX140-B did not affect systemic BP or body weight, and appeared to be well tolerated with a low overall dropout rate (10%).

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

Funding: Pharmaceutical Company Support - ChemoCentryx, Inc.

TH-OR032
A First in Human Study of Implantation of Neo-Kidney Augment, an Autologous Selected Renal Cell Population, in Type-2 Diabetic CKD Stage 3-4 Patients

Peter Stenvinkel,1 Torbjörn Lundgren,2 Jonas Wadstrom,3 Pontus Blomberg,1 Torkel Brismar,3 Randal K. Detwiler,2 Karolinska Univ Hospital, Sweden;1 Univ of North Carolina.

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

Methods: 7 male type-2 diabetic (108±11kg) patients (63±6yrs) with CKD were selected. After evaluation of renal function and radiology they underwent renal biopsy. Two cores were shipped to the manufacturing plant for cell isolation, culture, and product preparation. NKA was shipped back to the clinical centre (44±8yrd after biopsy) and injected into the left kidney.

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

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

TH-OR033
Selective Inhibition of CCR2/S Chemokine Receptors Reduces Macroalbuminuria in Subjects with Type 2 Diabetes and Overt Nephropathy

Jeremy D. Gale,1 Steven A. Gilbert,2 Samuel S. Blumenhalt,2 Sabhie E. Perera,2 Jeremy D. Gale,3,1 Steven A. Gilbert,2 Paul H. Scheele,1 Robert Webster,3 Christelle Huguet Perros.1 Pfizer Inc, Cambridge, MA;3 Zablocki VAMC, Milwaukee, WI;1 Renal Associates PA, San Antonio, TX;2 BCDiabetes, Vancouver, Canada.

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

Methods: The effect on albuminuria of the novel and specific dual CCR2/5 receptor antagonist, PF-0463817, was assessed in a multinational, randomized, double-blind, placebo-controlled, parallel group trial of subjects with Type 2 diabetes and overt nephropathy already receiving ACEi and/or ARB. Subjects with eGFR 20-75 mL/min/1.73m² and urinary albumin creatinine ratio (UACR) >300mg/g (33.9 mmol/m²) at baseline were assigned to receive PF-0463817 200mg (150mg if baseline eGFR <30 mL/min/1.73m²) or placebo (31). Douglas Gargiullo, William H. Scheele,1 Robert Webster,3 Christelle Huguet Perros.1 Pfizer Inc, Cambridge, MA;3 Zablocki VAMC, Milwaukee, WI;1 Renal Associates PA, San Antonio, TX;2 BCDiabetes, Vancouver, Canada.

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

TH-OR031
Efficacy in Diabetic Nephropathy in a Phase 2 Clinical Trial of Chemokine Receptor 2 Inhibitor CCX140-B

Richard J. Glasscock,1 Elena Henkel,2 Heidrun Mehlung,3 Christoph Hasslacher,1 Ioanna Gouni-Berthold,1 Vladimir Tsur,4 Antonia Potarca,2 Pirov Bekker,5 Thomas J. Schall,1 David Geffen School of Med;2 Technical Univ;3 Free Univ;2 Univ Heidelberg;2 Univ of Cologne;4 Charles Univ;5 ChemoCentryx.

Background: The orally administered inhibitor of C-C chemokine receptor 2 (CCR2) Chemokine Receptor 2 Inhibitor CCX140-B Efficacy in Diabetic Nephropathy in a Phase 2 Clinical Trial of Chemokine Receptor 2 Inhibitor CCX140-B was effective on UACR vs. 5 mg. CCX140-B treatment showed an improvement in fasting plasma glucose (−0.12 mmol/L). In a covariate analysis, CCX140-B was effective on UACR across patient groups. In a pre-specified subgroup with high baseline UACR (>800 mg/g creatinine), CCX140-B resulted in a placebo-corrected 28% improvement in albuminuria over 52 wks, and a slower rate of decline in eGFR. CCX140-B did not affect systemic BP or body weight, and appeared to be well tolerated with a low overall dropout rate (10%).

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

Funding: Pharmaceutical Company Support - ChemoCentryx, Inc.

TH-OR030
Semaphorin 3F (SEMA3F) Expression Is Reduced in Pregnancy Complicated by Preeclampsia (PE)

Giovanni Carlucci, Federica Trozza, Giuseppe S. Netti, Barbara Infante, Francesca Bruno, Pantaleo Greco, Marco Matteo, Stefania Carlucci, Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.

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

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

Results: SEMA3F placenta expression was significantly reduced in PE (Control 3.2±1.3 vs. PE 1.3±.6AU, p=0.01). In addition, SEMA3F level at the time of delivery was significantly lower in serum (2.0±4.4 vs 2.9±6.0 ng/mL, p=0.04), amniotic fluid (133.6±41.9 vs 202.4±102.2 ng/mL, p<0.01) and cord blood (58±27 vs 92±20 ng/mL, p<0.02). PE patients compared with normal pregnant women. SEMA3F level in maternal serum was significantly associated with placental weight (R²=0.802; p<0.001) and newborn weight (R²=0.532; p<0.01) at birth. In the prospective cohort study 14 women developed PE. In this setting, SEMA3F level in the amniotic fluid was lower in women developing PE compared to those with normal pregnancy (12.9±8.0 ng/mL vs 31±8.9 ng/mL, p<0.01).

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

Funding: Government Support - Non-U.S.
reduction in UACR of 8% (95% CI 1.9% to 23%) was observed in response to treatment with PF-04634817 using the pre-defined primary assessment of efficacy (Bayesian analysis with informative prior). Ad hoc analysis, of those with eGFR >60 mL/min/1.73m² at baseline, showed a placebo-adjusted reduction of UACR approaching 19%. However, interpretation of subgroups are difficult due to the 5:1 randomization and the presence of data outliers. Adverse events (AEs) were mostly mild, the most common treatment-related AEs being nausea, acne and diarrhea.

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

Funding: Pharmaceutical Company Support - Pfizer

TH-OR034

Bariictinib in Diabetic Kidney Disease: Biomarker Analysis from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study


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

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

Results: Reductions in 24h proteinuria compared with PBO were observed at 6 m of bari tx (LSM ratio vs PBO for 0.75mg BID, 1.5mg QD, 4mg QD; 0.59, 0.58, 0.56, 0.60, resp p<0.05). Benefits were maintained during a 1-2 m washout period. The proportion with 30% UACR decline was increased by bari tx. IP-10, MCP-1, and s-TNFr 1&2 decreased in a numerically dose-dependent manner. Estimated glomerular filtration rate by cystatin C was unchanged. At 6 m, only 4mg bari had decreased hemoglobin vs PBO (-1.01±0.05 g/dL). No other safety effects were observed.


Funding: Pharmaceutical Company Support - Eli Lilly and Company

TH-OR035

Patrimer Lowers Serum K+ and Preverts Current Hyperkalemia in CKD Patients ≥65 Years of Age on RAAS Inhibitors

Matthew R. Wei, David A. Bushinsky, Martha Mayo, Dahlia Garza, Yuri Stasiv, Daniel J. Wilson, Susan Arthur, Lance Berman, George L. Bakris, Univ of Maryland; Univ of Rochester; Relypsa, Inc; Univ of Chicago.

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

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

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

Results: 131 (54%) pts were ≥65 yr at BL. Consistent with overall results, primary endpoints were significant for pts ≥65 yr (Table). Overall and in pts ≥65 yr, 76% and 73%, respectively, had s-K+ 3.8 to <3.1 mEq/L (2° endpoint) at part A wk 4. More PBO pts (p=0.001) developed recurring HK in part B. In all pts, mild-moderate constipation was the most common AE in part A (11%).

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

Funding: Pharmaceutical Company Support - Relypsa, Inc

TH-OR036

The Microalbuminuria Intervention Study: Effects of Different Losartan Combination Antihypertensive Therapy in Patients with CKD, MIDLAND-CKD


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

Methods: Study design was randomized control trial. Eligible subjects were hypertensive CKD patients (aged 20-79) treated with ACEI or ARB more than 2 months, BP 140/90 mmHg and above, and suspected albuminuria. Suspected albuminuria was defined as albuminuria creatinine ratio (ACR) greater than 30 mg/gCr in a single spot urine analysis, or > albumin in urine dipstick test more than 2 times within 1 year. Exclusion criteria were renal insufficiency, prescription of CCB/diuretics, cardiovascular events within 6 months, abnormal liver function, and uncontrolled diabetes/hyperuricemia within 3 months. Written informed consent were obtained from all patients. This study was approved by the ethical committee and registered to UMIN (ID: 000004062). Patients were randomly assigned to group A (losartan and amiodipine) or B (combining agent of losartan and HCTZ12.5mg) for 6 months.

Results: 48 and 46 patients were assigned to group A and B. There was no significant difference in patient characteristics between 2 groups at baseline, and BP were well controlled in both groups. ACR were decreased in both groups at 3 and 6 months without statistical significance. Among patients with ACR 30mg/gCr and above, ACR was significantly decreased in group B compared to A at 3 and 6 months (-17.5 ± 7.4 vs -56.3 ± 37.3%, p<0.01 and -27.8 ± 63.4 vs -63.8 ± 34.0%, p<0.01). DeGFR were not significantly different in 2 groups.

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

Funding: Private Foundation Support
TH-OR037
Blood Pressure and Outcomes in Diabetic Kidney Disease: Results from the VA NEPHRON-D Trial
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Background: Proteinuric diabetic kidney disease (DKD) frequently progresses to end-stage renal disease (ESRD). Control of blood pressure (BP) delays progression, but the optimal BP to improve outcomes remains unclear. The objective of this analysis was to evaluate the relationship between BP and renal outcomes in proteinuric DKD.

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

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

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

Funding: Veterans Administration Support

TH-OR038
Hemoglobin (HGB) Response in a Phase 2b Study of AKB-6548 for the Treatment of Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD)
Bruce S. Spinowitz,1 Pablo E. Pergola,1 Volker H. Haase,2 Tasha M. Farmer,3 Charlotte S. Hartman,4 Bradley J. Maroni,1 New York University School of Medicine, Queens, NY; 2 Texas Children’s Hospital Association and University of Texas Health Science Center, San Antonio, TX; 3Vanderbilt Univ, Nashville, TN; 4Akebia Therapeutics, Inc., Cambridge, MA.

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

Methods: A randomized, double-blind, placebo-controlled study assessed HGB response of AKB-6548 over 20 weeks in CKD subjects with anemia. 210 subjects were enrolled into one of 3 groups: 1) ESA naïve with HGB £10.5 g/dL, 2) previously treated with ESA and HGB £9.5 and 12 g/dL (EOT) in 041 and at BL, 8 and 12 wks (EOT) in 053; [meanSE change from BL (A)]. Missing data were imputed by last observation carried forward.

Results: Data from 141 subjects with CKD-NDD and 55 subjects with CKD-DD were available. In both populations, SF-36 physical component summary and FACT-An scores improved compared to BL (p < 0.005 & 0.001, CKD-NDD; p=0.01 & 0.02, CKD-DD). SF-36 vitality norm-based domain scores (NBDs) and FACT-An anemia score increased by an average of >4 points. Benefits were seen particularly among those with low BL scores. In Study 053, subjects with BL SF-36 Physical Functioning NBDS <35 experienced a mean increase of 8.7 (p=0.005) and those with BL Vitality NBDS <50 increased by 6.7 (p=0.0001). Subjects with BL FACT-An Anemia score <55 increased 10.3 (p=0.0001), and those with BL FACT-An Total Score<15 increased 16.0 (p=0.005).

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

Funding: Pharmaceutical Company Support - FibroGen

TH-OR040
Hepcidin Response to Intravenous (IV) or Oral Iron in the Randomized FIND-CKD Trial of Patients with Non-Dialysis Dependent CKD (ND-CKD)
Carlo A. Gaillard,1 Andreas H. Bock,2 Fernando Carrera,1 Kai-Uwe Eckardt,2 David B. Van Wyck,1 Sukhvir Singh Bansal,2 Bernard Roubert,2 Maureen Cronin,3 Simon D. Roger,2 Iain C. Macdougall,4 1Univ. of Groningen, Groningen, Netherlands; 2Kantonsspital, Aarau, Switzerland; 3Euroaldia, Leiria, Portugal; 4Un. of Erlangen-Nuremberg, Erlangen, Germany; 5Davita Healthcare Partners, Denver, CO; 6King’s College Hospital, London, United Kingdom; 7Vifor Pharma Ltd, Gladbrugg, Switzerland; 8Renal Research, Gosford, NSW, Australia.

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

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

Results: 61 patients provided baseline and 1 post-baseline hepcidin values. Mean (SD) baseline hepcidin level was 4.0(3.2), 7.3(4.6) and 6.5(3.6) ng/mL in the high ferritin FCM, low ferritin FCM and oral iron groups. The mean (SD) endpoint value (i.e. the last post-baseline value) was 26.0(9.1),15.7(7.7) and 16.3(11.0) ng/mL, respectively. The increase in hepcidin from baseline was smaller with low ferritin FCM and with oral iron vs high ferritin FCM up to week 52 (all p<0.05). Correlations were significant between the post-baseline increases in hepcidin and ferritin (r=0.70, p<0.0001), TSAT (r=0.42, p=0.0008) or hemoglobin (r=0.30, p=0.0295) using endpoint values across all groups. The increase in hepcidin levels over the 12-month study generally mirrored the cumulative iron dose in all groups.

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

Funding: Pharmaceutical Company Support - Vifor Pharma, Gladbrugg, Switzerland
TH-OR041
Isolation of Live Nephrin Progenitors Cells Expressing Six2+ and Cited1+ from Human Embryonic Kidneys and Amniotic Fluid
Laura Perin, Stefano Da Sacco, Astig Petrovsky, Matthew Edward Thornton, Brendan Grubbs, Roger E. De Filippo.
Department of Pediatrics, Hospital for Sick Children, Toronto, ON, Canada; 2Department of Pathology, Hospital for Sick Children, Toronto, ON, Canada; 3Department of Pathology, University Health Network, Toronto, ON, Canada; 4Department of Pediatrics, University Health Network, Toronto, ON, Canada.

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

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

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

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

Funding: Private Foundation Support

TH-OR042
Novel Noninvasive Source of Kidney Progenitor Cells with Potential to Differentiate into Podocytes
Fanny Oliveira Arcolino, Silvia Zia, Katharina Held, Joris Vriens, Elii Papadimitriou, Benedetta Bussolati, Anke Raalijmakers, Karel Allegaert, Jan A. Deprest, Jaan Toelen, Lambertus P. ten Cate, Elena N. Levtchenko.

Background: Identification of human kidney progenitor cells (NPC) has been hampered by the availability of a non-invasive source of these cells. Here we report on the isolation of a novel human NPC from amniotic fluid (AF) using a combination of flow cytometry and cytometry.

Results: We identified the presence of kidney progenitor cell features with multipotent differentiation. We aimed to study urine of preterm neonates born before the completion of nephrogenesis for the identification of kidney progenitor cells (NPC). A whole transgenic mouse expressing WT1 and nephrin, deposition of collagen IV alpha3-4-5 and functional response to angiotensin II. Conclusions: Our preliminary results suggest the possibility of deriving and expanding for the first time, Six2+Cited1+ cells from hEK as well as from an exogenous source of cells like hAF without genetic manipulation. This system might represent an accessible and novel source of nephron progenitors that can guide studies of renal cell specification, thus increasing our knowledge on human renal development.

Funding: Private Foundation Support

TH-OR043
Pluripotent, Non-Tumorigenic, Human Mese cells Integrate into Glomeruli to Recover Function in a Chronic Kidney Disease Mouse Model

Background: Nephrology has not yet benefited from these advancements primarily due to lack of development of new model systems. Thus, there is a critical need for the development of in vitro models of human disease that can recapitulate disease pathologies and provide a means to test the efficacy of novel therapeutic agents.

Methods: We aimed to generate and characterize iPSCs from patients with different GRDs. Families with clinically diagnosed GRD were recruited from a Renal Genetics Clinic and given the option to consent for an informed consent to generate iPSCs. iPSCs were generated using transgene-free methods. Patient-derived iPSCs were cultured and used for a variety of different experimental approaches.

Results: 7 families (14 participants) were recruited with a variety of GRD diagnoses. Twelve families have been cultured and evaluated. Fibroblasts were isolated via skin biopsy and reprogrammed using non-integrating Sendai virus (21day protocol). Efficient differentiation of hPSCs into late PS followed by WT1+HOXD11+ cells was achieved. Multi-segmented nephron organoids derived from hPSCs were developed and used to model human diseases in vivo and to evaluate the efficacy of novel therapeutic agents.

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

Funding: Private Foundation Support

TH-OR044
Patient-Derived Induced Pluripotent Stem Cell (iPSC) Modeling of Genetic Renal Disease (GRD)
Andrew John Malled, Barbara Maier, Pei Xuan E., Minoru Takasato, Jane Sun, Ernst J. Wolvetang, Stephen I. Altmann, E. Edward Levtchenko, Naomi J. Tooze, John J. Thorne, The Univ of Queensland, Brisbane, Australia; 2Murdock Children’s Research Inst, Melbourne, Australia; 3Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane and Women’s Hospital, Australia; 4School of Medicine, UQ, Australia; 5Australian Inst of Bioengineering and Nanotechnology, UQ, Australia; 6Dept of Nephrology, Children’s Hospital at Westmead, Australia.

Background: Nephrology has not yet benefited from these advancements primarily due to lack of development of new model systems. Thus, there is a critical need for the development of in vitro models of human disease that can recapitulate disease pathologies and provide a means to test the efficacy of novel therapeutic agents.

Methods: We aimed to generate and characterize iPSCs from patients with different GRDs. Families with clinically diagnosed GRD were recruited from a Renal Genetics Clinic and given the option to consent for an informed consent to generate iPSCs. iPSCs were generated using transgene-free methods. Patient-derived iPSCs were cultured and used for a variety of different experimental approaches.

Results: 7 families (14 participants) were recruited with a variety of GRD diagnoses. Fibroblasts were isolated via skin biopsy and reprogrammed using non-integrating Sendai virus (21day protocol).

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

Funding: Private Foundation Support

TH-OR045
Multi-Segmented Nephron Organoids Derived from Human Pluripotent Stem Cells Model Kidney Development and Injury
Ryujii Morizane, Albert Q. Lam, Benjamin S. Freedman, Seiji Kishi, M. Todd Valerius, Joseph V. Boventteur, Medical Brabant and Western Hospital, BL, M.D.

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

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

Results: Efficient differentiation of hPSCs into late PS followed by WT1+HOXD11+ posterior IM enabled the induction of SIX2+SALL1+WT1+PAZ2+ NPCs with ~90% efficiency within 9 days. Treatment with Wnt and FGF signals induced differentiation into PAZ2+LHX1+ RVs, which spontaneously differentiated into multi-segmented nephron

Funding: Pharmaceutical Company Support - Clio inc., Government Support - Non-U.S.
structures containing podocytes (Nephrin+/PODXL+/WT1+), foot process formation shown by ENA, proximal tubules (LTL+CDH6+/AQP1+), loops of Henle (CDH1+/THP+), and distal tubules (CDH1+/BNR1+) in an organized, contiguous arrangement in both 2D and 3D culture. Inhibition of Notch signaling during organoid formation resulted in specific defects in proximal tubules, indicating that nephron organoids model kidney development. Moreover, treatment with the nephrotoxins, gentamicin or cisplatin, induced KIM-1 expression in LTL+ tubules in a dose dependent manner.

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

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

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

**Underline represents presenting author.**

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**TH-OR046**

A Developmentally Plastic Adult Mouse Kidney Cell Line Spontaneously Generates Multiple Adult Kidney Structures

**Tomoko Obara.** Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.

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

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

**Results:** We discovered that KKPS5 acquires renal progenitor surface markers and an alternative cell source and further develop into multicellular nephron-like structures within a few days in 3-D matrigel. Moreover, when these cells are engrafted into an alternative cell source and further develop into multicellular nephron-like structures in vitro. We are currently generating multiple populations of immortalized or primary human renal epithelial or progenitor cells, and increased cyst lining epithelial cell apoptosis in

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

**Funding:** Private Foundation Support

**TH-OR047**

Decellularized Renal Extracellular Matrix Scaffolds Serve as 3D Biological Templates for Regeneration of Nephron Structures by Human Kidney Cells

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

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

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

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

**Funding:** Private Foundation Support

**TH-OR048**

Systems Biology of Polycystic Kidney Disease Suggests It Is a Metabolic Disease

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

**Methods:** A total of 135 Pkd1+/–;Tg(Cre/Esr1) mice animals in which Pkd1 knockout was induced by tamoxifen at P40 were harvested between P100 and P210 and kidney/body weight curves were fitted for males and females separately. Gene expression in 50 kidneys was analyzed with Illumina arrays, followed by differential gene expression analysis using bioinformatic analysis. Predictions were tested using; 1) metabolite and complex lipids profiling in 14 male kidneys; 2) diet manipulations in 33 Pkd1+/–;Tg(Cre/Esr1) mice induced at P7 and harvested at P21 and in 52 Pkd1+;Tg(Cdh16-cre) mice harvested at P14.

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

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

**Funding:** NIDDK Support

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

**Underline represents presenting author.**
A Forward Genetic Screen Identifies a Calcium-Regulated Mitochondrial Metabolite Carrier as a Downstream Target of Polycystin-2

Methods: To identify evolutionarily conserved core components of the TRPP2 signaling pathway, we conducted an unbiased forward genetic screen in D. melanogaster for mutants that phenocopy the TRPP2 loss of function phenotype. To test the conservation of newly identified genes in vertebrates, the function of candidate genes was investigated in zebrafish.

Results: We identified a calcium-dependent mitochondrial metabolite carrier (MC) as a downstream target of TRPP2 in a large-scale mutagenesis screen for mutants that phenocopy loss of TRPP2 in D. melanogaster. Calcium regulation of this MC appears to be critical, since loss of MC in flies was rescued by WT MC, but not by MC with EF-hand mutations, which abolish calcium binding. In zebrafish, TRPP2 is essential for the establishment of LR asymmetry. Loss of TRPP2 results in polycystic kidney disease.

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

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

TH-OR044

Modeling Polycystic Kidney Disease Cystogenesis with Genome-Modified Human Pluripotent Stem Cells

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

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

Results: PKD hPSCs exhibited self-renewal and pluripotency characteristics comparable to isogenic controls, and differentiated into tubular organoids with similar efficiencies. Interestingly, in PKD hPSC cultures, we observed formation of large, transcribed cysts that suggest a role for PKD2 in PKD1 cyst formation. Cyst formation involved growth of cystic epithelium resulting in a cyst-like structure with LTL and surrounded hollow interiors devoid of cells. Time-lapse imaging revealed that cysts arose from a small minority of differentiating tubular structures. Importantly, isogenic control hPSCs, plated and differentiated in an identical manner to the PKD hPSCs, did not form cysts.

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

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

Funding: NIDDK Support, Private Foundation Support

TH-OR053

Inactivation of Ift88 Gene Rescues the Phenotype in a Genetic Model of Autosomal Dominant Polycystic Kidney Disease

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

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

Results: A protective effect in cystic lesions was observed in kidneys from Pkd2/- and Ift88/- double knockout mice. An increase in cillum length was detected in Pkd2 knockout mice, compared with wild type mice. A significant reduction of the number and length of cilia were found in Ift88 and Pkd2 double knockout mice. Ift88 knockout in the double knockout mice was also confirmed by western blot analyses. Comparative analyses of signaling events in both single and double knockout mice suggest the mammalian target of rapamycin (mTOR) pathway is activated in the early stage of cyst formation of Pkd2 single knockout mice and its aberrant activation is rescued in Ift88 knockout mice with Ift88 inactivation.

Conclusions: Inactivation of Ift88 rescues the polycystic phenotype in a genetic mouse model of ADPKD. mTOR signal pathway, a cilia-mediated pathway, appears to be involved.

Funding: NIDDK Support

TH-OR054

Other Signaling Pathways Rapidly Compensate for Loss of mTORC1 in Driving Cystic Kidney Disease

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

Methods: To conclusively define the cell-intrinsic role of mTORC1 for cyst development, the essential mTORC1 scaffolding protein Raptor was selectively inactivated in renal tubular cells lacking cilia due to deletion of Ift88.

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

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

Funding: Government Support - Non-U.S.
ANKS3 Mutation in Nephropathies Patients Leads to Cilia and Cytoskeleton Defects In Vitro and In Vivo in Zebrashift

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

**Results:** Using NGS, we identified a homozygous mutation (c.806 C>T, p.P269L) in ANKS3, in three siblings affected by late onset NPH with hepatic fibrosis. ANKS3 encodes a SAM domain and Ankyrin repeat containing protein which interacts with ANKSH, NEXK and NPHP3, three NPHP proteins located at the Inversin ‘Invs’ compartment (proximal part of the cilium) that controls essential ciliary signaling pathways during development and tissue homeostasis (Wnt/PCP). Surprisingly, ANKS3 did not localize at the Invs compartment but in apical cytoplasmic aggregates in tubular renal cells or at the basal body in fibroblasts. We provide evidence that the p.P269L mutation led to cilia length defects in patient’s fibroblasts and H.4x knockdown IMCD3 cells, associated with disorganization of the Invs compartment. Moreover, it affects the interaction of ANKS3 with NPHP1 and led to defects in tight-junction and lumen formation in 3D culture, reminiscent of NPHP1 knockdown. We next generated an ANKS3 zebrafish mutant (TALEN) that exhibits lateral defects in the retinal pigmented epithelium. Analyses revealed an absence of the retinal’s velsicle with a significant reduction both in number and length of cilia but motility defects likely explaining the laterality phenotype observed in mutant fish.

**Conclusions:** Altogether, these results indicate that ANKS3 plays a dual function, in the retina and the kidney, facilitating cilia length and protection from cellular morphological abnormalities in ciliopathies. Studying ANKS3 can provide insight for the cilia maintenance, supporting the causative effect of the mutation in the NPH patients.

Funding: Pharmaceutical Company Support - Novartis

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**TH-OR055**

**SDCCAG8 Regulates Ciligenesis by Mediating Endosomal Vesicle Docking to the Basal Body**

**Background:** Mutations in SDCCAG8 gene cause a retinal-renal ciliopathy with BBS-like features in affected humans (1). Our previous characterization of the orthologous Sdcag8-mouse model recapitulated the retinal-renal degeneration phenotypes and identified impaired DNA damage response signaling as an underlying disease mechanism in the kidney (2). However, several other phenotypic features of Sdcag8-/- mice remained unexplored. Here we have extended our studies of SDCCAG8 function.

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

**Results:** Sdcag8-/- mice have defective neural tube patterning and structural abnormalities of the skeleton, suggesting impaired Hedgehog (Hh) signaling. In cell culture, Sdccag8-/- IMCD3 cells, associated with disorganization of the Invs compartment, were positive for SMA and vimentin and negative for desmin, suggesting a myofibroblast phenotype. Interestingly, a number of vascular sections in lowest leaky protein also had desmin-positive contractile smooth muscle cells.

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

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**TH-OR056**

**Characterization of Cystic Kidneys in Mice Deficient in the Polarity Proteins DLG1 and CASK**

**Background:** Polycystic kidney disease involves dysregulation of tubular proliferation and cellular polarity leading to cystogenesis. Deletion of various apico-basal and planar cell polarity (PCP) proteins in mice, including members of the membrane-associated guanylate kinase (MAGUK) family, is sufficient for cystogenesis. DLG1-deficient mice exhibited bilateral hydronephrosis but only occasional unilateral renal agenesis or hypoplasia. Co-deletion or hypomorphic expression of DLG1 and CASK in nephron progenitors (via Six2Cre) affects ciliogenesis and interferes with Hh signaling. In cell culture (SILAC). Co-immunoprecipitation assay was performed in HEK293 cells.

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

**Results:** DLG1+/c; CASK+/c mice exhibit cysts as early as 90 days with severe but variable pathology by 9 months. Analysis of DLG1+/c; CASK+/c– tubule segments indicates proximal tubule origin of cysts and dysregulation of matrix proteins, but with preservation of apico-basal polarity. Ciliary length was up to 2-fold longer in the majority of DLG1+/c; CASK+/c– tubules, but was only longer in dilated DLG1+/c; CASK+/c– tubules. Curiously, while CAMP and Aβ42-induced dilations in wild-type embryonic renal tubules, DLG1+/c; CASK+/c– embryonic kidneys did not exhibit tubular dilations.

**Conclusions:** Our data indicate that DLG1 and CASK co-regulate renal development as well as homeostasis of renal epithelium independently of apico-basal polarity. IIH and arachidonic acid mediated cellular features consisting of variable proximal tubule morphology and unusual elongation of cilia. A CAMP-stimulated model of cystogenesis revealed a failure in PKA-dependent tubular dilations in DLG1+/c–; CASK+/c– embryonic kidneys. Coupled with cilia elongation and PKA effects on cilia function, these results indicate a previously unrecognized regulation of PKA by MAGUK family members in the kidney.

Funding: NIDDK Support

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**TH-OR057**

**Time-Dependent Endothelial Dysfunction following Arteriovenous Fistula Creation**

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

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

**Results:** Mean age was 63.3 ± 13.7 years and the prevalence of obesity (BMI >25 kg/ m²) was 49.1%. Mean serum leptin levels were 2.10 ±1.41 pg/mL (log transformed), and patients in the highest leptin tertile had significantly increased BMI, higher triglyceride, interleukin-6, and hs-CRP levels (P<0.001). AVF maturation failure occurred in 21 (35.6%) patients, and the failure rate progressively increased from the lowest to the highest leptin tertile (p<0.001). On histological examinations, increased leptin tertiles were closely associated with normal hyperplasia (13.3:3.45 vs. 18.2:15.2 vs. 30.3:14.3 mm in each tertile) as well as medullar fibrosis, the majority of cells were positive for SMA and vimentin and negative for desmin, suggesting a myofibroblast phenotype. Interestingly, a number of vascular sections in lowest leptin tertile also had desmin-positive contractile smooth muscle cells.

**Conclusions:** Obesity related fistula maturation failure may be mediated by higher serum leptin level - associated preexisting vascular diseases in ESRD patients.
Conclusions: Creation of AVF results in a time-dependent endothelial dysfunction worse 7 days after creation. Therapies targeted at restoring endothelial function via increasing nitric oxide production shortly after AVF creation may help improve AVF remodeling and inhibit neointimal hyperplasia. Later changes in endothelial-independent vascular function following AVF creation needs further evaluation.

Funding: NIDDK Support, Private Foundation Support

TH-OR060

Is Preoperative Vein Morphology Associated to Vascular Access Outcome? Maria Guedes Marques,1 Raquel Pina,1 Joaquim Ferreira,3 Pedro Maia,3 Teresa Mendes,1 Emanuel Ferreira,1 Helena Pinto,1 Nuno Oliveira,1 Ana Belmira,1 Luís Freitas,1 Armando Carreira,1 Mário Campos.1 1CHUC - Hospital Geral, 1CFUC - HUC.

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

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

Results: The majority of patients were male (64.4%); age 71.4 ± 15.1 years; 57.7% diabetic; 50% had central venous catheter at surgery time; maturation occurred in 53.8%. Intimal angiogenesis and media abnormality were both seen in 66.7% of patients in which VA didn’t mature, but only in 14.3% and 21.4% of the ones that matured, respectively. Chi-square analysis showed that both previous findings were significantly associated with VA failure (p = 0.006 and p = 0.020). Intimal and global wall thicknesses were 0.907 ± 0.0715 and 0.700 ± 0.2228mm in matured VA; 0.260 ± 0.0244 and 1.031 ± 0.3227mm in nonmatured VA, respectively (p = 0.006 and p = 0.005). Gender, age, diabetic status and catheter presence didn’t affect VA function.

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

TH-OR061

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

Background: We had demonstrated that far infrared (FIR) therapy could improve the access flow and unassisted patency of VA in an early pilot study. The aim of this study was to evaluate the efficacy of FIR therapy in 40 patients with advanced chronic kidney disease (CKD) by the definition of eGFR <20 ml/min/1.73m². Patients were randomized and equally allocated to FIR group (receiving FIR therapy for 40 minutes thrice weekly for 3 months) and control group (without FIR therapy). This study is aimed to evaluate (1) the effect of newly-created AV access on the markers of inflammation (hsCRP), endothelial function [asymmetric dimethyl arginine (ADMA) and L-arginine]. and oxidative stress [serum malondialdehyde (MDA), serum advanced oxidation protein products (AOPPs), blood glutathione (GSH), erythrocyte glutathione peroxidase (GPO), erythrocyte superoxide dismutase (SOD) activities], (2) the effect of FIR on access flow and the levels of the above-mentioned inflammatory, endothelial and oxidative stress markers in patients with advanced CKD in the first 3 months after the creation of AVF.

Results: Totally, 122 advanced CKD patients finished this study with 60 in FIR group and 62 in control group. In comparison with control patients, the patients in FIR group had lower mean values of incremental change of the plasma concentrations of hs-CRP [−0.681 ± 0.93 vs. 0.39 ± 0.46 mg/L, P = 0.04] and ADMA (+0.10 ± 0.05 vs. 0.02 ± 0.05, P = 0.02) but a higher incremental change of blood glutathione (2.45 ± 2.23 vs. -0.44 ± 0.67, P < 0.031) and access flow of AVF from 1st to 3rd month.

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

Funding: Government Support - Non-U.S.

TH-OR062

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

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

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

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

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

TH-OR063


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

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

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; Poster; PUB - Publication Only
Underline represents presenting author.

16A
Conclusions: This study demonstrates improvements associated with time to AVF use in incident patients initiating HD with a catheter at clinics participating in the RR program.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-OR064
Impact of Poverty and Health Care Insurance on Arteriovenous Fistula Use Among Incident Hemodialysis Patients

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

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

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

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

Funding: Other U.S. Government Support

TH-OR065
A Subset of CD64+/F4/80−CD11b+/CD11c− Macrophages Protects against Chronic Ischemic Kidney Injury

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

Methods: After 28 days of unilateral RAS in mice, stenotic kidneys were harvested and 3 Mf populations (Figure 1, black circles) quantified using polyrachel flow cytometry. CD11b+/CD11c−/CD64+/F4/80− macrophages (CD64+F4/80−CD11b+CD11c−) were expanded using a transgenic mouse model. Flow sorted CD64+F4/80−CD11b+CD11c− macrophages from kidneys harvested at the start of HD, the only exception being patients with VA healthcare benefits. Efforts to improve AVF use may require focusing on pre-ESRD care to be successful. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense, or the United States government].

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

Funding: Other U.S. Government Support

TH-OR066
Spliced XBP1 Rescues Renal Interstitial Inflammation due to Loss of Sec63 in Collecting Ducts

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Background: Sec63 is one of two genes which cause human autosomal dominant polycystic liver disease, and is located in the membrane of the endoplasmic reticulum (ER). A number of disease states alter ER function and result in ER stress, thus initiating the unfolded protein response (UPR). UPR is mediated by three major stress sensors, IRE1α, PERK and ATF6. In particular, IRE1α is the most conserved of the three branches and phosphorylation of IRE1α results in spliced XBP1 (XBP1s), a transcription factor that activates transcription of chaperones and proteins involved in ER-associated degradation. We have shown that loss of Sec63 and Xbp1 in collecting ducts causes phosphorylation of IRE1α and progressive renal interstitial inflammation leading to CKD (ASN, 2014 TH-OR162). It is known that phosphorylated IRE1α activates NFκβ, JNK, and NALP3 inflammasome. In the current work we investigated the interaction of the Sec63 and IRE1-XBP1 pathways and their role in CKD.

Methods: Animal models used in this study: WT (wild type), SKO (Sec63−/−;Phk1−/−;Pkhd1−/−;Ire1α−/−), DKO (Sec63−/−;Xbp1−/−;Ire1α−/−), and Xbp1 Δcre, as well as DKO:Ripk3−/− and DKO expressing a cre activated ROSA-XBP1s allele. The kidneys were removed and analyzed at P70.

Results: Analysis of NFκβ and JNK phosphorylation states were not different between WT, SKO and DKO. The histology in WT and SKO kidneys appeared normal. In contrast, DKO mice showed many inflammatory cells in the renal interstitium with decline in renal function. By removing IRE1α and Nalp3−/−, respectively, on the DKO background did not rescue the inflammation nor ameliorate decline in renal function. In addition, double knockout of Sec63 and IRE1α in the collecting duct also resulted in renal interstitial inflammation similar to what was observed in the DKO kidneys. Re-expression of a human XBP1 transgene that produces spliced XBP1 on the DKO background rescued the inflammatory phenotype.

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

TH-OR067
Specific Deletion of Rictor in Macrophages Ameliorates Macrophage Activation and Obstructive Nephropathy in Mice

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Background: Rictor/mTORC2 signaling is activated in both tubular and interstitial cells in mouse kidneys with obstructive nephropathy. Our published studies reported that Rictor/mTORC2 signaling mediates TGFβ1-induced fibroblast activation and kidney fibrosis. Regarding the critical role for macrophages infiltration in kidney fibrosis, deciphering the role and mechanisms for mTORC2 signaling in macrophage activation and its contribution to kidney fibrosis are very necessary.

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

Underline represents presenting author.
Methods: In this study, a mouse model with tamoxifen-induced macrophage-specific deletion of Rictor or primary and cultural macrophages from bone marrow were employed. 

Results: Here, we found that Rictor/mTORC2 signaling was activated in the kidney interstitial F4/80+ macrophages in mice with UUO nephropathy. A mouse model with tamoxifen-induced macrophage-specific deletion of Rictor was generated. Compared with the control, lower M1-like but higher M2-like marker expression was detected in Rictor-deleted kidney. In wild-type kidneys, lesion of graft, such as clogging and infarcts, was observed in TNF-R1-knockout mice. However, kidney injury was less severe and interstitial F4/80+ macrophages were markedly reduced in Rictor deleted mice. Additionally, the mRNA abundance for agonist-1, 1fz1, and YM1 were largely induced in wild type macrophages treated with IL-4, which were much less in Rictor-deleted macrophages.

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

Funding: Government Support - Non-U.S.

TH-OR068
Non-HLA Antibodies Targeting Angiotsins II Type 1 Receptor and Endothelin-1 Type A Receptor Induce mTOR Signaling and Endothelial Injury in Human Microvascular Endothelium

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Background: Functional non-HLA antibodies (Abs) targeting G protein-coupled receptors Angiotsins II Type 1 (AT1) and Endothelin-1 Type A (ETAR) are implicated in pathogenesis of renal transplant vasculopathy. Both antibodies activate calcium-G-protein related ERK 1/2. The molecular link between receptor stimulation and development of vascular obliterative lesion has not been fully established. We hypothesized the involvement of PI3K/Akt downstream signaling target mTOR and assessed functional consequences of AT1- and ETAR-activation by non-HLA Abs.

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

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

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

TH-OR069
Memory Effector T Cells and OX40 Signaling Could Contribute to Chronic T-Cell Mediated Rejection


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

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

Results: Using a FC2±2 and a FDR <0.05, we identified 164 genes differentially expressed in renal tissue of patients with chronic and 165 genes differentially expressed in acute TCMR, compared to CDs. Partial Least Square showed a clear difference in the gene expression profile of the three groups of biopsies. The study of gene pathways showed up-regulation of OX40 signaling, that is involved in the differentiation of CD8 memory effector T cell, and up-regulation of KLRG1, BLIMP1 and CD25 that characterized short-lived memory effector T cells. Interestingly, we found that OX40 signaling was specific for chronic TCMR. Next, the validation of the study focused on KLRG1, BLIMP1 demonstrated that these genes were expressed by CD8+ T cells in chronic but not in acute TCMR.

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

Funding: Government Support - Non-U.S.

TH-OR070
Dendritic Cell-Targeted CD40 DNA Vaccination Suppresses Th17 and Ameliorates Renal Injury in Experimental Autoimmune Glomerulonephritis

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

Methods: The rat EAG model was established by NC1 protein injection, and DEC-CD40 vaccination was administered at week 3 and week 6 after NC1 injection. Renal function and histology were assessed at week 12. TH subsets, key transcription factors and relevant cytokines in spleens, kidneys and lymph nodes were examined.

Results: Administration of DEC-CD40 DNA vaccine at week 3 and week 6 after NC1 injection reduced renal structural and functional injury in EAG. DEC-CD40 vaccination induced the number of TH17 cells and inhibited Th17 immune responses in kidney, spleen and lymph nodes, but did not alter the number of Th1, Th2 and Treg cells. Early and late treatment showed similar effects on kidney injury and Th17 immune responses, indicating DEC-CD40 vaccination has both preventative and therapeutic roles in EAG. Serum from rats with DEC-CD40 suppressed Th17 in vitro, but not Th1 differentiation. B cell activation and M1 macrophage polarization were inhibited when co-cultured with Th17 cells induced with DEC-CD40-EAG serum but not EAG serum.

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

Funding: Government Support - Non-U.S.

TH-OR071
Pharmacologic Targeting of Sirtuin-1 (Sirt1) Enhances Treg Function, Markedly Prolongs Renal Allograft Survival and Protects Against Renal Allograft Dysfunction


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

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

Results: Allograft recipients were divided into two groups, and treated with either a Sirt1 inhibitor, EX-527 (1 mg/kg/d for 14 days), or vehicle control. We found that allograft survival at 100 days post-Tx was 87.5% in the EX-527 group, but only 28.6% in control mice (P=0.037, Mantel-Cox test). Moreover, at 100 days post-Tx, the EX-527 treated group had lower BUN (71 ± 2.7 vs. 90 ± 3.6 mg/dI, P<0.001) and serum creatinine levels (0.33 ± 0.04 vs. 0.58 ± 0.02 mg/dI, P<0.001) than survivors in the control group. Histologic analysis of renal allografts retrieved after 100 days showed less allograft fibrosis (p=0.03) and less inflammation (p=0.01) in the EX-527 treated group. Together, these results suggest that Sirt1 inhibitors in effective at prolonging allograft survival and function. These data provide clear evidence that pharmacologic regulation of Treg Function is of demonstrable value in stringent allograft models, and provide a compelling rationale for testing of Sirt1 inhibitors in pre-clinical models.

Funding: Other NIH Support - NIAID
Regulation of the Apical Cotransporter NKCC2 by a Novel Kinase: TNK1
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Background: The apical cotransporter NKCC2 mediates NaC1 absorption by the thick ascending limb (TAL), maintaining blood pressure. Abnormally enhanced NKCC2 activity contributes to salt-sensitive hypertension. Phosphorylation of NKCC2 at Thr-96 and Thr-101 of the C-terminal region (NH2) regulates NKCC2 expression and function, and modulates TAL sodium reabsorption.

Methods: We measured NKCC2 activity by a microperfusion perfusion system during the in vivo micropuncture technique. We generated NKCC2 knockout mice (NKCC2−/−) and obtained TALs and measured total NKCC2, phosphorylation at Thr-96,101 and surface NKCC2 by surface biotinylation. We then performed in vitro phosphorylation assays confirmed a crosstalk between RAW264.7 and NRK49F with increased expression of IL-6 and secretion in IL-6 treated mice. We identified upregulated IL-6 expression and secretion in TALs from RAW264.7 and hypothesized, that inhibiting innate immune cells production and secret cytokines that might affect resident renal cells causing fibrosis and injury. Co-culture assays confirmed a crosstalk between RAW264.7 and NKCC2 with increased expression levels of IL-6, CTGF and miR-21 in NKCC2. Similar results were observed due to IL-6 treatment in kidney slices from GN.

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

TH-OR075
NKCC2 and Its Disease Causing Mutants

Background: Mutations in the apically located Na-K-2Cl cotransporter, NKCC2, lead to type I Bartter syndrome, and inherited kidney disorder associated with salt wasting, hypertension, and metabolic alkalosis. We have previously shown that wild type (WT) NKCC2 knockdown and its mutant Opt genome do not activate a glucose transporter (GLUT) to regulate to respond to IL-6 and 1-deoxymannojirimycin, two potent inhibitors of alpha-l,2-mannosidases, reduced NKCC2 expression was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging. NKCC2 stability was assessed by cycloheximide chase assay and confocal microscopy. NKCC2 and its mutants are subject to regulation by the endoplasmic reticulum-associated decay (ERAD). The aim of the present study was to identify the protein partners involved in ERAD of NKCC2.

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

Results: We identified Golgi alpha 1,2-mannosidase 1A (MANIA) as a specific binding partner of NKCC2. We showed that Golgi-situated α-1,2-mannosidases may also contribute to the ERAD of glycoproteins. Co-immunoprecipitation and co-immunolocalization experiments confirmed NKCC2-MANIA interaction in renal cells. They also showed that MANIA association involves mainly the immature form of NKCC2. MANA co-expression decreases cellular NKCC2 protein in a dose dependent manner. Cycloheximide chase assay showed that in cells over expressing MANIA, NKCC2 maturation is impaired. Importantly, MANIA co-expression had a more profound effect on the disease-associated NKCC2 folding mutants, A508T and M1012T. The MANA knockdown increases in NKCC2 expression and confers a phenotype resistance to the proteasome inhibitor MG132. Finally, kifunensine and 1-deoxymannojirimycin, too, potent inhibitors of alpha-1,2-mannosidases, reduced NKCC2 expression on NKCC2 regulation.

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19A
Inhibition of Mitochondrial Complex-1 Prevents the Downregulation of \( \text{NKCC2 and ENaC} \) in Obstructive Nephropathy  
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Background: Ureteral obstruction with subsequent hydrenephrosis is a common clinical complication. Downregulation of renal sodium transporters in obstructed kidneys could contribute to impaired urine concentrating capability and salt waste following the release of a ureteral obstruction. This study was undertaken to investigate the role of mitochondrial complex-1 inhibition in modulating sodium transporters in obstructive nephropathy.

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

Results: Following UUO, sodium transporters including NHE3, e-Na-K-ATPase, NCC, NKCC2, p-NKCC2, ENaCα, and ENaCβ were remarkably reduced by 60-90% contrasting to unaltered expression of ENaCβ, as determined by qRT-PCR, Western blotting, and immunohistochemistry. This global downregulation of sodium transporters was accompanied by striking reduction of mitochondrial DNA copy number (mtDNA), mitochondrial transcription factor (mtTFA), and mitochondria-encoded NADPH dehydrogenase 1 (mtNdi1) indicating a mitochondrial abnormality. Strikingly, specific inhibition of mitochondrial complex-1 by rotenone (500 µM in diet) completely abolished the downregulation of NKCC2, p-NKCC2, and ENaCα without affecting other sodium transporters. To study the potential mechanisms mediating the rotenone effects on sodium transporters, we examined a number of known sodium modulators, including PGE2, ET1, Ang II, natriuretic peptides (ANP, BNP, and CNP), and nitric oxide synthases (iNOS, nNOS, and eNOS) and found that all of them were strikingly elevated by 3 to 80 folds except for nNOS in kidney from rotenone treatment. However, after rotenone administration, only BNP with a 80-fold increase and iNOS with a 4-fold increase but not others were significantly reduced by 62% and 96%, respectively.

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

Funding: Government Support - Non-U.S.

TH-OR078

NLRP3 Inflammasome Activation Confers the Resistance to Loop Diuretics in Proteinuric Kidney Disease  
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Background: The resistance to loop diuretics is a known phenomenon in proteinuric patients, particularly in the patients with nephrotic syndrome. However, the pathogenic mechanisms remain elusive.

Methods: Kidney biopsy specimens of proteinuric patients and mouse kidneys tissues from albumin overloaded mice (daily 1 p injection of albumin for 12 days) were analyzed.

Results: In the present study, we analyzed Na-K-CI cotransporter (NKCCI, target of loop diuretics) expression in proteinuric patient kidneys via immunohistochemistry (IHC) and found a significant NKCC2 downregulation which was negatively correlated with proteinuria severity. Interestingly, in NKCC2 positive tubules (thick ascending limb, TAL), NLRP3 inflammasome was strikingly elevated and showed a positive correlation with proteinuria severity. These findings suggested a possibility that proteinuria may suppress NKCC2 expression via a NLRP3 inflammasome-mediated mechanism. To validate this hypothesis, NLRP3 WT and KO mice were subjected to albumin overload. Interestingly, albumin overload in WT mice resulted in a robust reduction of NKCC2 by 80% as determined by Western blotting, qRT-PCR, and IHC in accord with a specific induction of NLRP3 in TAL. Meanwhile, the downstream components of NLRP3 inflammasome as determined by Western blotting, qRT-PCR, and IHC in accord with a specific induction of NLRP3 in TAL. Meanwhile, the downstream components of NLRP3 inflammasome were remarkably activated. Importantly, such a mechanism of NLRP3 in TAL. Meanwhile, the downstream components of NLRP3 inflammasome were remarkably activated. Importantly, such a mechanism of NLRP3 inflammasome was specifically targeted to parvalbumin positive tubules in CA-SKAP KO mice, consistent with DCT-specific expression. CA-SKAP KO mice displayed significantly greater amounts of phosphorylated NCC than WT even though the abundance of CA-SKAP and WT-SKAP expression was comparable, verifying the constitutively active nature of the knockin. Telemetric measurements of blood-pressure (BP) revealed the CA-SKAP KO mice are hypertensive despite low renin and aldosterone levels. Elevated BP was further exacerbated by high salt diet and ameliorated by hydrochlorothiazide (HCTZ). CA-SKAP KO mice also displayed HCTZ-remediable metabolic acidosis, and elevated plasma potassium levels, comparable to mouse models of WKH FFHT.

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

Funding: NIDDK Support

TH-OR081

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

Background: The WKNA-OSR1 pathway has been shown to play a key role in ion homeostasis, regulation of extracellular fluid volume, and blood pressure (BP). STED (stereotaxic)(SPS1-related protein stress-responsive kinase-1 (OSR1) activate the renal carriers NKC22 and NCC by phosphorylation. SPK knockout mice (SPAK-KO) and OSR1 knockout mice display mild renal phenotypes, and may compensate for each other. We therefore generated SPAK-KO/OSR1-KO mice (DKO) to compare the effects of deleting both kinases with SPAK deletion alone.

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20A
Methods: To examine the effects of disrupting both SPAK and OSR1, we manipulated diet (Na) and KCNJ10 (K), and altered levels of phosphorylated NCC (pNCC) and phospho-NKCC2 (pNKCC2) and other relevant proteins. We also measured plasma and urine electrolytes, and the BP of SPAK-KO and DKO mice on different diets using telemetry.

Results: We found that DKO had lower pNCC (48% on low Na, p=0.02 & 40% on low KCNJ10) and pNKCC2 (56% on low Na, p=0.04 & 57% on low K diet, p=0.002) than SPAK-KO (100%). On normal diet we found lower pNCC in DKO (40%, p=0.01) than in SPAK-KO but surprisingly no difference in pNKCC2. Total-NKCC2 and total-NCC levels did not differ between the strains on any diet except on low K diet where total-NCC levels were reduced in SPAK-KO compared to DKO (42%, p=0.0003) than SPAK-KO but surprisingly no difference in total-NCC2. DKO displayed lower plasma potassium than SPAK-KO mice on normal (3.35 vs 3.71 mmol/L, p=0.05), low Na (2.83 vs 3.44 mmol/L, p=0.0001) and low K (2.08 vs 3.1 mmol/L, p=0.01), respectively. Unexpectedly, urinary Na did not differ between strains, and DKO did not show lower BP than SPAK-KO.

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

TH-OR082
Inducible Kidney-Specific KCNJ10 Knockout Mice Show a Salt Losing Phenotype
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Background: Missense mutations of KCNJ10 cause EAST/SesAME syndrome, which is characterized by epilepsy, ataxia, sensorineural deafness and a salt-wasting tubulopathy resembling Gitelman syndrome. KCNJ10 encodes Kir4.1 potassium channel, which resides in the basolateral membrane of the distal nephron. KCNJ10-/- mice have a severe phenotype and die during the first two weeks of life, limiting the usefulness of this model. Results obtained in young mice show reduced basolateral K conductance, sodium chloride transporter (NCC) and NHE3 activity, and Staurosporine related proline alanine rich kinase (abundance). Here, we determine the renal phenotype of kidney-specific KCNJ10-/- adult mice.

Methods: Doxycycline-inducible kidney-specific KCNJ10-/- mice were generated using the TetOn/CreLoxP system under the control of Pax8 promoter. Doxycycline was administered for three weeks to mice before generation. Results: Kir4.1 was absent in the KS-KCNJ10-/- mice, which displayed hypokalemia, hypochloremia with metabolic alkalosis, hyperuricemia, polyuria and renal loss of sodium and potassium (p<0.05). At protein level, we observed that disruption of KCNJ10 decreased the expression of NCC and pNKCC2 (Na+K+-Cl cotransporter) without affecting the levels of NKW4 (with no lysine kinase 4) and SPAK.

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

Funding: NIDDK Support

TH-OR083
HIV Vpr Antagonizes Mineralocorticoid Receptor Activity, Explaining Salt Wasting
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Background: Patients with HIV-associated-nephropathy (HIVAN) present with proteinuria but often lack edema, suggesting renal Na wasting. We have shown that the HIV accessory protein Vpr binds transcriptional regulators including the glucocorticoid-receptor and NKCC2 and inhibits MR activity, providing a molecular mechanism for renal salt wasting in HIVAN.

Results: We found that DKO had lower pNCC (48% on low Na, p=0.02 & 40% on low KCNJ10) and pNKCC2 (56% on low Na, p=0.04 & 57% on low K diet, p=0.002) than SPAK-KO (100%). On normal diet we found lower pNCC in DKO (40%, p=0.01) than in SPAK-KO but surprisingly no difference in pNKCC2. Total-NKCC2 and total-NCC levels did not differ between the strains on any diet except on low K diet where total-NCC levels were reduced in SPAK-KO compared to DKO (42%, p=0.0003) than SPAK-KO but surprisingly no difference in total-NCC2. DKO displayed lower plasma potassium than SPAK-KO mice on normal (3.35 vs 3.71 mmol/L, p=0.05), low Na (2.83 vs 3.44 mmol/L, p=0.0001) and low K (2.08 vs 3.1 mmol/L, p=0.01), respectively. Unexpectedly, urinary Na did not differ between strains, and DKO did not show lower BP than SPAK-KO.

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

TH-OR084
The Sodium/Proton Exchanger NHA2 Is a Novel Regulator of Sodium, Calcium and Blood Pressure Homeostasis in the Distal Convoluted Tubule of the Kidney
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Background: NHA2 (also known as SLC9B2) is a sodium/proton exchanger expressed in the kidney, but its function there remains unknown.

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

Results: We found NHA2 expression restricted to distal convoluted tubules in both murine and human kidney. By confocal imaging, NHA2 had an apical to subapical tubular localization. Blood pressure, measured by invasive telemetry, was significantly lower in NHA2 KO mice compared to WT mice on low, normal and high sodium diets. In addition, NHA2 KO mice exhibited reduced sodium chloride co-transporter (NCC) and NHE3 activity, and Staurosporine related proline alanine rich kinase (abundance). Here, we determine the renal phenotype of kidney-specific NHA2-/- adult mice.

Methods: NHA2-/- mice were generated using the TetOn/CreLoxP system under the control of Pax8 promoter. Doxycycline was administered for three weeks to mice before generation. Results: In male mice, NHA2-/- exhibited a reduced range in plasma sodium chloride (0.07 mmol/L, p=0.01), and an increased fractional Na excretion (2% vs 0.7%). We examined renal RNA expression of the thiazide-sensitive cotransporter (TSC), NHE, ATP1A1, NKCC2, NaPi-2A and only TSC was decreased in Vpr mice. As TSC expression is regulated by MR, we focused the effect of Vpr on MR function and mRNA expression in C1V1 cells. Vpr reduced aldosterone-stimulated MMTV and TSC promoter activity. We hypothesized that Vpr binds MR and inhibits its transcriptional activity. Using immunoprecipitation, we found that Vpr, but not Vpr with LXXLL motif mutations, bound recombinant MR. We reasoned that the interaction between Vpr and MR might interfere with the folding of the MR signal peptide, preventing nuclear entry, and thereby preventing MR from binding to promoter regions of target genes. We performed western blots using nuclear extracts from DCT cells and IHC, following exposure to Vpr and/or aldosterone. Vpr inhibited nuclear entry of MR. Using genome-wide ChIP sequencing with MR antibody in an NHA2 expressing cell line and using ChIP-sequencing, we found that the peak signal of TSC promoter was disappeared after treatment with Vpr.

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

Funding: NIDDK Support
**TH-OR086**

**Kidney Disease Associated Variants of Apolipoprotein L1 Changes in the C-Terminal Domain**

Nephropathy (DN) in BTBR ob/ob Mice Minseob Batorsky,1 Anna Batorsky,1 Hazel H. Szeto,2 Da-fu Dai,1 Kelly L. Hudkins,1 Charles E. Alpers,1 *Pathology, Univ of Washington School of Medicine, Seattle, WA; 2Pharmacology, Weill Cornell Medical College, New York, NY.*

**Background:** APOL1 risk variants associate with non-diabetic kidney diseases in African Americans; however, the mechanisms of variant APOL1-mediated kidney injury remain unknown. We have shown a SNARE protein VAMP8 interacts with the C-terminus of APOL1; APOL1 variants change the C-terminal amino acid sequence and attenuate this interaction. Given this, we hypothesize that the structures of variant APOL1s are altered and disrupt protein interactions.

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

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

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

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**TH-OR087**

**SS-31, a Peptide Targeting Mitochondria, Restores Podocytes in Diabetic Nephropathy (DN) in BTBR ob/ob Mice**

Dong Zhou,1 Hayan Fu,1 Roderick J. Tan,1 Youhua Liu,1 *Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; 2Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.*

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

**Methods:** We generated conditional knockout mice in which Wl was specifically ablated in podocytes by using the Cre-LoxP system. The mice were subjected to adriamycin or Ang II infusion, that Wl is dispensable for podocyte maturation, survival, and function under normal physiologic conditions. However, after adriamycin treatment for 7 days, podo-Wl-/- mice developed more severe podocyte injury and albuminuria than their control littermates. No albuminuria or overt pathologic lesions was observed up to 6 months of age, suggesting that Wl is dispensable for podocyte maturation, survival, and function under normal physiologic conditions. However, after adriamycin treatment for 7 days, podo-Wl-/- mice developed more severe podocyte injury and albuminuria than their control littermates. Surprisingly, ablation of Wl resulted in even more profound upregulation of β-catenin, accompanied by reduction and aberrant distribution of nephrin, Wilms tumor 1 (WT1), synaptopodin, and podocalyxin. In chronic injury induced by adriamycin or Ang II infusion, increased albuminuria, aggravated podocyte lesions, and increased apoptosis were evident in Podo-Wl-/- mice. Mechanistically, specific ablation of Wl in podocytes caused significant down-regulation of Dickkopf-3 expression. Meanwhile, NfAT1, a key downstream mediator in non-canonical Wnt signaling, was largely inhibited in Podo-Wl-/- mice after ADR injection.

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

**Funding:** NIDDK Support

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**TH-OR089**

**Ablation of Podocyte-Derived Wnts Aggravates Proteinuria and Kidney Injury**

Dong Zhou,1 Hayan Fu,1 Roderick J. Tan,1 Youhua Liu,1 *Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; 2Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.*

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

**Methods:** We generated conditional knockout mice in which Wl was specifically ablated in podocytes by using the Cre-LoxP system. The mice were subjected to adriamycin administration, and urine and kidney were analyzed at 7 days and 21 days, respectively. We utilized another proteinuric kidney disease model by chronic infusion of angiotensin II for 2 weeks.

**Results:** Mice with podocyte-specific ablation of Wnt(podo-Wl-/-) developed normally. No albuminuria or overt pathologic lesions was observed up to 6 months of age, suggesting that Wl is dispensable for podocyte maturation, survival, and function under normal physiologic conditions. However, after adriamycin treatment for 7 days, podo-Wl-/- mice developed more severe podocyte injury and albuminuria than their control littermates. Surprisingly, ablation of Wl resulted in even more profound upregulation of β-catenin, accompanied by reduction and aberrant distribution of nephrin, Wilms tumor 1 (WT1), synaptopodin, and podocalyxin. In chronic injury induced by adriamycin or Ang II infusion, increased albuminuria, aggravated podocyte lesions, and increased apoptosis were evident in Podo-Wl-/- mice. Mechanistically, specific ablation of Wl in podocytes caused significant down-regulation of Dickkopf-3 expression. Meanwhile, NfAT1, a key downstream mediator in non-canonical Wnt signaling, was largely inhibited in Podo-Wl-/- mice after ADR injection.

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

**Funding:** NIDDK Support
Blockade of Wnt/b-Catenin Signaling Exhibits Superior Therapeutic Efficacy Than Ras Inhibition in CKD

Zhen Li, Lili Zhou, Xue Hong, Youhua Liu,* and Christopher Lund O’Connor

Methods: Kidney tissue samples were collected from 41 patients who underwent unilateral necrosis surgery at the University of Michigan. The expression of miR-21 was assessed by qPCR. The expression of miR-21 was inversely correlated with proteinuria and increased mesangial index (p<0.001) compared to wildtype littersmates.

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

Funding: NIDDK Support, Other NH Support - NIA

Distinct Populations of FOXD1-Derived Renal Interstitial Cells Regulate Erythropoietin Production

Hanao Kobayashi, Volker H. Haase, Medicine, Vanderbilt Univ, Nashville, TN.

Results: Compared to ACEI, or ACEI plus ARB, ICG-001 displayed superior therapeutic efficacy in both models. ICG-001 almost completely abolished proteinuria, albuminuria, as well as inflammation, preventing cytokine induction, and recruitment of glomerular leukocytes and macrophages. MDM2 inhibition with nutlin-3a had identical protective effects in p53 knockout mice, with the exception of crescent formation. In vitro experiments confirmed the MDM2 requirement for induction of NF-kB-dependent cytokines in murine endothelial cells and podocytes, and a concomitant increase in podocyte size and mesangial index. In mice treated with nutlin-3a, miR-21 expression in glomeruli is positively associated with increases in mesangial index (p=0.003), podocyte cytoplasmic size (p=0.001), and increased mesangial index (p=0.001) compared to wildtype littersmates.

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

Funding: NIDDK Support, Other NH Support - NIA

TH-OR090

TH-OR091

Distinct Populations of FOXD1-Derived Renal Interstitial Cells Regulate Erythropoietin Production

Hanao Kobayashi, Volker H. Haase, Medicine, Vanderbilt Univ, Nashville, TN.

Background: In adults, the kidney is the main physiologic production site of erythropoietin (EPO), a hormone that is essential for normal erythropoiesis. However, renal EPO producing cells (REPCs) are derived and are heterogeneous with regard to HIF-2-dependent oxygen sensing and their histogenetic origin is ill-defined.

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

Results: Compared to ACEI, or ACEI plus ARB, ICG-001 displayed superior therapeutic efficacy in both models. ICG-001 almost completely abolished proteinuria, albuminuria, as well as inflammation, preventing cytokine induction, and recruitment of glomerular leukocytes and macrophages. MDM2 inhibition with nutlin-3a had identical protective effects in p53 knockout mice, with the exception of crescent formation. In vitro experiments confirmed the MDM2 requirement for induction of NF-kB-dependent cytokines in murine endothelial cells and podocytes, and a concomitant increase in podocyte size and mesangial index. In mice treated with nutlin-3a, miR-21 expression in glomeruli is positively associated with increases in mesangial index (p=0.003), podocyte cytoplasmic size (p=0.001), and increased mesangial index (p=0.001) compared to wildtype littersmates.

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

Funding: NIDDK Support, Other NH Support - NIA

microRNA-21 in Human Glomerular Aging

Christopher Lund O’Connor, Yifan Wu, Harkamal Singh Jhaai, Jeffrey B. Hodgin, Markus Bitzer. Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Background: Loss of podocytes is sufficient to cause progressive glomerulosclerosis (the podocyte depletion hypothesis). We have recently shown that podocyte loss and glomerular hypertrophy are clinical phenotypes of normal human aging (Hodgin, Bitzer, et al., JASN 2015) indicating that miR-21 plays a role in the pathogenesis of glomerular injury. We now explore the role of miR-21 in aging of human and mouse glomeruli.
Conclusions: Collectively, these results reveal a novel connection between bone marrow and kidney, and implicate myeloid progenitor cells as initiators of glomerular dysfunction with particular relevance to post-transplant FSGS.

Funding: NIDDK Support

TH-OR095

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

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

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

Results: In CRP+ mice, there were nearly refractory to renal IRI, whereas there was almost complete absence of MDSCs in the granulocytic subtype (g-MDSC) Gr-1 CD11b Ly6g Ly6c cells identified by flow cytometry of kidney digest cells in the injured kidneys. In stark contrast in CRPtg, wherein renal IRI was exaggerated, there was an abundance of g-MDSCs in the injured kidneys. Using in vitro T-cell proliferation assays we confirmed that these renal g-MDSCs were suppressive and in vivo CRPtg, depletion of g-MDSCs prior to renal IRI, resulted in increased renal CD4+ T-cell infiltration and reduced serum/urine biomarkers of AKI. Importantly, CRPtg treated with an anti-CD11b monoclonal antibody that specifically lowered human CRP levels, showed both dramatic improvement in renal biomarkers of AKI and dramatic reduction in renal infiltration of g-MDSCs after AKI.

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

Funding: NIDDK Support, Private Foundation Support

TH-OR096

C-Reactive Protein Promotes AKI by Impairing TEC Regeneration via the CD32-Smad3-P27 Dependent Inhibition of KD2/Cyclin E Mechanism Xiao Ru Huang,1 Weiyi Lan,1 Ying Tang,1 Yan-qi Lou,1 Hui Y. Lan,1 Department of Medicine & Therapeutics, Li Ka Shing Inst of Health Sciences, and Shenzhen Research Inst, The Chinese Univ of Hong Kong, Hong Kong, China; 2Department of Nephrology, The Third affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China; 3Department of Nephrology, Sun Yat-sen Memorial Hospital of Sun Yat-sen Univ, Guangzhou, China.

Background: We have previously shown that C-reactive protein (CRP) plays a pathogenic role in acute kidney injury (AKI) by inhibiting tubular epithelial cell (TEC) regeneration. The present study test a hypothesis that CRP may promote AKI via Smad3-p27 dependent inhibition of proximal tubule (KD2)-cyclin E-mediated TEC regeneration in vivo and in vitro.

Methods: The hypothesis was examined in a mouse model of AKI induced in human CRP transgenic/Smad3 knockout (CRP-Tg/Smad3-KO), CRP-Tg/Smad3-WT, CRP-WT/ Smad3-KO, and CRP-WT/Smad3-WT mice by clamping bilateral arteries for 45 minutes and in cultured HK-2 TECs.

Results: After 24 hours of AKI, CRP-WT/Smad3-WT showed a significant increase in serum levels of creatinine and severe tubular necrosis, which was further enhanced in CRP-Tg/Smad3-WT mice but blunted in CRP-Tg/Smad3-KO and CRP-WT/Smad3-KO mice. Further studies revealed that enhanced AKI in CRP-Tg/Smad3-WT mice was associated with a marked activation of TGF-b-Smad3, upregulation of p27, and inactivation of CKD2 kinase, thereby reducing cyclin E expression and impairing TEC proliferation as determined by BrdU incorporation and PCNA. In contrast, deletion of Smad3 in CRP-Tg mice prevented the development of AKI as demonstrated by normal serum levels of creatinine and suppressing the Smad3-p27 pathway, thereby promoting KD2/cyclin E-dependent TEC proliferation. In vitro studies confirmed these findings that CRP acted through its receptor CD32b to activate Smad3 signaling via both TGF-b-dependent and ERK/MAPK crosstalk pathways. Furthermore, we also found that activated Smad3 then bound directly to p27 to suppress KD2/cyclin E-dependent TEC proliferation, which was inhibited by a Smad3 inhibitor (SIS3).

Conclusions: CRP promotes AKI by impairing the TEC regeneration via the CD32-Smad3-p27 mediated inhibition of KD2/cyclin E mechanism.

Funding: Other NIH Support - RGC GRF 468711, CUHK3/CRF/12R, 973 program (2012C517705), CUHK FIS-A program.

TH-OR097


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

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

Results: PAD4 directly citrullinated NEMO in a cell free system as well as in HK-2 cells. In addition, PAD4 directly caused nuclear NFKB-p65 subunit translocation which was attenuated by NEMO neutralization. Furthermore, NEMO neutralization significantly attenuated PAD4-mediated induction of pro-inflammatory genes (MCP-1 by 59±11%, MIP-2 by 43±10%, TNF-α by 59±12% and IL-6 by 83±3%) in HK-2 cells (P<0.05, N=5-6). NEMO neutralization significantly attenuated PAD4-mediated exacerbation of ischemic AKI (PAD4+veh Cr(mg/dL)=2.4±0.4 vs. PAD4+NBP Cr=1.2±0.1, N=6, P<0.01) and renal inflammation (assessed with pro-inflammatory gene expression, neutrophil infiltration) in mice.

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

Funding: NIDDK Support, Other NIH Support - NIGMS

TH-OR098

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

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

Methods: We generated a novel mouse model to induce selective proximal tubule-specific adjustable injury by inducing the expression of diphtheria toxin receptor (DTR) in proximal tubules with variable prevalence (Ndrg1CreERT2;iDTR mice). For in vivo analysis, we utilized co-culture of renal fibroblasts and tubular epithelial cells.

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

Conclusions: Our data provide new evidence that proximal tubule injury triggers several features of CKD, and that the severity, frequency and prevalence of proximal tubule injury determine the progression to CKD. Our results indicate that fibrosis after AKI is secondary to tubular injury, and that treatment of fibrosis itself might not be enough to halt AKI-to-CKD progression. There is an urgent need to develop therapeutic strategies to protect proximal tubules from repeated injury and to restore healthy proximal tubular function.
Kidney injury than 3-month-old. In the aged mice, the kidney NAD heterozygotes. AKI was induced by cisplatin (20 mg/kg). Kidney damage was assessed and mechanism by which SIRT1 deficiency aggravates AKI.

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

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

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

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

**TH-OR102**

CRP Exacerbates Ischemia-Reperfusion Injury in the Kidney by Down-regulating Autophagy

**A. Bao**, 1 Mingjun Shi, 1 Brianna Flores, 1 Nancy Gillings, 1 Orson W. Moe, 1 Ming Chang Hu, 1 Charles and Jane Center for Mineral Metabolism and Clinical Research, UT Southwestern Medical Center; 2 Dept of Internal Medicine, UT Southwestern Medical Center; 3 Physiology, UT Southwestern Medical Center, Dallas, TX.

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

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

**Results:** Compared with LC-3-GFP mice, CRP;LC-3-GFP mice had higher serum creatinine (P<0.05), more tubular necrosis, and higher NGAL expression in the kidney after IRI. CRP addition exacerbated H2O2-increased LDH release from both primary cultured renal tubules and OK cells (P<0.01 respectively). Immunoblot showed lower LC-3 I/I ratio and higher p62, markers of autophagic dysfunction, in the kidneys of CRP;LC-3-GFP compared to LC-3-GFP mice after IRI, and in primary culture of renal tubules and OK cells treated with CRP + H2O2 compared to H2O2 alone. Immunohistochemistry showed much fewer LC-3-GFP puncta in kidneys of CRP;LC3-GFP compared to LC-3-GFP mice after IRI. Similarly, CRP addition reduced LC-3-GFP puncta induced by H2O2 in primary cultured renal tubules and in OK cells transfected with LC-3-GFP plasmid. Autophagy inducers (rapamycin and LiCl) rescued the impaired autophagy and blunted the LDH release from OK cells treated with CRP + H2O2 (P<0.05).

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

**Funding:** NIDDK Support
However, it is unclear how TSP1-SIRPα signaling contributes to IRI pathophysiology. We recently reported that signal regulatory inhibitory protein (SIRP)-α is expressed by renal tubular epithelial cells (TEC), that the protein regulates reactive oxygen species (ROS) in kidney demonstrated a 3-fold increase in superoxide in WT mice post-IRI (p<0.001) but no increase in SIRPa<sup>mut</sup> mice regardless of hematopoietic reconstitution, were fully protected against renal dysfunction, and blockade of SIRPα may provide a therapeutic strategy to modify IR-mediated damage.

**Background:** Ischemia reperfusion injury (IRI) is a major cause of acute kidney injury mediated by oxidative stress. We recently reported that signal regulatory inhibitory protein (SIRP)-α is expressed by renal tubular epithelial cells (TEC), that the protein regulates reactive oxygen species (ROS) in kidney demonstrated a 3-fold increase in superoxide in WT mice post-IRI (p<0.001) but no increase in SIRPa<sup>mut</sup> mice regardless of hematopoietic reconstitution, were fully protected against renal dysfunction, and blockade of SIRPα may provide a therapeutic strategy to modify IR-mediated damage.

**Results:**
- Expression of 3-nitrotyrosine protein modification was reduced in SIRPa<sup>mut</sup> compared to WT mice, although total renal expression of NADPH oxidase 1 and 2 were unchanged. In vitro, WT TEC displayed upregulation of ROS in response to TSP1 (p<0.01), which was not reflected in SIRPa<sup>mut</sup> cells. SIRPα is expressed by all renal cells, and chimeric mice were generated to explore differences in cell compartment contribution to IRI. SIRPα<sup>mut</sup> mice, regardless of hematopoietic reconstitution, were fully protected against renal dysfunction, tubular damage and ROS generation following IRI.

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

**Funding:** NIDDK Support

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**TH-OR104**

**“Urine Sediment” the Ignored Treasure Chest in the Search for Biomarkers in Acute Kidney Injury**

**Nithin Karakala, Juan Carlos Silver, Tally Naveh-May, Tally Naveh-May, Olena Andrukhova**

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

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

**Results:** We identified 479 proteins in sediment (from the AKI 3 and 40 in No AKI). We identified 556 proteins from the no AKI samples, 239 proteins were present only in the sediment and 126 were identified only in the supernatant. In AKI 3 samples we identified 570 proteins, 169 proteins were unique to the sediment and 174 to the supernatant. The molar abundance percentage of BB proteins in the AKI 3 sediment and no AKI sediment was 3.7 and 27.6% and MX proteins was 2.7 and 14.6% respectively.

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

**Funding:** Other U.S. Government Support

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**TH-OR105**

**FGF23 Drives Progression of Chronic Kidney Disease in Mice**

**Olena Andrukhova, Svetlana Slavic, Sathish Kumar Murali, William G. Richards, Reinhold Erben**

**Background:** Circulating fibroblast growth factor 23 (FGF23) is associated with disease progression in both chronic kidney disease (CKD) and chronic kidney injury (AKI).

**Methods:** Here, we elucidate the role of Fgf23 and its co-receptor Klotho in pathogenesis of CKD in mice by a dual approach, using genetic loss-of-function together with pharmacological inhibition models. CKD was induced by 5/6 nephrectomy in 3-month-old C57BL/6 female mice, vitamin D receptor (VDR) knockout mice, Fgf23<sup>VDR<sup>−/−</sup></sup>, and Klotho<sup>VDR<sup>−/−</sup></sup> compound mutant mice. All mice were kept on a rescue diet

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**TH-OR106**

**In Vivo Role of Klotho in the Renal Proximal Tubules**

**Norkio Ide, 1 Hannes Olsson, 1 Tatadoshi Satô, 1 Junichi Hanai, 1 Tobias E. Larsson, 2 Beate Länko, 1 2 Dept of Oral Medicine, Infection, and Immunity, Harvard School of Dental Medicine, Boston, MA, 1 Dept of Medicine, Div of Nephrology, Interdisciplinary Medicine and Biotechnology, Medicine, Boston, MA, 1 Div of Renal Medicine, CLINTEC, Karolinska Ins, Stockholm, Sweden.**

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

**Methods:** No single Cre strain provided effective Klotho deletion in all proximal tubule segments. Therefore, proximal tubule-specific Klotho knock-out mice were generated and crossed by crossing Pecp (phosphoenolpyruvate carboxykinase), K, (Kidney androgen-regulated protein), or SLC34A1 (sodium phosphate cotransporter-2a)-cre with Klotho<sup>−/−</sup> mice.

**Results:** Klotho deletion was confirmed by qPCR, Western, and IHC. Fgf23-Klotho signal regulates phosphate homeostasis, so mineral parameters and regulatory factors were measured. In Pecp-KL and SLC34A1-KL mice, urine phosphate excretion significantly decreased. This was not clearly detected in Kap-KL mice, despite increased renal NaPi2a mRNA and protein levels. Challenge of KL-KAP mice with high phosphate diet resulted in a significant decrease of urine phosphate excretion compared with WT. Serum phosphate level remained normal in all mouse lines. In summary, Klotho deletion in renal proximal tubules leads to a slightly decreased phosphate excretion with no changes in serum phosphate levels.

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

**Funding:** Other U.S. Government Support

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**TH-OR107**

**The Increased Bone Fibroblast Growth Factor 23 Expression Is Mediated by the Fibroblast Growth Factor Receptor in Experimental Uremia**

**Ronen Levy, Ali Hassian, Karina Durlacher, Justin Silver, Tally Naveh-May, Minerva Center for Calcium and Bone Metabolism, Nephrology, Hadassah Hebrew Univ Medical Center, Jerusalem, Israel.**

**Background:** Serum FGF23 is markedly elevated in CKD and has been associated with poor long-term outcomes. FGF23 expression is increased by activation of the FGF receptor 1 (FGFR1) in rats with normal renal function and in vitro in UMR106 osteoblast-like cells. We now demonstrate a role for FGF4 in the regulation of FGF23 in a mouse model of acute kidney injury (AKI) due to high dose folic acid (FA), in rats with adenine high phosphorus induced CKD and in UMR106 osteoblast-like cells.

**Methods:** Mice were injected with 250 mg/kg folic acid to induce AKI and sacrificed at 3 and 6 h. The FGF4 inhibitor PD173074 was given to the mice 1 h before FA. Rats were fed an adenine high phosphorus diet for 14 d and PD173074 given for the last 2 d of the diet. Serum biochemistry, FGF23 and PTH levels were analyzed and calvaria FGF23 mRNA levels measured by qRT-PCR. FGF23 mRNA PD173074 were added to UMR106 cells for 24 and 48 h and FGF23 mRNA levels measured.

**Results:** FA increased serum BUN and phosphate levels as expected from 3 h. Calvaria FGF23 mRNA and serum FGF23 levels were increased 2-3 fold at 6 h. PTH levels increased 6-fold from 3 h after FA. The FGF4 inhibitor PD173074 prevented the FA induced increase in both FGF23 mRNA and serum levels but had no effect on serum PTH levels. A more prolonged uremia due to an adenine high phosphorus diet for 14 d resulted in high levels of serum PTH (30-fold increase) and FGF23 (3.5-fold increase). PD173074 decreased
serum FGF23 and mRNA levels with no effect on PTH in the adrenomedullin induced uremic rats. Addition of FGF2 to UMR106 cells increased FGF23 expression that was also prevented by PD173074.

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

TH-OR108
Acute and Chronic Inflammation Raises the Blood Levels of FGF23 in Normal Mice
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Background: High levels of FGF23 are not fully explained by abnormal mineral metabolism in CKD. We and others found association of FGF23 with inflammation in CKD patients, but knowledge about the role of inflammation in FGF23 regulation is limited.

Methods: Inflammation was induced in B6 mice as follows (n=5 each Gr): Gr1-acute inflammation: single IP injection of 3.3 mg/kg of LPS (E.Coli 0111:B4) or vehicle control (Vb); Gr2-chronic pulsatile inflammation: daily IP injections of 3.3 mg/kg of LPS x 2 weeks; Gr3-chronic persistent inflammation: SQ injection of pellets releasing 2 mg/kg/day of LPS plus Vh daily injection x 2 weeks; and Gr4-acute on chronic inflammation: SQ LPS pellets x 2 weeks and single IP LPS injection before sacrifice. Plasma FGF23 (c-term) and TNFα levels and spleen weight measured at sacrifice.

Results: In Gr1, FGF23 levels were 0.5±0.1 ng/ml 5 hours after LPS injection vs. 0.2±0.04 ng/ml in Vh (p=0.001). In Gr2, FGF23 was 0.2±0.02 ng/ml after 2-week daily LPS injections vs. 0.14±0.04 in Vh (p=0.02). In Gr3, FGF23 was 0.8±0.6 after 2-weeks LPS pellet vs. 0.14±0.04 ng/ml in Vh (p=0.04). In Gr4, FGF23 was the highest i.e., 1.3±0.7 after 2-week LPS pellets and single LPS injection, vs. 0.14±0.04 in Vh (p=0.006). TNFα levels rose significantly in Gr3 and Gr4 vs. Vh (respectively 11.0±0.8, 14.0±8.8, and 8.0±0.8 pg/ml). Spleen weights were significantly higher in Gr3 and Gr4 as further indication of presence of inflammation. Summary: Both acute and chronic exposure to LPS caused inflammation and stimulated the synthesis of FGF23. The effects of acute and chronic LPS exposure seemed to be synergistic.

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

Funding: NIDDK Support

TH-OR109
FGF23 Directly Targets Hepatocytes to Promote Inflammation in CKD
Saurav Singh,1 Alexander Grabner,1 Karla J. Schramm,1 Christoph Yanucil,1 Alexis J. Sloan,1 Ansel P. Amaral,1,2,3 Myles S. Wolf,1 Christian Faul.1 Medicine, Univ of Miami Miller School of Medicine, Miami, FL;1 Medicine, Northwestern Univ Feinberg School of Medicine, Chicago, IL.

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

Since hepatocytes express high levels of FGFR4, we postulate that FGF23 can directly target the liver.

Methods: Using HepG2 cells, a hepatocellular carcinoma cell line, and primary mouse hepatocytes, we analyzed signal transduction and expression of inflammatory cytokines, including C-Reactive protein (CRP) and interleukin-6 (IL-6) upon FGFR23 treatment. FGF23 was injected intravenously into wild-type mice for 5 days, and FGF4R knockout mice were fed a 2% phosphorus diet for 12 weeks. 5/6 nephrectomized rats were administered an FGF4R-specific blocking antibody.

Results: FGF23 induces expression of inflammatory cytokines in hepatocytes by activating calcineurin/NFAT signaling in an FGFR-dependent and α-klotho-independent manner. Elevation of serum FGF23 in wild-type mice via injections of recombinant FGF23 or administration of a high phosphate diet increases CRP levels in liver and blood. High phosphate diet does not elevate CRP expression in FGF4R knockout mice. Pharmacologically blocking FGF4R blockade reduces the expression of CRP in rats with CKD.

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

TH-OR110
Differential Effects of Calcitriol on FGF23/Klotho System and LVH in Experimental Uremia
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Background: Vitamin D (vitD) deficiency and excess of circulating FGF23 are significant contributors to cardiovascular (CV) mortality in CKD patients. In vivo, vitD metabolites downregulate FGF receptors and FGFRs and activate calcineurin/NFAT signaling (LVH). However, vitD is a known stimulator of FGF23 synthesis in the bone, and thus, may have paradoxical effects on the CV phenotype in CKD. Here, we investigated the effects of vitD on the FGF23 signaling cascade mediated LVH in experimental uremia.

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

Results: Cardiac Fgfr2 levels, Fgfr1 and Fgfr4 mRNA, and LVH were increased significantly in 5/6Nx rats compared with controls. The calcineurin-NFAT signaling pathway was activated in uremia demonstrated by enhanced calcineurin accompanied by a strong reduction of phosphorylated NFAT protein. Pro-hypertrophic genes were increased in myocardial tissue of 5/6Nx rats. In general, vitD treatment of 5/6Nx rats resulted in reduced cardiomyocyte cross-sectional area. Although, cardiac Fgfr2 levels, and Fgfr1 and Fgfr4 mRNA were further stimuli by vitD, vitD treated 5/6Nx rats showed reduced activation of NFAT ameliorating cardiac remodeling processes and LVH. Interestingly, renal Klotho expression was markedly reduced in uremic animals, and almost normalized after vitD treatment.

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

TH-OR111
FGF4R Activation Is Sufficient to Induce LVH in Mice
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Background: Previously, we demonstrated that fibroblast growth factor (FGF) 23 is a causal factor in the pathogenesis of left ventricular hypertrophy (LVH). FGF23 directly targets cardiac myocytes via FGF receptors (FGFR) and activates calcineurin/NFAT signaling. Mammals express four FGF4R isoforms (FGFR1-4). Using two loss-of-function approaches (delivery of a blocking antibody in a rat model of chronic kidney disease (CKD) and gene deletion in mice), we could show that FGF4R is required for the development of LVH in rodents with high FGF23. To confirm this finding in a gain-of-function approach, we studied a genetic knock-in mouse model carrying a FGF4R mutation (G385R) that causes constitutive and ligand-independent activation of FGF4R.

Methods: We studied 6 months old homozygous FGF4R-G385R knock-in mice and wild-type littermates. LVH was assessed echocardiography, H&E staining of cardiac cross sections, and cross sectional area of individual myocytes. We analyzed cardiac fibrosis by Picrosirius Red staining and qPCR. Activation of calcineurin/NFAT signaling in cardiac tissue was studied by qPCR and Western blot analysis, and serum levels of cleaved FGF23 were determined by ELISA.

Results: Compared to wild type littermates, FGF4R-G385R mice develop LVH as evident by significantly increased LV wall thickness, cross sectional myocyte area and ejection fraction. FGF4R-G385R hearts are not fibrotic, and show a significant elevation of NFAT target gene expression. Although serum FGF23 levels were increased in FGF4R-G385R mice, the elevation did not correlate with the cardiac phenotype.

Conclusions: Activation of FGF4R per se is sufficient to induce LVH in mice independently of serum FGF23 levels. We postulate that FGF4R is part of a novel pro-hypertrophic signaling pathway in the heart that could be activated in patients with cardiomyopathies. FGF4R blockade might not only serve as a novel pharmacological intervention for LVH in CKD patients with elevated FGF23, but also in patients with primary cardiac disease and increased FGF4R activity in the heart.

Funding: NIDDK Support, Private Foundation Support

TH-OR112
Downregulation of Thrombomodulin Expression in Endothelial Cells by Fibroblast Growth Factor-23 and Klotho
Kenji Tanaka,1 Yoko Oyama,1 Tarek Doghmi,1 Yunchun Sang,1 Karuna Kanthashree, Nara, Japan;1 Dept of Laboratory and Vascular Medicine, Kagoshima Univ Graduate School of Medical and Dental Sciences, Kagoshima, Japan;1 Dept of Pharmacology, Faculty of Dentistry, Mahidol Univ, Bangkok, Thailand.

Background: Chronic kidney disease (CKD) is regarded as a state of excessive fibroblast growth factor-23 (FGF-23) and a Klotho (KL) deficiency. Moreover, the increased mortality risk in CKD patients associated with cardiovascular disease and endothelial dysfunction. Increasing evidence demonstrates that thrombomodulin (TM)
plays an important role in endothelial barrier. The mechanism responsible for the linkage of FGF-23 with TF and FGF-23/ KL dose-dependently. Our results imply that TF response by FGF-23/ KL is markedly decreased when HUVECs were stimulated with 10 ng/ml FGF-23/ KL whereas Cells were visualized by double staining for TM expression and nucleus.

Results: SDS-PAGE and flow cytometry analysis shows that TM expression was markedly decreased when HUVECs were stimulated with 10 ng/ml FGF-23/ KL whereas FGF-23 and FGF-23/ KL dose-dependently. Our results imply that TM response by FGF-23/ KL is a possible mechanism that leads to vascular complications in CKD patients.

Funding: Private Foundation Support

TH-OR114
Tenapanor, an NHE3 Inhibitor, Reduces Serum Phosphate in Patients with CKD Stage 5D and Hyperphosphatemia

Methods: Tenapanor, an NHE3 inhibitor, was studied in a randomized, controlled, double-blind, placebo-controlled study (NCT02081534) examining the effect of tenapanor on serum phosphate in patients with CKD stage 5D (hemodialysis).

Results: After a 1–3-week washout period of phosphate binders, 162 patients with baseline serum phosphate 6.0–<10.0 mg/dl and ≥1.5 mg/dl increase from pre-washout levels were randomized to placebo or one of six tenapanor groups (1, 3, 10 or 30 mg bid, or 3 or 30 mg qd) for 4 weeks. Blood samples were collected weekly. The primary endpoint was change in serum phosphate from baseline. Dose–response analysis was a secondary endpoint.

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

Funding: Pharmaceutical Company Support - AstraZeneca

TH-OR115
Racial Differences in Association of Serum Calcium with Mortality and Incident Cardio- and Cerebrovascular Events

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

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

Results: The mean age (SD) was 60.6 (13.5), and the mean eGFR (SD) was 83.3 (15.4) ml/min/1.73m². 15.5% of patients were AA, with a mean baseline CA of 9.5±0.4 mg/dl. Over a median follow-up of 8.2 years, there were 47,790 (15.7%) deaths, 8,129 (2.7%) strokes, and 6,675 (2.0%) CHD events in AA, compared to 299,137 (21.1%), 30,300 (2.1%) and 34,304 (2.4%) events in whites. A U-shaped association between CA and mortality was present in both races, but AA patients experienced lower risk relative to white patients with CA=8.8 mg/dl (Figure, p<0.01 for interaction). No associations were found between CA and CHD/stroke in either race.

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

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

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

Funding: NIDDK Support, Veterans Administration Support

TH-OR116

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

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

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

Results: Among all patients, usual LDL-C was positively, and approximately log-linearly, associated with risk of AVE (HR per 1 mmol/L [39 mg/dL], higher LDL-C: 1.38 [95% CI 1.22-1.56]). Compared to patients with low CRP, patients with high CRP were at higher risk, but the relationship between LDL-C and AVE risk was similar in both groups (HR per mmol/L 1.29 [1.07-1.54] and 1.43 [1.21-1.69] respectively, p for interaction=0.58). E/S was similarly effective at reducing MAE in patients with low and high CRP. (Rate Ratio 0.84 [0.81-0.86] and 0.83 [0.79-0.86] respectively, p for heterogeneity=0.96). Sensitivity analyses gave similar results.

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

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

TH-OR117

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

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

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in patients with non-dialysis dependent CKD. Patients with non-dialysis dependent CKD stages 3-5 with no history of kidney transplantation were included in the analysis. Statin use was ascertained from pharmacy dispensing records in 2012 and 2013.

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

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

Funding: Veterans Administration Support

TH-OR118

Associations of Conventional Echocardiographic Measures with Incident Heart Failure and Mortality: The Chronic Renal Insufficiency Cohort Study Ruth F. Dhib,1 Amanda Hyre Aynder,2 Wei Yang,2 Alan S. Go,3 Martin Keane,4 Rajat Dey,2 Nisha Bansal,5 Raymond R. Townsend,6 Michael Shlipak,1 Univ of California, San Francisco/SF VAMC; 1Univ of Pennsylvania School of Medicine; 2Kaiser Permanente, California; 3Temple Univ School of Medicine; 4Univ of Washington.

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

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

Results: Among 2964 participants, 45% were women, 54% were non-white race, mean(SD) age was 59±11years, mean(SD) eGFR was 44±17ml/min/1.73m² at baseline. Over a median[1QRR] follow up of 6.5 [5.7-7.6] years, 262 participants developed incident HF, and 470 participants died. In both men and women, LVMI was a strong, independent predictor of incident HF and mortality, even after adjustment for BNP and troponin T.

<table>
<thead>
<tr>
<th>Characteristics (%)</th>
<th>CKD Stage undetermined (n=147, 508)</th>
<th>CKD Stage 3A (n=457, 528)</th>
<th>CKD Stage 3B (n=194, 470)</th>
<th>CKD Stage 4 (n=51, 299)</th>
<th>CKD Stage 5 (n=5, 999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Using statin</td>
<td>% Using statin by comorbidity</td>
<td>% Using statin by comorbidity</td>
<td>% Using statin by comorbidity</td>
<td>% Using statin by comorbidity</td>
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</tr>
<tr>
<td>62.6</td>
<td>57.8</td>
<td>61.6</td>
<td>61.3</td>
<td>53.6</td>
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</tbody>
</table>

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

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

Funding: NIDDK Support

TH-OR119
Prevalence and Prognostic Significance of Apparent Treatment Resistant Hypertension in Chronic Kidney Disease: A Report from the CRIC Study

George Thomas,1 Dawei Xie,2 Hisang-Chu Chen,3 Amanda Hyre Anderson,2 Lawrence J. Appel,2 Carolyn S. Brecklin,1 Paul E. Drawz,7 John M. Flack,2 Edgar R. Miller,3 Susan P. Steigerwald,2 Raymond R. Townsend,2 Matthew R. Weir,9 Jackson T. Wright,9 Mahhoob Rahman.2 1Cleveland Clinic, Cleveland, OH; 2CIRC Investigators.

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

Methods: We analyzed data on 3367 hypertensive participants in the Chronic Renal Insufficiency Cohort (CRIC) to determine prevalence, associations, and clinical outcomes of ATRH in non-analysts CKD patients. ATRH was defined as blood pressure >160 mm Hg on ≥3 antihypertensives, or use of ≥4 antihypertensives with BP goal at baseline.

Results: The prevalence of ATRH was 40.4%. Older age, male gender, black race, diabetes, and higher BMI were independently associated with significantly higher odds of having ATRH. Compared to participants without ATRH, after adjustment for common covariates, participants with ATRH had a higher risk of clinical events (composite of myocardial infarction (MI), stroke, peripheral arterial disease (PAD), congestive heart failure (CHF), and all-cause mortality (HR [95% CI]) (1.18 [1.12, 1.25]); renal events (ESRD or 50% decline in GFR) (1.28 [1.11, 1.46]); CHF (1.77 [1.42, 2.16])); and all-cause mortality (1.24 [1.01, 1.5]). The subset of participants with ATRH and BP goal at ≥4 medications also had significantly higher risk of composite of MI, stroke, PAD, CHF, and all-cause mortality (HR [95% CI]) (1.30 [1.12, 1.51]) and CHF (1.68 [1.32, 2.12]) compared to those without ATRH. The association between ATRH and CHF and renal outcomes differed depending on baseline GFR interaction (p<0.05). ATRH was associated with significantly higher risk for CHF and renal events only among those with GFR ≥30 ml/min/1.73 m².

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

Funding: NIDDK Support, Other NIH Support - Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NINHICATS UL1TR000003, Hopkins University Ul1 Ul1 TR000424, University of Maryland GCRC M01 RR-16500, Clinical and Translational Science Collaborative of Cleveland, UL1TR000439 from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research. Michigan Institute for Clinical and Health Research (MICHR) UL1TR000433, University of Illinois at Chicago CTSI UL1RR029879, Tulane University Translational Research in Hypertension and Renal Disease P30MO13337, Kaiser Permanente NINHIC UCSR-CTS1 UI1 RR-024131

TH-OR120
Aryl Hydrocarbon Receptor Is Activated during Chronic Kidney Disease and Is Associated with Mortality

Stephane Burtey,1 Paul E. Drawz,7 John M. Flack,2 Richard Raphael,2 Katia Bellum,7 Marion Ramachandran,2 Paul C. Goldfarb,2 D. Yang,1,2 Edgar R. Miller,3 Steve Mcknight,1,2 Michael S. Denison,3 Philippe Brunet.2 1Aix-Marseille Univ; 2AP-HM; 3UC Davis.

Background: Aryl hydrocarbon receptor (AhR) is a transcription factor activated by numerous pollutants, like dioxin. Its activation is associated with cardiovascular risk. Indoxyl sulfate (IS) and indole-3 acetic acid (IAA) are uremic toxins associated with cardiovascular disease. They are agonists of AhR. Our goal was to study whole blood expression of AhR target genes (CYP1A1, CYP1B1 and ATRH).

Results: The sera of patients with CKD stage 5D and CKD stage 3-5 activated AhR (means: 53.6 and 45.6 AU; 95% CI [45.6-61.6] and [32.6-58.7] respectively) compared to controls (means: 2.1 AU; 95% CI [0.5-3.8]). The activating effect of CKD serum sera from controls (mean: 2.1 AU; 95% CI [0.5-3.8]). The activating effect of CKD serum compared to patients with value below.

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

Funding: Government Support - Non-U.S.

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

TH-OR121
Associations of Urine Kidney Injury Biomarkers and All-Cause Mortality in the CRIC Study

Meyeon Park,1 Chi-yuan Hsu,1 Alan S. Go,2 Dawei Xie,2 Xiaoming Zhang,1 Sushrut S. Waikar,4 Joseph V. Bonventre,4 Josef Coresh,3 Robert G. Nelson,1 Harold I. Feldman,2 Paul L. Kimmel,3 Vasan S. Ramachandran,2 Kathleen D. Liu.4 1UCSF; 2Kaiser Permanente of Northern California; 3UC, Philadelphia, PA; 4University of Pennsylvania; 5Harvard, Welch Center for Prevention; 6NHI; 7Boston Univ.

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

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

Results: Mean age of study participants was 59.5 (± 8.8) years; 46% were women; 45% were white, 38% were black. 50% had diabetes mellitus and 34% had cardiovascular (CV) disease. After adjustment for baseline eGFR, albuminuria, age, sex, race, CV comorbidities, and medications, those in the highest quintile (Q5, >2290.3 pg/g) of KIM-1/cr levels and in the highest two quintiles of NGAL/cr (Q5, >64 ng/g; Q4, >20.2 ng/g) relative to the lowest (Q1: KIM-1/cr <661.3 pg/g; Q1: NGAL/cr <2.6 ng/g) had an increased risk of death [KIM-1/cr Q5 vs Q1, hazard ratio (HR) 1.6 (1.1-2.3); NGAL/cr Q5 vs Q1 HR 1.8 (1.2-2.8); Q4 vs Q1 HR 1.5 (1.2-2.3)]. Both analytes were also associated with death when levels were expressed as a continuous variable [HR for log SD increase of KIM-1/cr=1.21 (1.06-1.39); HR for log SD increase of NGAL/cr=1.22 (1.07, 1.39)]. NAG/cr was associated with death in the continuous analysis only [HR for log SD increase of NAG/cr=1.2 (1.04-1.37)]. LFABP/cr was not associated with death.

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

Funding: NIDDK Support

TH-OR122
Endogenous Klotho Is Expressed in Human Heart and May Associated with Fibrosis

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

Methods: Human arterial appendage specimens were collected during cardiac surgery from individuals with and without CKD. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. CKD was defined as eGFR<60 ml/min/1.73 m³. Fibrosis was quantified digitally using trichrome stained sections. Paraffin embedded cardiac tissue was obtained commercially. Westen blot and immunohistochemical assay were used to detect protein expressions of Klotho, FGF23 and FGF3. Klotho mRNA expression was assessed with RT-PCR.

Results: We confirmed that FGF23 is expressed in human heart. Our results show that endogenous Klotho and its co-receptor FGFR3 are expressed in human arterial appendage and left ventricle both in protein and mRNA levels. Our results also showed that cardiac fibrosis is negatively correlated with eGFR. Among individuals with CKD, we hypothesized that ongoing kidney injury would associate with an increase in fibrosis.

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

TH-OR123
Circulating TNF Receptors Predicts Cardiovascular Disease in CKD Patients

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Background: Cardiovascular disease (CVD) is the main public health problem patients with CKD. However, there is no definitive biomarker for predicting CVD morbidity and mortality in CKD. The aim of this study is to evaluate the role of circulating tumor necrosis factor receptors (cTNFRs) as a predictor of CVD risk in patients with CKD.
Methods: We recruited 1,078 patients with CKD from 11 centers prospectively between 2008 and 2012. The levels of cTnFIR1 and cTnFIR2 were determined by performing enzyme-linked immunosorbent assay (ELISA). The correlation coefficient between cTnFRs and various values was measured using a Pearson’s correlation test. Cox regression analysis was used to calculate the hazard ratio (HR) of CVD.

Results: Among a total of 1,078 patients, 57.2% were men and mean age was 50.4±15.7 years. 261 participants (24.2%) had DM. The mean serum creatinine was 1.91±1.0 mg/dL, UPCR was 2.2±2.7 g/g creatinine, hs-CRP was 0.6±2.4 mg/L. cTnFIR1 was 271±917 and cTnFIR2 was 587±387 pg/mL. Serum cTnFIR2 was correlated with the cTnFIR1 (r=0.827), each other. In addition, age, BMI, UPCR, and eGFR were significantly correlated with cTnFIR1 (r=0.43 for age, r=0.15 for BMI, r=0.20 for UPCR, r=-0.63 for eGFR, p<0.001 for all).

Conclusions: The cTnFIR1 and cTnFIR2 can be used as independent risk factors for CVD, independent of eGFR and UPCR. Furthermore, cTnFIR2 can be a relevant predictor for CVD in patients on dialysis.

TH-ORI24

Fibroblast Growth Factor 23 and Risk of Atrial Fibrillation in Chronic Kidney Disease: The CRIC Study


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

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

Results: Among a total of 1,078 patients, 57.2% were men and mean age was 50.4±15.7 years. 261 participants (24.2%) had DM. The mean serum creatinine was 1.91±1.0 mg/dL, UPCR was 2.2±2.7 g/g creatinine, hs-CRP was 0.6±2.4 mg/L. cTnFIR1 was 271±917 and cTnFIR2 was 587±387 pg/mL. Serum cTnFIR2 was correlated with the cTnFIR1 (r=0.827), each other. In addition, age, BMI, UPCR, and eGFR were significantly correlated with cTnFIR1 (r=0.43 for age, r=0.15 for BMI, r=0.20 for UPCR, r=-0.63 for eGFR, p<0.001 for all).

Conclusions: cTnFIR1 and cTnFIR2 associate with CVD and other risk factors in CKD, independent of eGFR and UPCR. Furthermore, cTnFIR2 can be a relevant predictor for CVD in patients on dialysis.

FR-ORI01

Effects of Cyclosporine on Renal Handling of Divalent Cations in Claudin 16-Deficient Mice

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Background: Calcineurin inhibitors tacrolimus and cyclosporine are instrumental for immunosuppression after organ transplantation but cause substantial renal side effects including hypomagnesemia and hypercalcuria. The tight junction protein Claudin 16 (Cltn16) mediates paracellular reabsorption of divalent cations along the cortical thick ascending limb and has been implicated in the adverse effects of cyclosporine. We have compared the transport of divalent cations (Ca++ and Mg++) in Clnd16(-/-) mice with wild-type (Clnd16+/+) mice.

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

Results: Physiological analysis revealed baseline hypomagnesemia and hypercalcuria in Clnd16(-/-) mice. Administration of cyclosporine induced marked hypomagnesemia in WT mice but did not significantly alter plasma magnesium levels in Clnd16(-/-) mice. In contrast, cyclosporine-induced increase in urinary calcium was significantly stronger in Clnd16(-/-) mice compared to WT controls along with more pronounced decrease in plasma calcium levels in Clnd16(-/-) mice. Cyclosporine stimulated distal sodium transporters leading to sodium retention in both genotypes.

Conclusions: In sum, our data corroborate the pivotal role of Clnd16 in the renal magnesium and calcium handling and suggest that Clnd16 may be involved in the cyclosporine-induced renal magnesium loss and hypomagnesemia, since genetic deletion of Clnd16 prevented these effects. In contrast, the strong manifestation of cyclosporine-induced hypercalcuria in Clnd16(-/-) mice suggests that cyclosporine may affect transcellular calcium reabsorption pathways rather than the Clnd16-mediated paracellular transport.

FR-ORI02

Ogr1 and Acid-Induced Hypocalcuria

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

Methods: Wild type (OGR1+/+) and an OGR1 mice-deficient model (OGR1−/−) were subjected to metabolic acidosis (50 mM NH4Cl) or non-acidoic control condition for 1 hour. Kidney and basic physiological parameters were collected from blood and urine.

Results: Basal urinary Ca++ excretion was similar in OGR1−/− and +/+ mice, except for a higher plasma pH in the 1 day metabolic acidosis group (7.20±0.02 vs. 7.15±0.03, p<0.001) in OGR1−/− mice. In contrast to wild type mice, OGR1−/− mice showed increased Ca++ excretion, lower Ca++ reabsorption and lower Mg++ excretion. OGR1−/− mice compared to wild-type mice showed increased urinary Ca++ excretion under metabolic acidosis which may explain the diminished Ca++ reabsorption under metabolic acidosis which may explain the diminished Ca++ reabsorption in OGR1−/− mice.

Conclusions: OGR1 is involved in the hypermagnesemia and hypercalcuria developed during metabolic acidosis, by a mechanism involving the Ca++ channel, TRPV5.

Funding: Government Support - Non-U.S.

FR-ORI03

Conditional Nfat5 Knockout Causes Impaired Urinary Concentrating Ability with Renal Diabetes Insipidus and Hypertension without Renal Medullary Injury

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Background: This study addressed the effects of inducible deletion of Nfat5 in adult mice on the expression of components of urinary concentration, i.e. AQP-2, CIC-K1, barttin, and UT-A1. In parallel, Nfat5-dependent osmoreceptive genes AR, HSP70, and others were determined along with renal functional, morphological, and systemic parameters.

Methods: Mice with tamoxifen-inducible deletion of Nfat5 were established. At the age of 4-8 weeks, conditional Nfat5 KO mice or control animals were fed with a diet rich in fructose and a low NaCl diet.

Results: Adult mice with tamoxifen-inducible deletion of Nfat5 developed severe diabetes insipidus with increased urinary NaCl excretion and decreased urinary concentrating ability.

Conclusions: Tamoxifen-inducible deletion of Nfat5 caused a loss of urinary concentrating ability with concomitant renal diabetes insipidus and hypertension. The results suggest that Nfat5 plays an important role in renal diabetes insipidus and hypertension.
containing tamarixan for further 3-4 weeks. Subsequently, the expression of NFT5 target genes was determined by qPCR. Western blot analysis, and immunohistochemistry in different kidney zones in animals with access to free water or in mice that were water deprived for 24 h. Urine and blood electrolyte and urea concentrations were determined by standard methods.

Results: Adult mice with conditional deletion of NFT5 showed 80-90% reduced expression of NFT5 in all tissues tested, particularly in renal medullary regions. Accordingly, the NFT5 target genes AQP-2, CIC-K1, barttin, UT-A1, AR, and HSP70 were substantially downregulated. Consistently, these NFT5-deficient mice had renal diabetes insipidus, reduced urinary concentrating ability, dehydration, and hypernatremia, particularly following water deprivation. In contrast to constitutive NFT5 knockout animals, inducible deletion in adult mice was not associated with renal medullary injury or hydronephrosis.

Conclusions: Deletion of NFT5 causes renal diabetes insipidus-like phenotype by diminished expression of genes essential for urinary concentration. Despite reduced expression of osmoregulatory genes in the renal medulla, histological evidence of medullary cellular injury was not detectable. The lack of damage might be a consequence of diminished expression of osmoprotective genes in the renal medulla, histological evidence of medullary injury, and the role of NFT5 in the regulatory renal tubular fluid transport.

FR-OR004
Effect of Concurrent P2Y2 Receptor Deletion and P2Y12 Receptor Blockade on Lithium-Induced Nephrogenic Diabetes Insipidus in Mice
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Background: Chronic lithium (Li) administration for bipolar disorder causes nephrogenic diabetes insipidus (NDI), characterized by polyuria, natriuresis and kaliuresis, resulting in a debilitating condition. Previously we reported that mice lacking ATP/UTP-activated P2Y2 receptor are significantly, but not completely resistant to Li-induced polyuria. Recently in a mouse model we observed that pharmacological blockade of ADP-activated P2Y12 receptor offers near complete amelioration of Li-induced polyuria. However, there were differences between these two approaches in terms of natriuresis, kaliuresis and blood Li levels. Hence, we tested the concurrent effect of both in mice.

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

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

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

Funding: Veterans Administration Support

FR-OR005
The V-ATPase B1 Subunit Polymorphism p.E161K Is Associated with Impaired Urinary Acidification in Recurrent Stone Formers
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Background: Mutations in the V-ATPase B1 subunit gene ATP6V1B1 cause autosomal-recessive distal renal tubular acidosis. We previously identified a single nucleotide polymorphism (SNP) in the human V-ATPase B1 subunit (c.481G>A; p.E161K) that displayed greatly diminished pump function in vitro.

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

Results: 32 of 555 (5.77 %) of the patients examined were heterozygous for the p.E161K SNP, the remaining 523 patients (94.23%) carried two wild-type alleles. Adjusted for sex, age, BMI and dietary acid and alkali intake, p.E161K carriers displayed a higher trough urinary pH (5.34 vs 4.89; p=0.009) than wild-type patients. 14.58 % of wild-type patients and 52.38% of p.E161K carriers were unable to acidify their urine below 5.3 and thus had incomplete distal renal tubular acidosis.

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

Funding: Government Support - Non-U.S.

FR-OR006
Proximal Tubule-Specific Glutamine Synthetase Deletion Alters Basal and Acidosis-Stimulated Renal Ammonia Excretion
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Background: Glutamine synthetase (GS) mediates the recycling of NH₃, and glutamate back to glutamine. In the kidney, the majority of GS is expressed in the proximal tubule where it may decrease net ammoniagenesis and limit ammonia available for net acid excretion. This study’s purpose was to determine the role of proximal tubule (PT) GS in normal acid-base homeostasis and in the renal response to metabolic acidosis.

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

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

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

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FR-OR007
The B1 H'-ATPase (Atp6v1b1) Subunit Is Required for Non-Type A Intercalated Cell Function and Defense against Alkalosis
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Background: The final urine pH is fine-tuned by type A and non-type A intercalated cells (A-ICs and non-A-ICs) in the connecting tubule (CNT) and collecting duct (CDD) involving the action of vacuolar H-ATPases. Mutations in the B1 subunit of H-ATPase (Atp6v1b1) in man cause distal renal tubular acidosis due to its importance in acid secretion by type A-ICs. Non-type A-IC also express the vacuolar H⁺-ATPases (V-ATPases) involved in proton (H⁺) secretion. Mutations in the B1 subunit affect the function of the V-ATPases that are present in the CNT and CDD and may result in decreased acid secretion. In addition, B1 subunit mutations may affect the function of Na⁺-H⁺ exchangers (NHEs) that are present in the connecting duct and collecting duct.

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

Results: Induction of metabolic alkalosis resulted in a more pronounced alkalosis in B1 deficient mice associated with increased blood bicarbonate, hypokalemia, and hypochloremia. Furthermore, while, pendrin localization was preserved, total pendrin expression was reduced and pendrin activity was altered in B1 deficient mice whereas the relative abundance of pendrin expressing cells was increased. In parallel, H-ATPase activity in non-type A-IC from B1 deficient mice was significantly reduced. Finally, the E and A subunits of H-ATPase did not associate with the basolateral domain of B1 deficient non-type A-ICs leading to the non-association of V; domain while basolateral expression of A4 subunit, part of the V0 domain, was not disrupted.

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

Funding: Government Support - Non-U.S.
Comparing the Effect of Combination of Acetazolamide and Hydrochlorothiazide Followed by Furosemide versus Combination of Hydrochlorothiazide and Furosemide Followed by Furosemide in Treating Refractory Edema Associated with Nephrotic Syndrome: A Randomized, Double-Blind Trial

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Background: The CI/HCO3 exchange and Na/Cl cotransporter (NCC) play important role in distal tubule salt reabsorption. A recent animal study has shown simultaneous inhibition of pendrin and NCC by acetazolamide and hydrochlorothiazide, respectively results in significant diuresis. The aim of this study was to evaluate the efficacy of combination of acetazolamide and hydrochlorothiazide followed by furosemide in treatment of refractory edema associated with nephrotic syndrome. Methods: In this randomized, double-blind trial we enrolled 20 patients with nephrotic syndrome who had refractory edema despite receiving maximum furosemide dose. All patients had GFR-60 ml/min.1.73m². After a 2 week washout period when patients received no diuretics, they were randomly assigned to 2 equal groups. Group 1 received 250-mg oral acetazolamide and 50-mg oral hydrochlorothiazide daily for 1 week. Group 2 received 40mg oral furosemide and 50-mg oral hydrochlorothiazide daily for 1 week. Then patients in both groups received 40-mg oral furosemide daily for 2 weeks. The primary outcome was the amount of change in weight from baseline to the end of the treatment phase. Results: Although weight reduction occurred in both groups, it was significantly higher in group 1 as compared to group 2 at the end of first week (±1.4±0.52 vs. ±0.65±0.4) kg (p<0.001) and of third week of treatment phase (±3.04 vs. ±1.15±0.47 kg, p<0.001). Increase in 24-hour urine volume was also significantly higher in group 1 at the end of treatment phase. Serum Na and K levels were in reference range in all the patients during the treatment phase.

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

Small-Molecule Inhibitors of Pendrin (SLC26a4) Augment the Diuretic Action of Furosemide

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Background: Diminished kidney function as occurs in Chronic Kidney Disease (CKD) causes salt sensitive hypertension. By using 2Na-Magnetic Resonance Imaging (2Na-MRI) technology we recently could detect Na+ storage in humans, which was associated with hypertension. Whether impaired Na+ excretion in CKD results in tissue Na+ accumulation and if kidney transplantation affects tissue Na+ stores is not known.

Methods: We recruited 32 patients with CKD Stage 4 and 5 prior to preemptive living donor transplantation or dialysis treatment and 30 age- and gender-matched control subjects. 2Na-MRI at 3Tesla was used to quantify muscle and skin Na+ of the lower leg, 24 hours after kidney transplantation/dialysis as well as 3 and 6 months after living donor transplantation. Additionally, clinical parameters including blood pressure as well as blood and urine samples were assessed.

Results: Compared to healthy control subjects, CKD-patients showed increased muscle and skin Na+ content (skin 15.8±1.8 vs. 23.1±2.2, p<0.0001; muscle 15.8±1.8 vs. 21.0±3.9, p<0.001). Despite these differences in tissue Na+, serum Na+ concentration did not vary between both groups. Restoration of kidney function by successful renal transplantation in 15 CKD patients was accompanied by reduced blood pressure (mean arterial pressure 104±12 vs. 94±11, p<0.01) and mobilization of tissue Na+ from muscle (21.4±3.1 vs. 18.4±2.9, p<0.01) and skin (24.4±6.2 vs. 19.2±4.5, p<0.01) 6 months post-transplantation.

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

Increased Synthesis of Liver Erythropoietin in Patients with Chronic Kidney Disease

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

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

Results: Despite higher Epo levels (15.75 (11.3 - 24.2) mU/L) compared to healthy controls (8.4 (7.56 - 8.98) mU/L, p<0.01), CKD patients were moderately anemic ([Hb]: 113 ± 11 g/dL). Half of the patients presented higher Epo levels than expected from the calculated values corrected for anemia. Glycosylation was increased in CKD patients (34 ± 12%; measured as percent migrated isoform, PMI,open bars ) when compared to healthy controls (8.6 ± 1%; p<0.01, black bars) and rhEpo samples (1.4:1.4 p<0.01, hatched bars), whereas the pattern did not differ from umbilical cord plasma (50 ± 10 %, p>0.05, lined filled bars) which is known to contain mainly liver derived Epo.

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

Funding: Government Support - Non-U.S.
Associations Among Erythroferrone and Biomarkers of Erythropoiesis and Iron Metabolism, and Treatment of Long-Term Erythropoiesis-Stimulating Agents in Patients on Hemodialysis

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

Methods: Blood samples were obtained from 39 patients before HD sessions on day 0 (baseline) for baseline cross-sectional analysis. Twenty patients who were injected with either CERA (N = 10) or DA (N = 10) at the end of the dialysis week (day 0), who were not iron-deficient (ferritin < 100 ng/mL and transferrin saturation < 20%) and had hemoglobin levels > 9 g/dL were from among the 59 patients. Blood was sampled serially before HD sessions on days 3, 5, 7 from patients on DA and on the same days and day 14 from those on CERA to assess impact of ESA on iron metabolism including ERF.

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

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

Dynamics of ESA Resistance Index in Incident Hemodialfiltration and High-Flux Hemodialysis Patients

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

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

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

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

Serum Ferritin Variations and Mortality in Incident Hemodialysis Patients

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

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

Results: Patients were 63±15 years old, 44% female, 32% African-American, and 60% diabetic. In patients with baseline serum ferritin ≥200 ng/ml, a rise in serum ferritin ≥400 ng/ml/quarter was associated with higher all-cause mortality during the 5-year follow-up compared with no change in serum ferritin (<100 to <100 ng/ml).
Conclusions: Rapid rise in serum ferritin levels >400 ng/ml during the first 6 months after ESA initiation is associated with higher 3-year mortality in patients with elevated baseline serum ferritin. Studies evaluating the conditions influencing these serum ferritin changes and their associations with mortality are needed.

Funding: NIDDK Support

FR-OR015
Decreasing ESA Dosage Can Be a Factor of the Increase in Ferritin Under the Administration of Ferric Citrate with Improving ESA Resistance Index

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

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

Results: The factor of the increase in ferritin was associated with not only the dosage of ferric citrate but also the degree of decrease in ESA dosage (Q1= dosage was decreased in the course of study. Q1.5 to Q3 = dosage was not changed. Q3= dosage was increased.).

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

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

Funding: Pharmaceutical Company Support - TORII PHARMACEUTICAL CO.

FR-OR016
Triferic Maintains Hemoglobin and Iron Balance Long Term: Open-Label Phase III Extension Studies


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

Methods: Patients who completed the Phase 3 randomized controlled treatment studies (RCT) could continue in the open-label (OL) extension studies for up to 18 months of combined participation. In the OL extensions, patients received ESA according to their site protocol and IV iron could be administered for presumed development of iron deficiency. Results: Approximately 70% of patients completed the pivotal RCT and enrolled in the OL extension, providing a total of 412 patient-years of exposure to Triferic. Triferic administered long term (up to 18 months) reliably delivered iron with every treatment. Triferic administered via dialysate maintained Hgb while not increasing iron stores or increasing ESA doses. The safety profile was similar to that observed in the pivotal Phase 3 RCT studies. No anaphylaxis was observed in over 45,000 individual doses administered in this program.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

FR-OR017
Longer Sustained Reduction of Serum Hepcidin Level (Hep) During the Treatment of Anemia with Epoetin Beta Pegol (CERA) As Compared to Epoetin Beta (rEPO) in Predialysis Stage 5 CKD Patients

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

Methods: Twenty-three patients were subjected to the study; age 70±13 [SD] y/o, m/f=15/8, DM=6/29; Baseline Hb=11.7±1 g/dl, serum ferritin (SFe) 257±42 µg/L, transferrin saturation (TSAT) 29±9%. Patients were assigned randomly to 2 groups, being treated with either rEPO (n=13) or CERA (n=10). Their baseline data were as follows; Hb 9.8±0.9 (rEPO) vs. 11.3±1 (CERA) g/dl, serum iron (SFe) 75±22 vs. 97±17 mg/dl, TSAT 28±8 vs. 31±9%, ferritin 129±117 vs. 173±91 ng/ml, albumin 3.7±0.5 vs. 3.6±0.6 g/dl, IL-6 3.2±2.8 vs. 3.8±2.3 ng/ml, hsCRP 1038±2539 vs. 1730±4191 ng/ml, and Hep 34±19 vs. 52±29 ng/ml, respectively. Hep was estimated in the morning, SFe and Hep were measured before and on the 2nd, 4th, 7th, 14th and 28th day. On the first day, circadian variation of SFe and Hep was evaluated.

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

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

FR-OR018
Clinical Pharmacology, Efficacy, and Safety of the Anti-Hepcidin Spiegelmer Lexaptepid Pegol

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

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

Results: Lexaptepid increased iron concentrations and prevented the serum iron decrease after endotoxin challenge in healthy subjects. In patients with myeloma / lymphoma and functional iron deficiency, 2 doses/week of lexaptepid over 1 month increased hemoglobin by 1 g/dl in patients with low reticulocyte Hb and high soluble transferrin receptor. In ESA-hyporesponsive dialysis patients, cross-over comparison with placebo showed increases in serum iron concentrations following lexaptepid administration, consistent with its anti-hepcidin action.
The recruitment of hemodialysis patients for twice weekly treatment with lexaptapid for one year is ongoing in a randomized controlled trial. Lexpaptapid was well tolerated by healthy subjects and patients.

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

**FR-OR019**

**Neutrophil Gelatinase-Associated Lipocalin (NGAL) Is Associated with Iron Status in Anemic Patients with Chronic Kidney Disease**

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

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

**Results:** The CKD patients with TSAT ≤ 30% had lower serum NGAL values than those with TSAT > 30% (274.9 ± 228.3 vs. 994.7 ± 232.2 ng/ml). In univariate analysis, serum NGAL correlated with eGFR (r = -0.367, P < 0.001), CRP (r = 0.253, P < 0.001), TSAT (r = -0.296, P < 0.001), and ferritin (r = 0.259, P < 0.001). In multivariate regression analysis, TSAT (β = 0.370, P < 0.001) was independently associated with serum NGAL in addition to CRP (β = 0.296, P < 0.001) and ferritin (β = 0.259, P < 0.001). In multivariate regression analysis, TSAT (β = 0.370, P < 0.001) was independently associated with serum NGAL in addition to CRP (β = 0.296, P < 0.001) and ferritin (β = 0.259, P < 0.001). However, ferritin lost its association with serum NGAL (β = 0.093, P = 0.132).

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

**FR-OR020**

**Safety and Hemoglobin Effect of Sotatercept, Administered Intravenously and Subcutaneously, for Maintenance of Hemoglobin in Hemodialysis Subjects: Interim Analysis of a Phase 2 Study**

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**Background:** An ongoing randomized study is evaluating intravenous (IV) and subcutaneous (SC) sotatercept, an ActRIIA-IgG1 fusion protein ligand trap, for maintenance of hemoglobin (Hb) in ESA-naïve or switching from a prior erythropoietin-stimulating agent (ESA) in end-stage kidney disease (ESKD) subjects on hemodialysis (HD).

**Methods:** In part 1 of a 2-part phase 2 study, ESA-responsive ESKD/HD subjects with Hb between 10 and 12 g/dl were switched from ESA and randomized to open-label sotatercept (IV: 0.1 and 0.2 mg/kg; SC: 0.13 and 0.26 mg/kg) given every 14 days for up to 8 doses; a third dose group level of IV and SC is enrolling. Pharmacokinetic, safety, tolerability, and Hb effect were assessed. Intraepisode dose escalation was not permitted. Treatment failures (Hb < 9 g/dl) were rescued with ESA or ESA transfusion.

**Results:** Among subjects receiving sotatercept (N=30; IV: 0.1 mg/kg [n=7], 0.2 mg/kg [n=8]; SC: 0.13 mg/kg [n=7], 0.26 mg/kg [n=8]), 1 adverse event (AE) occurred in 100%, 67%, 57%, and 57%, respectively. Serious AEs occurred in only the IV 0.1 mg/kg group (29%). AEs were mostly mild/moderate, unrelated to study drug, relatively similar across groups, and generally consistent with subject medical histories.

- No dose- or route-dependent effects were seen in home blood pressure (BP); no injection site or hypersensitivity reactions were observed. At the end of the 99-day treatment phase, mean change from baseline Hb was -0.5 g/dl (IV 0.1 mg/kg), 0.3 g/dl (IV 0.2 mg/kg), 0.3 g/dl (SC 0.13 mg/kg), and -0.3 g/dl (SC 0.26 mg/kg), 57%, 12%, 43%, and 13%, respectively, for the IV 0.2 mg/kg group, 3 subjects discontinued after the first dose.

- Conclusions: IV and SC sotatercept demonstrated acceptable safety in ESKD/HD, with no dose- or route-dependent effects on home BP. Enrollment in the highest dose group is ongoing.

**Funding:** Pharmaceutical Company Support - Study was sponsored by Celgene Corporation.

**FR-OR021**

**The Role of Activin in the CKD-MBD**

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**Background:** At its inception, the CKD-MBD consists of vascular calcification, an osteodystrophy, decreased alakto and stimulation of skeletal osteocyte FGFC23 secretion. We have shown that inhibition of activin signaling through the activin type 2A receptor (ActRIIA), induced by CKD inhibits vascular calcification. Here, the other components of the CKD-MBD are analyzed.

**Methods:** CKD with hyperphosphatemia and 60% reduction in GFR (CKD-3) was induced at 14 weeks age of in our ldf/+ mouse fed high fat fed model of vascular calcification. Some CKD mice were treated with RAP-011 (a type 2 activin receptor, ActRIIA, ligand trap).

Skeletal histomorphometry and microCT imaging, renal klotho levels, serum chemistries and FGFC23 and PTH levels were measured. Activin loko and ActRIIA levels were measured by elisa, RT-PCR, westerns and IHC.

**Results:** Activin levels in the circulation were 10 fold elevated. The ldf/+ high fat fed model harbor a low turnover osteopontic osteodystrophy that was converted by CKD-3 to a high turnover state characterized by PTH levels of 430pg/ml (7 fold elevated), hyperphosphatemia, increased osteoblast numbers,and surfaces, increased osteoclast numbers and eroded surfaces, increased bone formation rates (BFR) but a significant decrease in BFR/osteoblast. CKD-3 decreased renal tubular klotho levels and produced marked (10 fold) elevations in FGFC23 levels. Inhibiting activin by an ActRIIA ligand trap surprisingly reduced osteoblast number and surfaces, decreased BFR but increased FGFC23 levels to normal in RAP-011 treated CKD mice. RAP-011 treatment did not affect hyperphosphatemia, PTH levels or FGFC23 levels. Inhibiting activin signaling increased renal tubular klotho levels.

**Conclusions:** Activin is a critical factor in the pathogenesis of the CKD-MBD causing alakto deficiency, vascular and skeletal disease, and surprisingly playing a key role in the osteoblast dysfunction of CKD heretofore attributed solely to PTH and FGFC23.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Celgene

**FR-OR022**

**Increase in Trabecular Bone Volume by Inhibition of GSK-3β in Uremic Mice**

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**Background:** Bone fracture increases the risk of hospitalization and mortality in patients with chronic kidney disease (CKD). Bone volume is closely related to the risk of fracture in CKD. Studies have shown that inhibition of glycogen synthase kinase (GSK)-3β, a critical component of Wnt/β-catenin signaling pathway, increases bone volume through inhibition of β-catenin. However, it remains unknown whether inhibition of GSK-3β increases bone volume in uremia.

**Methods:** The present in vivo study was performed to determine whether inhibition of GSK-3β could increase bone volume in ademine-induced CKD mice. Wild type mice were divided into three groups. One group was fed a control diet (CNT) and the other two groups were fed a diet containing 0.2% ademine with or without lithium chloride (LiCl), a GSK-3 inhibitor; CKD and CNT-LiCl group. GSK-3β heterozygous knockout mice were also fed a diet containing 0.2% ademine (CKD-GSK-3β-/-). Bone and blood samples were collected after 6 weeks and trabecular (Tb) and cortical (Ct) bone were analyzed by micro-computed tomography.

**Results:** CKD mice developed azotemia, hyperphosphatemia, and secondary hyperparathyroidism, followed by a decrease in Ct bone thickness and no change in Tb bone volume after 6 weeks. Treatment with LiCl increased Tb bone volume, accompanied by polyuria and polydipsia. Tb bone volume increased in CKD-GSK-3β-/- mice compared with CNT and CKD mice. There were no significant differences in kidney function, hyperphosphatemia, hyperparathyroidism, and Ct bone thickness among three CKD groups.

**Conclusions:** Inhibition of GSK-3β increased Tb bone volume in ademine-induced uremic mice.
FR-OR023
Sclerostin Knock-Out Protects from Uremia-Induced Cortical Bone Loss in a Murine Model of Chronic Renal Failure
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Background: Renal osteodystrophy (ROD) affects the majority of patients with advanced chronic kidney disease (CKD) and is characterized by progressive bone loss. This study investigates the role of sclerostin-knockout mouse model in a murine model of CKD.

Methods: Severe CKD was surgically induced in sclerostin-knock-out-mice (SOST-KO-CKD) and wild-type (WT-CKD). Mice with normal kidney function serve as controls (SOST-KO-CTRL, WT-CTRL). After 3 months of CKD, blood was drawn and vertebrae and tibia were collected for histomorphometric and pCT analyses.

Results: Cortical thickness (Ct.Th) of the tibia was significantly higher in sosto-k-o mice compared to wt-ckd mice (p<0.001). WT-CKD mice had lower Ct.Th compared to WT-CTRL (p<0.05), whereas no significant differences in Ct.Th were found between SOST-KO-CKD and SOST-KO-CTRL groups. Compared to WT-CKD mice, SOST-KO-CKD mice had higher trabecular number (p<0.001) and trabecular thickness (p<0.001) and lower trabecular separation (p<0.001). Mineral density of trabecular bone was higher (p<0.001) in SOST-KO-CKD mice compared to WT-CKD animals. In the lumbar vertebrae, bone volume/tissue volume was higher in SOST-KO-CKD mice compared to the WT-CKD group (p<0.001). Osteoid maturation time and mineralization lag time were not influenced by SOST-KO.

Conclusions: Sclerostin knock-out leads to increased bone mass and improved microarchitecture but does not alter osteoid mineralization in a murine model of CKD. Inhibition of sclerostin warrants further studies as a promising approach to prevent bone loss in CKD.

Funding: Clinical Research Support

FR-OR025
Chronic Kidney Disease Is Associated with Progressive Increase in Arterial Stiffness and Bone Loss Over 1 Year
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Background: To assess changes in arterial stiffness, bone structure and markers in stage 4-5 chronic kidney disease (CKD) compared with healthy controls.

Methods: In this prospective, single-centre, observational study, bone indices using peripheral quantitative computerized tomography (pQCT) were obtained. Sclerostin (scl), CTX, CRP, cBMD, trabecular bone mineral density (tBMD), strength-strain index (SSI), bone mineral content (BMC), cortical area, cross-sectional area (cCSA), bone and vascular parameters (PWV, FMD, SMI) were all assessed. Baseline measurements were compared with 12 months.

Results: Forty CKD (mean estimated glomerular filtration rate (eGFR):19.5 ± 6.7 mL/ min/1.73m2) and 42 controls (eGFR:88.6 ± 12.9 mL/ min/1.73m2) completed follow-up. At baseline, CKD subjects had a significant decline in cBMD (-0.87%,p<0.01), tBMD (-1.70%,p<0.03), BMC (-5.0%,p<0.01), SMI (-3.79%,p<0.02) and an increase in PWV by 1.3/s/(16.7%,p<0.001). Serum phosphate, calcium, parathyroid hormone and skil did not significantly change over 12m. FGF23 levels increased [240[141(919.28)][390.6(160.979.7)],p<0.001 and was independently associated with changes in cBMD and PWV. Bone and vascular parameters remained unchanged in controls.

Conclusions: CKD was associated with bone structure and greater increases in arterial stiffness and FGF23 levels over 12 months.

Funding: Pharmaceutical Company Support - Shire Australia, Private Foundation Support, Clinical Research Support

FR-OR026
Vascular Calcification Is Mediated by ERK-Dependent Upregulation of Pit1 via Rac1/NADPH/MR Activity
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Background: Vascular calcification (VC) is a mayor mortality risk factor in patients with chronic kidney disease. During VC, vascular smooth muscle cells (VSMC) of the tunica media transdifferentiate into osteoblast-like cells. High extracellular phosphate (HP) promotes VC through the induction of the sodium-dependent phosphate cotransporter (Pit1) activity, increased NADPH oxidase activity (Nox1) and the expression of osteochondrogenic factors (OCF). Recent studies indicate that antagonists of the mineralocorticoid receptor (MR) ameliorate/prevent experimental VC and arteriosclerosis in mice. The small GTPase Rac1 modulates MR and Nox activity in VSMC. However, the role of Rac1 on vascular calcification remains unknown. We hypothesize that in VC, HP activates MR via Rac1 leading to induction of Nox and ERK1/2 activity, promoting VC.

Methods: Effects of HP on VSMC were evaluated in rat aortic VSMC (A7r5). Inhibitors of Rac1 (NSC23766), MR (spironolactone) and Nox1 (apocynin) were used to determine signaling pathways involved in the activation of ERK caused by HP. Nox activity was determined using the Hyper H2O2. Biosensor. At 75% confluence, cells were stimulated with HP, HP+NCS23766 or HP+apocynin to determine the role of Rac1 and MR on HP-induced H2O2 production. n=4-5 per group.

Results: HP increased Pit1 mRNA, OCF mRNA (cbfa1 and Sox9) and Nox1 mRNA (p<0.05 vs. normal phosphate (NP)) and caused mineralization. Aldosterone (100nM) potentiated the effect of HP on mineralization and gene expression (p<0.05). Incubation in the presence of spironolactone (10uM) completely prevented all the effects of aldosterone. Inhibition of Rac1 and NADPH oxidase activity prevented HP-induced H2O2 production (2.6% NP; 25% HP; 1.8% NP+HC at 20 min of stimulus; p<0.05 vs. HP). The presence of Rac1 or 1 μM of the MR antagonist spironolactone in culture medium suppressed HP-induced activation of ERK (2.7 times at 10 min; p<0.05 vs. 0 min).

Conclusions: We conclude that high phosphate-dependent calcification is mediated by ERK-dependent upregulation of Pit1 via Rac1/NADPH/MR activity.

Funding: FONDECYT4113050, BMH POH-016-F; Government Support - Non-U.S.

FR-OR027
Inhibition of Wnt Signaling and Matrix Metalloproteinases Attenuates Calcium and Phosphate Induced Calcium and Phosphate Induced Calcifications in Vascular Smooth Muscle Cells
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Background: The trans-differentiation of vascular smooth muscle cells (VSMC) into an osteoblast-like phenotype and matrix remodeling are essential in the pathogenesis of vascular calcifications in patients with chronic kidney disease (CKD). We have previously shown that the matrix metalloproteinases (MMP)-2 and -9 facilitate VSMC calcifications and, vice versa, their inhibition attenuates this process [1]. We studied the effects of calcifying conditions, recombinant MMPs and MMP-inhibitors on signal transduction in VSMC.

Methods: Mimicking the disturbed mineral balance during CKD, the trans-differentiation/calcification of murine VSMC was induced by a calcification medium (CM) containing elevated concentrations of calcium and phosphorus (Ca/P). MMP activities were modulated by recombinant MMP-2 or -9 and selective MMP inhibitors. Wnt activation was induced by a recombinant Wnt agonist and assessed in reporter plasmid (pGL4.49[Luc2P/TCP1)]2) or competitive EMSAs. MMP-2 and 9 CM-induced VSMC: MMP-2/9 secretion and mRNA expressions were determined by sandwich assays and qPCR, respectively.

Results: CM-induced calcifications in VSMC were accompanied by enhanced Wnt-signaling. Even under normal culture conditions, Wnt activation with a Wnt agonist induced VSMC calcifications associated with enhanced mRNA expression and secretion of MMP-2 and -9. These Wnt-conditioned VSMC was associated with significant losses of N-cadherin. Treatment of VSMC with recombinant MMP-2/9 induced a time-delayed Wnt-activation after 72h.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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FR-OR028
Calciphylaxis Is Characterized by Vitamin K Deficiency and Impaired Matrix Gla Protein Carboxylation Seager U, Ngweke
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Background: Calciphylaxis, a dermal arteriolar calcification disorder linked with high mortality, has unclear pathogenesis. We investigated vitamin K metabolism and its effects on vitamin K dependent carboxylation in calciphylaxis patients, Matrix Gla Protein (MGP) in, calciphylaxis patients.

Methods: We prospectively recruited 20 ESRD patients with biopsy-confirmed calciphylaxis and obtained plasma samples and clinical information at the time of calciphylaxis diagnosis. Plasma samples and clinical information were also obtained from 20 controls (ESRD patients without calciphylaxis) matched to cases by age, sex, race, and calciphylaxis diagnosis. Plasma levels of Proteins Induced by Vitamin K Absence (PIVKA-II) a sensitive measure of vitamin K deficiency, carboxylated MGP (c-MGP), and uncarboxylated MGP (uc-MGP) were measured using ELISA assays. MGP-carboxylation status was derived by calculating c-MGP/uc-MGP ratio (MGP ratio). Prevalence of vitamin K deficiency (defined by PIVKA-II level ≥2 ng/mL) was compared between cases and controls using Chi-square analysis. MGP ratios were compared between cases and controls using a Mann Whitney U test and multivariable linear regression.

Results: Prevalence of vitamin K deficiency was higher in cases compared to controls (90% vs. 50%, P=0.006) including in patients not on warfarin; vitamin K antagonist therapy (83% vs. 35%, P=0.014). Median MGP ratio was lower in cases compared to controls (1.29 vs. 2.42, p=0.001) including in patients not on warfarin (1.64 vs. 2.98, p<0.001).

Conclusions: High prevalence of vitamin K deficiency and its potential impact on MGP carboxylation in calciphylaxis call for a therapeutic trial of vitamin K supplementation in calciphylaxis.

Funding: Private Foundation Support

FR-OR029
Dialysis with Medium Cut-Off (MCO) Filters Reduces In Vitro Calcification of Human VSMC: Lessons from a Randomized Clinical Trial Daniel Ziecker,1 Markus Stor,2 Matthias Girndt,3 Roman Friedler,2 Kevin Willy,1 Ralf Schindler,1 1Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin; 2Dept of Internal Medicine II, Martin-Luther-University; 3Research & Development, Gambro Dialysatoren GmbH, Hechingen.

Background: Vascular calcification is increased in CKD patients, partly caused by insufficient removal of inflammatory proteins with conventional dialysis filters. We assessed whether dialysis with MCO filters, which allow elimination of middle-sized inflammatory proteins with only limited permeability for albumine, influences vascular calcification in vitro.

Methods: 50 patients were dialysed in a randomized controlled clinical “first-in-man” trial with a MCO and a Highfluxfilter for four weeks in a randomized order. To test for longterm effects the patients were continued on their filter for eight more weeks. After each phase serum samples were drawn. In human VSMC calcification was induced and serum samples were added. After 7-12 days in vitro calcification was assessed via Alizarin red and Alkaline phosphatase assays and normalized to WST-8.

Results: In multivariable analyses adjusted for clinical characteristics, vitamin K deficiency was associated with a 48% reduced MGP ratio (P=0.004).

Conclusions: High prevalence of vitamin K deficiency and its potential impact on MGP carboxylation in calciphylaxis call for a therapeutic trial of vitamin K supplementation in calciphylaxis.

Funding: Private Foundation Support

FR-OR030

Background: SNF472, an intravenous (i.v.) formulation of myo-inositol hexaphosphate, is being developed for treating calciphylaxis and for preventing vascular calcification progression in patients with end-stage renal disease on hemodialysis. It selectively inhibits the final common pathway in the etiology of vascular calcification, the formation and growth of hydroxyapatite (HAP) crystals. Non-clinical investigations showed adequate evidence of efficacy and safety to warrant a first study in humans.

Methods: A double-blind, randomized, phase 1 clinical trial was performed in two cohorts of 8 male healthy volunteers (HV) and one cohort of 8 hemodialysis (HD) patients. Single ascending doses of 0.5, 5, 9 and 12.5 mg/kg of SNF472 were administered through 4-hour i.v. infusion to HV into a forearm vein. HD patients received a single i.v. dose of 9 mg/kg through the dialysis tubing before the filter during the 4 hours of dialysis. Safety parameters, including extensive ECG monitoring, were recorded. Blood samples were obtained up to 24h for safety and pharmacokinetics. A PD (pharmacodynamics) assay was used to assess the potential of ex vivo formation of HAP crystals.

Results: SNF472 was well tolerated and no systemic adverse events were observed. Several HV reported irritation at the infusion site. This effect was concentration-dependent (not dose-dependent). In HD patients SNF 472 is diluted 500-fold in the dialysis system before reaching the patient and no local irritation occurred. No effects were seen in safety parameters, including ECG. Ionized calcium was slightly below the lower limit of normal in HV at 12.5 mg/kg. The 5, 9 and 12.5 mg/kg doses produced measurable plasma concentrations above the anticipated EC50 (5µM) and showed a 70-80% reduction in the ex vivo HAP crystal formation PD assay. HD patients had similar SNF472 plasma concentrations (suggesting low SNF472 clearance through the dialysis membrane) and PD effects to HV. Plasma ionized calcium levels were stable.

Conclusions: The data available suggests a favourable benefit/risk ratio of SNF472 and supports further studies in the target population. Supported by RETOS COLABORACION RTC-2014-2460-1.

Methods: We used Medicare claims to examine trends in % of patient-months with PD during 2007-2014, for patients incident during the current year, prior year and 2 years prior. The study period includes 3 pre-PPS years (2007-09), a transition year when the PPS was anticipated but not yet implemented (2010) and the first 4 years of the PPS (2011-14).

Results: PD continued to increase as a % of patient-months through the transition and post-bundle period. Initial increases occurred in the current and prior year cohorts with a trailing increase in the 2 year cohort, reaching 10.7%, 11.9% and 7.4%, respectively by 2014 (vs. 6.0%, 7.1% and 6.1% in 2007). Growth stalled in the current year cohort during 2014, coincident with PD supply shortages.

Conclusions: PD use continued to increase under the PPS and is now reflected in increases among patients incident 2 years prior, suggesting that the initial increases among newer patients are translating into longer-term modality tenure. PD fluid shortages are coincident with a staffing of growth among patients incident in 2014. Monitoring modality trends among newer patients are translating into longer-term modality tenure. PD fluid shortages are a primary cause of ESKD.

Funding: Other U.S. Government Support

FR-OR032
The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS): Preliminary Findings from the First Year
Jeffrey Perl,1 Junhui Zhao,2 Brian Bieber,3 Yun Li,4 Simon J. Davies,5 David W. Johnson,6 James A. Sloan,6 Hideki Kawanishi,7 Bruce M. Robinson,2 Francesca Tentori,2,8 "St. Michael’s Hospital, Univ of Toronto, Toronto, ON, Canada; 2Aor Research Collaborative for Health, Ann Arbor, MI; 3Univ of Michigan, Ann Arbor, MI; 4Univ Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 5Princess Alexandra Hospital, Brisbane, Queensland, Australia; 6Baxter Healthcare Corporation, Deerfield, IL; 7Tsuchiya General Hospital, Hiroshima, Japan; 8Vanderbilt Univ, Nashville, TN.

Background: The PDOPPS is a prospective cohort study underway in the United States (US), Canada, Japan, and the United Kingdom, in collaboration with the International Society for Peritoneal Dialysis. PDOPPS aims to understand the impact of clinical practices on patient outcomes, including patient and technique survival. Here, we present results from the first year of data collection.

Methods: 170 randomly selected facilities and 6000 patients will participate in the initial study. A stratified random selection of facilities has yielded national samples of facilities and patients, with 20-45 patients per site. Clinical, demographic, biochemical, and treatment data are collected at 4-month intervals. Follow up is 3-years or until death, kidney transplantation, or 120-days after a change in permanent dialysis modality. Early descriptive data are presented for the three countries.

Results: To date, 99 facilities and 2211 patients have been recruited. Selected patient and treatment characteristics vary widely across countries (Table 1).

Table 1: Selected patient and treatment characteristics in the three initial PDOPPS countries

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Canada</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.2</td>
<td>61.6</td>
<td>65.0</td>
</tr>
<tr>
<td>Female</td>
<td>49%</td>
<td>39%</td>
<td>36%</td>
</tr>
<tr>
<td>Time on PD, years</td>
<td>1.9</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>29%</td>
<td>35%</td>
<td>31%</td>
</tr>
<tr>
<td>Glomerulonephritis*</td>
<td>14%</td>
<td>15%</td>
<td>32%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>27%</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td># of PD patients/facility</td>
<td>39</td>
<td>75</td>
<td>33</td>
</tr>
<tr>
<td># of overnight exchanges</td>
<td>15</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>&gt; 1 daytime exchange</td>
<td>36%</td>
<td>49%</td>
<td>20%</td>
</tr>
<tr>
<td>APD</td>
<td>73%</td>
<td>41%</td>
<td>26%</td>
</tr>
<tr>
<td>CAPD</td>
<td>27%</td>
<td>59%</td>
<td>74%</td>
</tr>
<tr>
<td>Residual kidney function</td>
<td>3.9</td>
<td>3.5</td>
<td>4.9</td>
</tr>
<tr>
<td>residual peritoneal membrane function, and dialysis adequacy</td>
<td>3.9</td>
<td>3.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Urine volume, L/24hr</td>
<td>0.71</td>
<td>0.92</td>
<td>0.77</td>
</tr>
<tr>
<td>D/P creatinine</td>
<td>0.67</td>
<td>0.75</td>
<td>0.69</td>
</tr>
<tr>
<td>Total Kt/V</td>
<td>2.32</td>
<td>2.11(5.3)</td>
<td>1.82</td>
</tr>
</tbody>
</table>

As of May 2015; results are shown as mean ±SD
1% facility N=56, patient N=607; Canada facility N=20, patient N=488; Japan facility N=18, patient N=254
Data collection from Australia and the United Kingdom is just underway.

Background: Hyponatremia is common in hemodialysis patients and has been linked with higher mortality risk. In peritoneal dialysis (PD) patients, few studies have examined the association of hyponatremia with mortality which have shown mixed findings. We sought to examine predictors of hyponatremia in a national PD cohort, and hypothesized that lower serum sodium (Na) is associated with higher death risk.

Methods: We examined a 5-year (1/2007-5/2011) cohort of 4687 incident PD patients from a large US dialysis organization with one or more serum Na measures within the 1st 91-days of dialysis. We examined predictors of baseline hyponatremia (Na<140mEq/L) using case-mix/laboratory adjusted logistic regression models. We then examined the association of Na with all-cause mortality. Baseline and time-dependent Na as a proxy of long- and short-term exposure—mortality associations, respectively, were estimated using Cox models with 3 adjustment levels: Unadjusted, case-mix, and case-mix+laboratory adjusted.

Results: Having diabetes, lower residual kidney function, albumin, PTH, and higher glucose, calcium, and ferritin were associated with higher risk of hyponatremia. Baseline Na levels <140mEq/L were associated with higher mortality across all 3 models (ref: Na 140–142mEq/L). In time-dependent analyses, Na levels <140mEq/L were also associated with incrementally higher death risk in case-mix models. After further adjustment for laboratory covariates, Na—mortality associations persisted for levels <134mEq/L.

FR-OR033
Risk Factors and Sequelae of Hyponatremia in a National Peritoneal Dialysis Cohort
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Background: Hyponatremia is common in hemodialysis patients and has been linked with higher mortality risk. In peritoneal dialysis (PD) patients, few studies have examined the association of hyponatremia with mortality which have shown mixed findings. We sought to examine predictors of hyponatremia in a national PD cohort, and hypothesized that lower serum sodium (Na) is associated with higher death risk.
FR-OR034
Center-Specific Factors Associated with Peritonitis Risk - A Multi-Center Registry Analysis
Ann-Claire Nadeau-Fredette,1,2 David W. Johnson,1,2 Carmel M. Hawley,1,2 Elaine M. Pascoe,1 Yeoung Jee Cho,1 Philip A. Clayton,2 Sunil V. Badve,1 Kamal Sud,1 Monique Renee Borlace,1,2 Neil Boudville,2 Stephen P. McDonald.1 1Princess Alexandra Hospital, Australia; 2Australia and New Zealand Dialysis and Transplant Registry; Maisonneuve-Rosemont Hospital, Canada.

Background: Previous studies have reported significant variation in peritonitis rates across dialysis centers. Limited evidence is available to explain this variability. This study aimed to assess the center-level predictors of peritonitis and their relationship with peritonitis rate variation.

Methods: This registry study included all incident peritoneal dialysis (PD) patients treated in Australia between October 2003 and December 2013. The primary outcome was peritonitis rate, evaluated in a mixed effects negative binomial regression model assuming a negative binomial distribution with a natural log link function and a binomial distribution with a logit link function, respectively. Models included random effects to accommodate PD center-specific variability.

Results: Data from 24 SCOPE sites that provided peritonitis rates for the 12 mos prior to Collaborative launch were included in the analysis. In the first 36 mos, 751 catheter insertions in 644 pts, 644 training sessions and 7,977 follow up encounters were captured. Compliance with the follow up bundle increased from 11% to 88% (p<0.001) over the 36 mos, but neither insertion (22% to 36%, p=0.064) nor training compliance (75% to 71%, p=0.105) increased significantly. The peritonitis rate decreased significantly (p=0.026) from an average monthly rate of 0.052 (95% CI 0.036, 0.076) pre-launch to 0.035 (95% CI 0.026, 0.047) at 36 mos, figure 1.

Conclusions: Using quality improvement methodology pediatric dialysis units participating in SCOPE significantly increased implementation of standardized follow up care practices and significantly reduced peritonitis rates. Efforts to increase compliance with insertion and training bundles and further reduce infection rates are ongoing.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.

40A
FR-OR037
In-Hospital Mortality Outcome of Cirrhotic Patients with End Stage Renal Disease on Hemodialysis versus Peritoneal Dialysis
Mark Abi Nader,1 Fernando Rodrigo Aguilar,1 Michael S. Lipkowitz,1 Parasaram Krishnamoorthy,2 Ping Li,1 Serban A. Dragoi,1 Alex Montero,1 Wen Shen,1 Chiangani Nilubol,1 Judith Gordon.1 1Nephrology and Hypertension, Georgetown Univ Hospital, Washington, DC; 2Internal Medicine, Mount Sinai School of Medicine.

Background: Renal disease is a common complication in cirrhotic patients related to electrolyte and acid-base alterations, inadequate response to diuretic drugs, and hemodynamic instability, often leading to end stage renal disease (ESRD) with need for dialysis. Little is known about the preferred dialysis modality in these patients. We aimed to compare the mortality outcomes between cirrhotic patients on either Hemodialysis (HD) or peritoneal dialysis (PD).

Methods: Nationwide Inpatient Sample database between 2005 and 2012 was queried. Patients with ESRD (ICD9 585.5) and liver cirrhosis (ICD9 571.2, 571.5, 571.6, 572.3; 572.4) were included in the study. Patients having hepatocellular carcinoma were excluded (ICD9 155.0). Both groups were matched, undergoing propensity matching by score, for chronic conditions including anemia, diabetes mellitus, hypertension, hepatic encephalopathy, esophageal variceal bleeding, gastrointestinal bleeding (GIB), paracentesis, hepatitis C as well as sex, race, Charlson Comorbidity Index and age. Logistic regression was used for multivariable analysis.

Results: 28,622 cirrhotic patients with incident ESRD were identified. 1.7% of them were on PD. After propensity score matching and multivariable regression analysis, cirrhosis on HD had higher mortality compared to PD patients [4.79% vs 2.70% P = 0.024]. Age >65 and female gender were significant predictors of mortality in both HD and PD groups. Anemia was associated with less mortality rate.

Conclusions: Cirrhotic patients admitted to the hospital for dialysis have higher mortality when started on HD compared to PD.

FR-OR038
AQP1 in Peritoneal Dialysate as Predictive Biomarker of Integrity of the Peritoneal Barrier and Ultrafiltration Efficiency
Simone Corcuelo,1 Maria Celeste Nicoletti,2 Roberto Corciulo,2 Roberto Russo,1 Giuseppe Grandaliano,1 Maria Svelto,1 Giuseppe Procino,3 Loreto Gesualdo.1 1Dept of Emergency and Organ Transplantation, Univ of Foggia, Foggia, Italy; 2Dept of Biosciences, Biotechnologies and Biopharmaceuticals, Univ of Bari, Bari, Italy; 3Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, Italy.

Background: The water channel Aquaporin 1 (AQP1) plays a pivotal role in the mechanism of free water ultrafiltration during peritoneal dialysis (PD). Whether or not AQP1 exclusively expressed in peritoneal capillaries or also in the mesothelial cells (MC) is still debated. It has been hypothesized that decreased expression or function of AQP1 may be responsible for some cases of ultrafiltration failure (UFF). Plasma membrane proteins are released in biological fluids through the exosome pathway to an extent proportional to their abundance at the plasma membrane.

Methods: In this work we investigated the localization of AQP1 in human peritoneum and its presence in exosomes isolated from PD effluent.

Results: Proteomic analysis of peritoneal-derived exosomes showed a significant expression of AQP1. Interestingly, the same samples were devoid of the endothelial marker CD31 but were positive for the mesothelial marker mesothelin, thus suggesting a mesothelial, rather than endothelial origin for these vesicles.

Conclusions: Despite being older and sicker, patients with diuretic Rx had lower mortality. While more striking in incident patients, association was also seen in non-incident patients. If diuretic Rx is a marker of RRF or independently associated with better outcomes remains to be elucidated.

FR-OR039
Vascular Endothelial Cell Damage Is an Important Factor in the Development of Encapsulating Peritoneal Sclerosis
Mitsuziho Tawada,1 Yasuhiko Ito,1 Chieko Hamada,2 Kazuho Honda,1 Massashi Mizuno,1 Yasuhiro Suzuki,1 Fumiko Sakata,1 Shoichi Maruyama,2 Yoshifumi Takei,3 Seiichi Matsuo.1 1Nephrology, Nagoya Univ, Nagoya, Japan; 2Nephrology, Juntendo Univ, Tokyo, Japan; 3Pathology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Encapsulating peritoneal sclerosis (EPS) is a rare, but serious and life-threatening complication of peritoneal dialysis (PD); however, the precise pathogenesis remains unclear and predictors have not yet been established. The present study aimed to determine predictors of EPS in peritoneal membrane tissues obtained at catheter removal.

Methods: Eighty-three biopsy samples (10 EPS, 73 non-EPS) were assessed by pathological and immunopathological techniques to identify predictors of EPS. Tissue samples obtained at the time of catheter removal for reasons of peritonitis and a peritonitis episode within the past one month were not included. Furthermore, based on these analyses, the effects of PD solution on human umbilical vein endothelial cells (HUVEC) were studied.

Results: Univariate analysis of the pathological findings associated a thickened peritoneal membrane (P < 0.045), new membrane formation scores (P = 0.006), decreased ratio of lumen diameter to vessel diameter (L/V ratio, P < 0.001), CD31-negative vessels (P = 0.021) and fibrin deposition (P < 0.001) with the development of EPS. Stepwise Firth’s multivariate logistic regression analysis identified glucose exposure scores (odds ratio 2.03, P = 0.011) among clinical factors, the L/V ratio (AUC, 0.899; OR, 0.50; P = 0.002) and fibrin deposition (OR, 8.50; P = 0.023) among the pathological factors as independent predictors of EPS. Multivariate logistic regression analysis of the 10 patients with EPS and 20 controls matched for PD treatment period, diabetes and PD solution (acidic or neutral pH) identified decreased L/V ratio as an independent predictor. In cultured HUVEC, acidic condition and high glucose concentration of PD solution induced necrosis and apoptosis, respectively.

Conclusions: Vascular endothelial cells that become damaged mainly by bioincompatible PD solution might induce vascular leakage leading to EPS, and could serve as a predictor of EPS.

Funding: Government Support - Non-U.S.

FR-OR040
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Background: Peritonitis is one of the major complications of peritoneal dialysis (PD) and contributes to technique failure and mortality in PD patients. The aim of this study was to evaluate the effects of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) on pathogen identification and clinical outcomes in PD-related peritonitis.

Methods: Ninety-eight causative microorganisms of monomicrobial PD-related peritonitis were identified using conventional standard methods, and 57 were identified using MALDI-TOF MS method. The time to pathogen identification using different identification methods was evaluated and compared. The outcome characteristics were time to dialysate effluent white blood cell <100/mm³, length of hospital stay, catheter removal/transfer to hemodialysis, and in-hospital mortality.

Results: MALDI-TOF MS allowed the direct pathogen identification from positive blood cultures accounting for 94.9% of all cases. MALDI-TOF MS method could identify unique microorganisms in 63.3% of cases and increased the identification rate by 25%. The time to pathogen identification using MALDI-TOF MS was significantly lower (P < 0.001) compared to conventional methods. The incidence of severe peritonitis was significantly higher (P = 0.004) in patients with MALDI-TOF MS-negative cultures.
the causative microorganisms of PD-related peritonitis earlier than the conventional standard method. The average time saved was 64 hours for all pathogens, 52 hours for Gram-positive bacteria, 65 hours for Gram-negative bacteria, 37 hours for Staphylococcus species, 68 hours for Streptococcus species, and 67 hours for E. coli and Klebsiella species. MALDI-TOF MS method group had a shorter length of hospital stay than the conventional standard group (5.2 ± 4.8 days versus 8.2 ± 4.5 days, P = 0.001).

Conclusions: We demonstrate the clinical effects of pathogen identification using MALDI-TOF MS in PD-related peritonitis. Integration of MALDI-TOF MS with blood culture system can promote early pathogen identification and timely pathogen-directed antibiotic therapy, and may confer outcome benefit. We propose that it is time to speed up the pathogen identification in PD-related peritonitis.

Funding: Government Support - Non-U.S.

FR-OR041
Higher Systolic Blood Pressure Variability Is Associated with Increased Mortality, Coronary Heart Disease, Stroke, and End Stage Renal Disease
Margit K. Mikkelson,1 Miklos Zsolt Molnar,2 Jun Ling Lu,3 Lenar T. Yessayan,4 Elvira Gosmanova,5 Kamary Kalantar-Zadeh,6 Csaba P. Kovesty,7,8,12 YFA Medical Center, Memphis, TN; 7Univ of Tennessee Health Science Center, Memphis, TN; 3Henry Ford Hospital, Detroit, MI; 9Univ of California, Irvine, CA.

Background: Blood pressure does not remain constant, but instead fluctuates dynamically. The implications of this variability in blood pressure are not yet fully understood.

Methods: From among 3,285,684 US veterans with normal eGFR during 2005-2006, we identified 2,685,157 patients who had more than 7 outpatient blood pressure measurements. Systolic blood pressure variability (SBPV) was measured using the standard deviation (SD) of all SBP values (normally distributed) in one individual. Associations of SD quartiles (<10.28, 10.28-12.68, 12.69-15.60, ≥15.61 mmHg) with all-cause mortality, coronary heart disease (CHD), stroke, and end stage renal disease (ESRD) was examined using Cox models adjusted for age, gender, race, and baseline eGFR, comorbidities, BMI, SBP, DBP, and antihypertensive medication use.

Results: Higher SBPV was associated with significantly higher risk of all-cause mortality, CHD, stroke, and ESRD. In fully adjusted models SD quartiles 2 through 4 (compared to the first quartile) were associated with mortality hazard ratios of 1.10, 1.32, and 1.79; CHD hazard ratios (95%CI) of 2.12, 3.60, and 6.01; stroke hazard ratios of 2.05, 3.64, and 6.72; and ESRD hazard ratios of 0.88, 1.32, and 4.48.

Conclusions: Higher SBPV is associated with increased risk for mortality, CHD, and stroke independent of confounders. The highest SD quartile was associated with increased risk for ESRD. The effect of interventions that lower SBPV on mortality will need to be examined in clinical trials.

Funding: NIDDK Support, Private Foundation Support

FR-OR042
Left Ventricular Mass in Early Autosomal Dominant Polycystic Kidney Disease
Vincente E. Torres,1 Ronald D. Pzorzence,2 Kaleab Z. Abebe,2 Kyongtae Ty Bae,3 Peter G. Czarnicki,4 Robert W. Schrier,4 Theodore I. Steinman,5 Susan Spillane,6 Charity G. Moore,7 Tyfts; ’U of Pittsburgh; ’Brigham and Women’s; ’U of Colorado; ’BIDMC, ’Mayo Clinic, for the HALT PKD Investigators.

Background: Autosomal dominant PKD (ADPKD) associates with hypertension and left ventricular hypertrophy (LVH). HALT PKD study A was designed to assess the effect of intensive BP control and dual renin angiotensin blockade on progression of total kidney volume (TKV) and left ventricular mass (LVM).

Methods: 543 subjects with eGFR ≥60 ml/min aged 15-50 were randomized to losinopril (L) and placebo (P) with two levels of BP control: standard (SBP) (120-130/70-80 mmHg) vs low (LBP) (95-110/65-75 mm Hg). Cardiac magnetic resonance measurement of LVM was done at baseline, 24, 48, and 60 months. LVM adjusted for body surface area was expressed as LVM index (LVMi, g/m²).

Results: The prevalence of LVH at baseline was <1%. LBP reduced LVMi compared to SBP (p<0.001) but there was no effect of dual blockade (p=NS). There was no impact of baseline parameters (eGFR, age, systolic BP, TKV, serum K, urine Na or K, albuminuria, urine aldosterone, sex) on the BP effect on LVMi. Higher baseline TKV and systolic BP had significant associations with more rapid LVMi decline (p<0.001); a trend of lower baseline eGFR also associated with LVMi decline (p=0.07); females had significantly reduced LVMi decline vs males (p=0.001) irrespective of BP group.

Conclusions: LVMi decreased significantly after intensive vs standard BP control. Larger TKV, higher systolic BP, male sex, and possibly decreased eGFR were associated with a greater reduction in LVMi, irrespective of the level of BP control. Patient factors associated with a worse kidney outcome predicted improvement in LVMi after a long period of carefully controlled BP. BP reduction in ADPKD shows cardiac benefit and should be a focus of treatment.

Funding: NIDDK Support, Private Foundation Support

FR-OR043
Asymmetric and Symmetric Dimethylarginine and Sympathetic Nervous System Traffic After Renal Denervation in Patients with Resistant Hypertension: A Longitudinal Study
Carmine Zoccali,1 Gino Seravalle,2 Bosca Quarti Trevano,3 Domenico Spaziani,1 Filippo Scalise,1 Carla Augurdo,1 Patrizia Pizzini,1 Giovanni Tripepi,1 Grazia D’arrigo,1 Giuseppe Mancia,2 Guido Grassi,3 Francesca Mallamaci.1 1Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, CNR-IFC, Reggio Calabria, Italy; 2Istituto Autologico Italiano, Milano, Italy; 3Clinica Medica, Dipartimento di Scienze della salute, Univ Milano-Bicocca, Milano, Italy; 4Unità Operativa di Cardiologia, Ospedale Magenta, Milano, Italy; 5Cardiologia Interventistica, Policlinico di Monza, Monza, Italy; 6IRCCS Multimedica, Sesto San Giovanni-Milan, Italy.

Background: The plasma concentration of the endogenous inhibitor of nitric oxide synthase asymmetric dimethyl arginine (ADMA) associates with sympathetic activity in patients (pts) with chronic kidney disease but the driver of this association is unknown.

Methods: In this longitudinal study (followup 2 weeks-6 months) we performed repeated measurements over time of muscle sympathetic nerve activity (MSNA), plasma levels of ADMA and symmetric dimethyl arginine (SDMA) and blood pressure (BP) and heart rate (HR) in 14 pts with drug-resistant hypertension who underwent bilateral renal denervation. Stability of ADMA, SDMA, BPs and MSNAC over time (6 months) was assessed in 2 historical control groups of patients maintained on stable anti-hypertensive treatment.

Results: Time integrated changes in MSNAC following renal denervation ranged from -40.6% to +10% (average -15.1%) and these changes were strongly associated with the corresponding changes in plasma ADMA (r= 0.62, P=0.02) and SDMA (r=0.72, P=0.004). Changes in MSNAC went along with simultaneous changes in standardized systolic (r=0.65, P=0.01) and diastolic BP (r=0.61, P=0.02). In the historical control groups, no change in ADMA, SDMA, BPs and MSNAC levels over 6 months was recorded during a 6-months follow up.

Conclusions: In pts with resistant hypertension changes in sympathetic activity after renal denervation associate with simultaneous changes in plasma levels of ADMA and SDMA. These observations are compatible with the hypothesis that the sympathetic nervous system exerts an important role in modulating circulating levels of ADMA and SDMA in this condition.

Funding: Government Support - Non-U.S.

FR-OR044
Intensive Blood Pressure Lowering and Kidney Function Decline Among Persons with prior Lacunar Stroke: The SPS3 Randomized Trial
Carmen A. Peralta,1 Leslie Mcclure,2 Rebecca Scherzer,1 Michael Shlipak,1 Carole White,3 Oscar Benavente,3 Pablo E. Pergola,3 1UCSF, 2UAB, 3UTHSC, 4UCSF, 5UBC.

Background: The effect of intensive blood pressure (BP) lowering on kidney function among persons with vascular disease and preserved glomerular filtration rate (eGFR) is not known.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.

42A
Methods: SP53 was a multi-center trial to test effectiveness of two BP targets on secondary prevention of stroke. In a post-hoc analysis of 2611 participants randomized to lower SBP (<130 mmHg) vs. higher (130-149 mmHg) with yearly creatinine measures, we evaluated differences in annualized eGFR decline and rapid decline (>30% ml/min/1.73m²) using linear mixed models and logistic regression, respectively.

Results: Mean age was 63±11; 949(36%) were diabetic, mean eGFR was 80±19 and 410(16%) had eGFR <60 ml/min/1.73m² at randomization. At 9 months, achieved SBP was 137±15 mmHg in higher vs. 127±14 mmHg in the lower BP group, and differences persisted throughout follow-up (mean 3.2 years). Relative to higher BP arm, use of ACE/ARB, diuretic and calcium channel blocker were all increased by 20% among persons in the lower BP arm. Compared with higher, lower BP target had faster eGFR decline. Differences were most pronounced during the first year, whereas rates of eGFR decline did not differ between assigned BP groups after year 1.

FR-OR046
Effect of Uric Acid Lowering on Ambulatory Blood Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial
Ciaran Joseph McMullan,1 Lea Borgi,1 Gary C. Curhan,2 Naomi D.L. Fisher,3 John P. Forman,3 1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Endocrine Div, Brigham and Women’s Hospital, Boston, MA.

Background: Higher levels of uric acid are associated with higher blood pressure (BP) in a number of recent cohort studies, suggesting that uric acid may be a target for prevention of hypertension. However, the effect of lowering serum uric acid on BP is unclear.

Methods: We performed a randomized, double-blind, placebo-controlled trial of normotensive individuals with body mass index (BMI) ≥25 and uric acid level ≥ 5.0 mg/dL; subjects were randomized to receive either allopurinol 300/600mg, probenecid 500/1000mg or placebo daily for 8 weeks. Mean 24 hour systolic BP (24hSBP) was measured using 24 hour ambulatory blood pressure monitoring at baseline and 8 weeks.

Results: By the end of the trial, 22, 24 and 26 participants assigned to receive probenecid, allopurinol and placebo, respectively, had adequate 24 hour BP measurements at baseline and 8 weeks. Uric acid levels changed over 8 weeks from means of 5.9, 5.6 and 5.6 mg/dL to 3.5, 2.9 and 5.8 mg/dL in the probenecid, allopurinol and placebo groups, respectively. 24hSBP was not reduced after 8 weeks of uric acid lowering: from 127±10 mmHg to 124±8 mmHg (p-value=0.25) in the probenecid group; 125±9 to 124±10 mmHg (p-value=0.71) in the allopurinol group; and 121±9 to 122±10 mmHg (p-value=0.61) in the placebo group. Similarly, treatment had no effect on 24 hour diastolic BP.

Conclusions: In contrast to observational studies, this randomized, double-blind, placebo-controlled trial found that uric acid lowering does not improve mean 24 hour BP in normotensive individuals with high uric acid levels, suggesting that uric acid may not be a modifiable target for prevention of hypertension.

Funding: NIDDK Support

FR-OR047
Central Role for Altered Arginine Metabolism in Salt-Sensitive Hypertension in CKD: A Metabolomic Profiling Study
Anna V. Mathew,1 Adil Jadoon,1 Jaeman Byun,1 Robin L. Padilla,2 Peter Kotanko,2 Scott L. Hummel,1 Brenda W. Gillespie,1 Rajiv Saran,3 Subramaniam Pennathur.1 1Univ of Michigan, Ann Arbor; 2RR, New York.

Background: As the nitrogen donor in nitric oxide (NO) synthesis by NO synthase (NOS), arginine and its metabolic products are integrally linked to blood pressure (BP) regulation, however their role in chronic kidney disease (CKD), salt sensitivity and BP response has not been systematically studied. We explored if arginine metabolites alter with sodium restriction and predict favorable blood pressure in response to dietary sodium restriction (DSR).

Methods: Samples from 34 subjects enrolled in the LoSalt trial, a randomized crossover trial of CKD 3-4 patients who underwent DSR (<2g/day) were utilized. Targeted metabolomic analysis of arginine metabolome in pre and post DSR plasma and urine was performed by isotope dilution liquid chromatography mass spectrometry including N3,N6-dimethylarginine (ADMA), N3,N6'-dimethylarginine (SDMA), N6-monomethyl-L-arginine (NMA), arginine and citrulline. Salt sensitivity was determined by salutary changes to volume status and BP as measured by bioelectrical impedance spectroscopy (whole-body, segmental and calf) and 24-hour ambulatory blood pressure monitoring (ABPM). Pearson correlation assessed the associations between the metabolites and clinical parameters.

Results: After 4 weeks of DSR, mean urinary sodium decreased by 73 ± 71 mmol/24hr and 24-hour systolic BP reduced by 10.8 ± 13.8 mmHg. Higher urine ADMA/creatinine ratio correlated with lower total body water at baseline (r=-0.57; p<0.01). Changes in urine ADMA/creatinine ratio (r=-0.46) and urine NOS inhibition index (NIL, ADMA+SDMA/SDMA-r, -0.46) negatively correlated with changes in mean arterial ABPM (p<0.05). Urine Total Arginine Metabolism Index (TAMI, ADMA+SDMA+NMA/arginine, r=-0.47, p<0.05) negatively correlated with change in extracellular volume.

Conclusions: Our results strongly implicate altered arginine metabolism and NOS inhibition with BP response following DSR. Further research should examine whether urinary markers of altered arginine metabolism (ADMA, NIL and TAMI) can consistently serve as markers of salt sensitivity in both CKD and non-CKD subjects following DSR.

Funding: Private Foundation Support
FR-OR048

Mutations in TBX18 Cause Dominant Urinary Tract Malformations via Transcriptional Dysregulation of Ureter Development

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the leading cause of CKD in children. Identification of monogenic causes of CAKUT permits the first insights into disease mechanisms.

Methods: We performed whole exome sequencing in a large kindred followed by high-throughput sequencing in individuals with CAKUT. Furthermore, we performed a transcriptional reporter assay, protein-protein and protein-DNA interaction studies, as well as in vivo studies in Xenopus laevis.

Results: We identified a heterozygous truncating mutation (p.G337Vfs*19) of the T-box transcription factor 18 gene (TBX18) in all 7 affected members of a large kindred. We also detected 2 mutations (p.H524Y and p.K163E) in 3 of 1,295 unrelated families with CAKUT. TBX18 is essential for development of the ureteric mesenchyme and ureteric smooth muscle cells. We found that all 3 TBX18 mutant proteins still dimerize with the wild type protein, but had prolonged half-life, and exhibited reduced transcriptional repression. The mutation p.K163E altered a residue critical for TBX18-DNA interaction, resulting in impaired TBX18-DNA binding. In vivo overexpression in Xenopus laevis revealed decreased biological activity on pronephric kidney development for p.G337Vfs*19 and p.K163E.

Conclusions: We discovered dominant negative TBX18 mutations as a novel cause of human CAKUT that act via lack of repression of TBX18 transcriptional activity. Our studies implicate ureter smooth muscle cell development in the pathogenesis of human CAKUT.

FR-OR049

ACTN4 Mutations Lead to Increased Contractility of Human Podocytes in Response to Injurious Stimuli and Matrix Stiffening

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Methods: We used traction force microscopy to quantify contractile forces exerted by immortalized human podocytes on their underlying substrate. Immunofluorescence staining was used to examine the localization of ACTN4 and actin. We transduced podocytes transfected with mutant ACTN4 into more contractile in response to the injurious stimulus TGF-beta compared to podocytes transfected with WT ACTN4. We also found that podocytes seeded on a stiff substrate (26 kilopascal) and transfected with mutant ACTN4 are more contractile than podocytes transfected with WT ACTN4. This difference in contractile force between WT and mutant was blunted when podocytes are seeded on a softer substrate (1 kilopascal). Additionally, mutant ACTN4 transfected podocytes show much more prominent actin stress fibers, which are largely absent from WT ACTN4 transfected podocyte.

Conclusions: We demonstrated that mutations in the ACTN4 ABD resulted in increased podocyte contractility in response to injury. Our observations raise the hypothesis that the contractility of podocytes by pharmaceutical agents in vivo might mitigate podocyte disease due to ACTN4 mutation.

Funding: NIDDK Support

FR-OR050

Assessing Two Novel Steroid-Resistant Nephrotic Syndrome Candidate Genes Using the Drosophila Model

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Background: Steroid-resistant nephrotic syndrome (SRNS) is a genetically heterogeneous disease. Using exome sequencing we previously identified two homozygous, potentially damaging, missense variants in ADD3 and KAT2B in the affected members of a consanguineous family presenting syndromic SRNS. The first gene encodes adducin, an important regulator of the actin cytoskeleton, and the second the lysine acetyltransferase KAT2B responsible for histone acetylation.

Methods: To describe the importance of ADD3 and KAT2B on podocyte function and the impact of the mutations we used the Drosophila model KD and rescue experiments with the WT and mutant genes were performed using the GALA4-UAS system in Drosophila nephrocytes, the fly counterparts of podocytes. Defects at a molecular and ultrastructural level were assessed using immunostaining and electron microscopy and functional assays were used to assess the filtration/endocytic functions of nephrocytes.

Results: In 3º instar nephrocytes, adducin KD, but not KAT2B KD, disrupted the actin cytoskeleton, delocalized the slit diaphragm protein Kirre and led to decreased filtration/endocytosis. At the ultrastructural level ADD3 KD led to decreased number of slit diaphragms and foot process effacement. At the adult stage, both adducin and KAT2B KD induced a reduction of nephrocytes. While KAT2B rescue experiments are still pending, the WT but not the mutated form of ADD3 rescued the ADD3 KD phenotypes, namely the actin cytoskeleton defects and Kirre mislocalization.

Conclusions: These findings suggest that ADD3 plays a major role on podocyte morphology and function and that ADD3 mutations maybe causative to some forms of SRNS. However the impact of the KAT2B mutation in the patient phenotype cannot be excluded.

Funding: Government Support - Non-U.S.
FR-OR052
Defects of the Nuclear Pore Proteins NUP93, NUP205, or Exportin-5 Link Nephrotic Syndrome to Disrupted SMAD Signaling  Daniela A. Braun, 1 Carolin Sadowski, 1 Stefan Kohl, 1 Svetlana Lovric, 2 Susanne Astrinidis, 3 Shazia Ashraf, 1 Werner Lukas Pabst, 1 Weiwen Tan, 2 Jennifer A. Lawson, 1 Merlin Airik, 1 Richard P. Lifton, 3 Heon Yung Gee, 2 Wolfram Antonin, 2 Friedhelm Hildebrandt 1,4, 13 Nephrology, Boston Children’s Hospital, Boston, MA; 2,3 Friedrich Miescher Laboratory, Max Planck Society, Tübingen, Germany; 4 Dep. of Genetics, Yale Univ School of Medicine, New Haven, CT; 5 Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid resistant nephrotic syndrome (SRNS) is a frequent cause of end-stage renal disease in the first decades of life. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis. However, additional genes and disease mechanisms remain unknown.

Methods: We combined homozygosity mapping with whole exome sequencing (WES) in 100 individuals with SRNS. To identify additional mutations, we screened our cohort of ~800 individuals with SRNS by microfluidic multiplex PCR (Fluidigm Access Array®) and next generation sequencing. We examined nuclear translocation of SMAD4, utilized a luciferase reporter construct under the control of a SMAD responsive element, and performed co-immunoprecipitation to test the pathogenicity of the identified human disease alleles.

Results: By WES and multiplex PCR, we identified mutations in the genes NUP93, NUP205, or XPO3 (encoding for nucleoporin 93, 205 and exportin-5) in 8 unrelated families with SRNS. All individuals had early onset SRNS with rapid disease progression. We show that all three proteins localize to WT1 positive podocyte precursor cells in developing rat kidney. Human mutations in NUP93 disrupt the assembly and integrity of the nuclear pore complex (NPC). A human mutation in NUP205 abrogates the interaction with NUP93 within the NPC. We demonstrate that NUP93 and exportin-5 interact with the transcription factor SMAD4, and that human mutations of NUP93 abrogate this interaction. Furthermore, human mutations of NUP93 interfere with SMAD dependent transcription downstream of BMP7.

Conclusions: We identify mutations of NUP93, NUP205, or XPO3 as novel monogenic causes of steroid-resistant nephrotic syndrome in humans, and implicate disrupted SMAD signaling in its pathogenesis.

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FR-OR053
A Heterozygous Rare Variant in IL-1R Contributes to Autosomal Dominant FSGS in an African American Kindred  Gizemon Hall, 1,3,4 Jose A. Gomez, 1 Peter J. Lavin, 2 Eugene K. Kovalik, 2 Peter J. Conlon, 1 Rasheed A. Gbadegesin 1,2,3,4 1 Internal Medicine, Duke Univ; 2 Pediatrics, Duke Univ; 3 Nephrology, Duke Univ; 4 Duke Molecular Physiology Inst, Duke Univ; 5 Trinity College, Ireland; 6 Beaumont Hospital, Ireland.

Background: FSGS is a disorder characterized by podocyte injury, focal glomerular scarring, nephrotic syndrome and rapid progression to ESKD. Although FSGS disproportionately affects African Americans (AA), there is no report of a causal FSGS gene identified in an AA index kindred. Here we report the discovery of a rare heterozygous missense variant in the interleukin-1 receptor (IL-1R) as contributory to autosomal dominant (AD) FSGS in an AA kindred from the US.

Methods: We identified an AD kindred with six affected individuals spread over three generations. We performed whole-exome sequencing on three affected members of the family. We confirmed all pathogenic variants by direct sequencing and performed co-immunoprecipitation to test the pathogenicity of the identified rare variant in IL-1R.

Results: We identified a segregating heterozygous rare variant (K47R) within the ligand binding domain of IL-1R in the kindred. The variant was absent from 8,600 Caucasian chromosomes and has a minor allele frequency of 0.003 in the AA population in EVS. The change is conserved in evolution and is considered damaging by in silico prediction. We confirmed the expression of IL-1R in kidney and podocytes by RT-PCR, immunohistochemistry, and immunoblot analyses. Because IL-1R is known to signal through the JAK/STAT pathway, we examined the effect of IL-1R expression on STAT3 activation and proliferation in podocytes. We determined that IL-1R expression enhances basal STAT3 activation and induced hyperproliferation.

Conclusions: We report the identification of a heterozygous rare variant in IL-1R as a contributor to AD FSGS in an AA kindred. IL-1R is expressed in the kidney and podocytes and overexpression of IL-1R significantly enhances basal STAT3 activation and podocyte proliferation.

Funding: NIDDK Support

FR-OR054
Genetic Investigation and Phenotypic Characterization of Uromodulin Associated Kidney Disease  Christine Gass, 1,2 Monica Arenas Hernandez, 2 Anthony Marinaki, 2 Gopalakrishnan Venkat-Raman, 1 Jennifer Conlon, 1,3,4 (Wessex Kidney Centre, Portsmouth Hospitals Trust, Portsmouth, United Kingdom; 2 ‘Genetic and Genomic Medicine, Univ of Southampton, Southampton, United Kingdom; 3 Purine Research Laboratory, St. Thomas’ Hospital, London, United Kingdom.

Background: Uromodulin associated kidney disease (UAKD) is a difficult to diagnose, rare autosomal dominant genetic disorder caused by mutations in the UMOD gene. We aimed to determine the frequency and distribution of pathogenic UMOD mutations in a familial kidney disease cohort and to investigate any distinguishing clinical features.

Methods: CKD patients with a family history (FHx) of renal disease were ascertained from a large tertiary renal center through a questionnaire study and database search. Patients with a FHx suggesting an unknown genetic diagnosis or UAKD were recruited. DNA was extracted from blood or saliva and sequenced for UMOD exons 3-5. Phenotypic characteristics were compared between patients with and without UMOD mutations, with significance testing in SPSS.

Results: Of 3,760 patients in CKD stages 3-5, 131 patients with a compatible FHx were identified and recruited. Of these, 30 patients (23%) from 17 families had 11 distinct pathogenic UMOD mutations. In 12 patients (9%) from 7 families this was previously unsuspected. UAKD patients had significantly lower protein creatinine ratios (median 28, versus median 222, Mann-Whitney U = 0.001), less hematuria (23% (p = 0.003)) and more electrolyte abnormalities (28% (p = 0.02) and severe anemia (2% (p = 0.049) pre renal replacement therapy (RRT)). There were no statistically significant differences in uric acid, gout, all-cause hospitalization, dialysis, mortality, or RRT. UAKD patients were younger at presentation.

Conclusions: UAKD is common amongst familial nephropathy patients, and is poorly predicted by clinical features. Hyperuricaemia or gout, both typical of early UAKD, did not distinguish from prevalent familial nephropathies, but less proteinuria and haematuria did. More electrolyte abnormalities in UAKD could be due to an alteration in tubular water permeability; the reason for less anaemia is unclear. Having demonstrated a high prevalence of UAKD, we advise UMOD testing guided by family history regardless of typical phenotype.

Funding: Private Foundation Support

FR-OR055
Chaperone Therapy in Stem Cells Derived from Fibroblasts with Missense Mutations in X-Linked Alport Syndrome  Dongmiao Wang, 1 Sharon D. Ricardo, 2 Judith A. Savage, 1 Medicine, The Univ of Melbourne (Melbourne Health), Melbourne, VIC, Australia; 3 Anatomy and Developmental Cell Biology, Monash Univ, Clayton, VIC, Australia.

Background: Forty % of mutations in X-linked Alport syndrome are caused by missense changes, often where Gly is substituted with another amino acid. Chaperone treatment has been useful in other diseases due to missense mutations. The aim of this study was to produce iP cells from fibroblasts from a male with X-linked Alport syndrome and determine the effects of the chemical chaperone, 4 phenyl butyric acid.

Methods: Stem cells were made by the Ricardo laboratory from skin fibroblasts from a male with X-linked Alport syndrome due to p.G624D. He had developed renal failure at the age of 54, and had hearing loss, but no lenticonus or central retinopathy. Stem cells were induced to become podocytes, and examined for collagen IV a1 – ab expression, and for markers of ER stress (ATF6, HSPA5, DDIT3), autophagy (ATG5, BECN1, ATG7) and apoptosis (CASP3, BAD, BCL2) using qRT-PCR (Applied Biosystems 7500). Levels of collagen IV a5 chain were quantitated in an in-house inhibition ELISA. These measurements were repeated after incubation with the chemical chaperone, 10 mM 4-phenyl butyric acid.

Results: The iP expressed collagen IV a3 and a4 mRNA consistent with a podocyte phenotype. Levels of collagen IV a5 mRNA and protein were not different from those in normal male fibroblasts. However levels of both intra and extracellular collagen IV a5 were reduced suggesting degradation. The Alport iP had increased transcripts for HSPE5, and apoptosis (CASP3 and BCL2) compared with normal. Incubation with 4 phenyl butyric acid, resulted in a reduction in all markers of autophagy and of CASP3.

Conclusions: iP cells derived from Alport fibroblasts represent a model system in which to examine novel treatments. Chemical chaperone therapy has beneficial effects on cells derived from individuals with Alport syndrome due to missense mutations.

Funding: Private Foundation Support

Key: TH = Thursday; FR = Friday; SA = Saturday; OR = Oral; PO = Poster; PUB = Publication Only
Underline represents presenting author. 45A
Massively Parallel Sequencing (MPS) in Diagnostically Refractory Genetic Renal Disease (GRD) Andrew John Mallett,1,2 Chiara Patel,2,3 Joanna Crawford,4 Bruce Bennett,5 Melissa H. Little,1,6,7 Helen G. Healy,1,2 Stephen I. Alexander,1 Valentine Hyland,6 Cas Simons,6 * Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane and Women’s Hospital, Australia; 2School of Medicine, The Univ of Queensland, Australia; 3Genetics, Health Queensland, RBWH, Australia; 4Inst for Molecular Bioscience, UQ, Australia; 5Depts of Molecular Genetics and Nephrology, Children’s Hospital at Westmead, NSW, Australia; 6Molecular Genetics Laboratory, Pathology Queensland, Australia; 7Murdoch Children’s Research Inst, Melbourne, VIC, Australia.

Background: GRD accounts for 10% of adults and 50% of children with end stage kidney disease. An unknown proportion of cases remain refractory to current clinical genetic tests. Advances in MPS enable attempts to address this in a research setting. We aimed to utilize MPS with pedigree analysis in unresolved cases of GRD.

Methods: Families with clinically diagnosed GRD were recruited in whom clinical genetic testing was either negative or not available. Whole exome sequencing was undertaken and analyzed with custom in house bioinformatics assessment tools accounting for all inheritance patterns. Identified variants of interest were confirmed using Sanger sequencing in clinical laboratories.

Results: 14 families (62 participants) were recruited with a variety of GRD diagnoses and modes of inheritance. A molecular genetic diagnosis has been resolved in 5 families. The identified mutations included (compound heterozygous), IFT440 (compound heterozygous), HNF1A (heterozygous), COL4A5 (hemizygous) and INR4 (mtDNA) genes. All have been confirmed in a clinical diagnostic laboratory and reported back to the participants with further genetic counseling. Research continues in the remaining 9 families, including application of whole genome sequencing. No reportable incidental genetic findings were identified.

Conclusions: MPS confirmed and clarified a clinical genetic diagnosis in 5/14 families with previously and diagnostically refractory GRD. These results were integrated into clinical practice and defined an emerging strategy of MPS for the delivery of clinical care. Further studies are required to resolve the remaining families.

Funding: Private Foundation Support

The B Cell Survival Cytokine BAFF Promotes Murine Lupus Nephritis via Activation of TACI, Not BAFF Receptor Shaun W. Jackson,1,2 Nicole Scharping,1 Holly Jacobs,1 Tanvi Arkatkar,1 David Rawlings,1,2 Seattle Children’s Research Inst, Seattle, WA; 3Dept of Pediatrics, Univ of Washington, Seattle, WA.

Background: Many renal diseases have a genetic basis, although definitive genetic confirmation of precise etiology is rarely sought, in spite of the value of genetic screening in patients with ESRD both to confirm a diagnosis and to guide the evaluation of living related kidney donors, who may be at increased risk of ESRD.

Methods: To enable comprehensive screening for genetic diseases, we developed a panel that combines targeted genomic enrichment with massively parallel sequencing to simultaneously interrogate 120 genes implicated in 75 renal diseases. To validate this panel, we studied 20 controls and 20 patients with presumed genetic renal disease, four of whom underwent and analyzed with custom in house bioinformatics assessment tools accounting for all inheritance patterns. Identified variants of interest were confirmed using Sanger sequencing in clinical laboratories.

Results: 14 families (62 participants) were recruited with a variety of GRD diagnoses and modes of inheritance. A molecular genetic diagnosis has been resolved in 5 families. The identified mutations included (compound heterozygous), IFT440 (compound heterozygous), HNF1A (heterozygous), COL4A5 (hemizygous) and INR4 (mtDNA) genes. All have been confirmed in a clinical diagnostic laboratory and reported back to the participants with further genetic counseling. Research continues in the remaining 9 families, including application of whole genome sequencing. No reportable incidental genetic findings were identified.

Conclusions: MPS confirmed and clarified a clinical genetic diagnosis in 5/14 families with previously and diagnostically refractory GRD. These results were integrated into clinical practice and defined an emerging strategy of MPS for the delivery of clinical care. Further studies are required to resolve the remaining families.

Funding: Private Foundation Support
Novel Anti-Peroxidasin Antibodies Are Part of the Autoimmune Milieu in Preclinical and Clinical Goodpasture's Disease

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Background: The phospholipase A2 receptor (PLA2R) is the major autoantigen in idiopathic membranous nephropathy, with two recently identified epitopes of unknown clinical significance.

Methods: Fifty PLA2R1-positive patients sera were screened by western blot on a series of PLA2R1 deletion mutants covering the ten extracellular domains. We identified epitopes in the CyR, CTLD1 and CTLD7 domains and confirmed the reactivity against these three domains with soluble forms of each domain using a new ELISA in 69 PLA2R1-positive patients.

Results: Domain-specific ELISAs allowed stratifying 69 PLA2R1-positive patients into three subgroups: 23 CyR, 14 CTLD1 + CyR and 32 CTLD7 + CTLD1 + CTLD7. Median ELISA titers measured using the full-length PLA2R1 antigen were not statistically different between patients' subgroups. The 23 patients with anti-CyR restricted activity were younger (p=0.008), had less nephrotic range proteinuria (p=0.018) and exhibited more spontaneous remission (p=0.03), lower rate of renal failure progression (p=0.0025) and less end-stage kidney disease (p=0.01) during follow-up. Indeed, 31/69 patients had poor renal prognosis according to KDIGO (urinary protein/creatinine ratio over 4 g/g or 6 gFR=45 ml/min/1.73m 2 at end of follow-up). High anti-PLA2R1 activity and epitope spreading beyond CyR epitope were independent risk factors of poor renal prognosis in multivariable cox regression analysis. Epitope spreading during follow-up was associated with disease worsening (n=3), whereas reverse spreading from CTLD7 profile back to CyR was associated with favorable outcome (n=1).

Conclusions: In the PLA2R1 PL profile, the epitope spreading during follow-up is a powerful tool to monitor disease severity and stratify patients into subgroups with different renal prognosis.

Funding: Government Support - Non-U.S.

FR-OR064

Intravascular Extensions Allow Renal DC to Capture Bloodborne Antigens and Mediate T Cell Migration into the Kidney

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Background: We have previously shown that the kidney, a non-barrier, highly vascularized organ possesses an extensive monocyte-derived DC network with around 25% of DC sampling intravascular antigens (Ag) by extending projections into the lumina of cortical postcapillary venules. Here, we hypothesized that renal DC have an active role in immune surveillance via (1) capturing intravascular antigens such as bacteria and immune complexes (IC) and (2) mediate Ag-specific T cell migration into the kidney.

Methods: 2-Photon Intravital Microscopy (2PM) and flow cytometry was performed on C57BL/6 J mice we observed (1) DC uptake of bacteria from the intravascular space immediately after injection (2PM and flow cytometry) and (2) a 41% increase of DCs with intravascular processes after E.coli injection (2PM). DC also took up i.v. OVA-IC, (2PM). Furthermore, in the setting of a systemic CFP-OVA E.coli infection, OT-1 T cells migrated into the kidney (2PM and flow) with 2PM showing stable DC-T cell interactions and DC (green)-mediated T cell (red) migration into the kidney (figure 1) (blood-cyan).

Conclusions: In the PLA2R1 PL profile, the epitope spreading during follow-up is a powerful tool to monitor disease severity and stratify patients into subgroups with different renal prognosis.

Funding: Government Support - Non-U.S.
Results: Using flow cytometry of renal biopsies we were able to demonstrate the presence of CD4+/Foxp3+ Treg1 cells in the inflamed kidney of patients with ANCA-GN. Interestingly, Treg1 cells in the kidney displayed a gut homing phenotype (CCR6+, CCR9+, ICOS+, IL-7Ralpha+ CD103+), indicating that renal Treg1 cells have been primed in the intestine. Tracing intestinal cells by photoconversion in Kaede mice, we could demonstrate that intestinal colonisation proportionally induced Treg1 cell in the nephritic kidney originated from the small intestine. In line, using germ free mice, we were able to show that renal Treg1 response and consecutive tissue injury in crescentic GN depends on intestinal Treg1 cells. Finally, we demonstrated that treatment of nephritic mice with intestinal microbiota depleting broad-spectrum antibiotics reduced renal Treg1 response and attenuated kidney damage.

Conclusions: These data indicate that pathogenic Treg1 cells in glomerulonephritis, originate from the intestine, migrate into the kidney and induce injury of the renal tissue. This finding might have significant implications for the treatment of renal autoimmune disorders.

Funding: Government Support - Non-U.S.

FR-OR067
T-Bet Activation in Regulatory T Cells Is Required for General Fitness, Antibody Production and Control of Th1 Responses in Crescentic Glomerulonephritis
Anna Nosko, Malte A. Kluger, Paul Diesenhof, Simon Mehling, Claudia Wegescheid, Gina Treg, Robert A. Stahl, Ulf Panzer, Oliver M. Steinmetz

Background: Mechanisms responsible for down regulation of pathogenic Th1 immunity remain widely unknown. Recently, it was proposed that activation of the Th1 characteristic transcription factor T-bet optimizes Foxp3+ regulatory T cell (Treg) function to counteract Th1 responses.

Methods: Nothing is known about the role of T-bet+ Treg1 cells in inflammatory disease. We studied their function in the NTN model of acute crescentic glomerulonephritis (GN).

Results: Kneys of nephritic wild type mice showed increasing percentages of Treg1 cells during the course of NTN, indicating their functional importance. Naïve Foxp3+ T-bet+ mice (Treg1), lacking Treg1 cells, showed spontaneous skewing towards Th1 immunity. In the absence of Treg1 cells, NTN was aggravated in terms of renal failure, histology and inflammatory cell infiltration with selectively elevated renal and systemic Th1 responses. Analyses of Tregs from Treg1 mice revealed unaltered systemic numbers, activated Th1-like T cell production and in vivo suppressive function. However, expression of the Th1 characteristic trafficking receptor CXCR3 was absent on T-bet deficient Tregs, resulting in significantly reduced renal Treg infiltration. In addition to diminished renal trafficking, overall fitness of Tregs from Treg1 mice was greatly impaired. In competitive co-transfer experiments into lymphopenic hosts, T-bet deficient Tregs were outcompeted by wildtype Tregs in terms of proliferation and expression levels of Foxp3. Furthermore, T cell dependent humoral immunity was impaired in Treg1 mice, indicating that T-bet activation in Tregs plays a hitherto unrecognized role for antibody production.

Conclusions: Our data indicate the critical role of regulatory T cells in crescentic GN. These Treg1 cells are characterized by activation of the transcription factor T-bet, which enhances their overall fitness, directs antibody responses and optimizes their capacity to down-regulate Th1 responses by inducing CXCR3 expression.

FR-OR068
Predicting the Lifetime Risk of End-Stage Renal Disease in Kidney Donor Candidates
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CKD Prognosis Consortium

Background: A tool to comprehensively evaluate the lifetime risk of ESRD in potential living kidney donors could help standardize transplant center acceptance criteria.

Methods: We developed statistical equations to predict the lifetime incidence of ESRD according to a person’s baseline demographic and health characteristics before kidney donation. Data sources included prevalence estimates from NHANES, ESRD incidence from USRDS, and ESRD risk associations in low-risk subgroups of 7 general population cohorts (N=4,580,454). Developed equations were applied to the general population (using NHANES) and the recent US donor population (using the OPTN registry) and made available in an online risk calculator (www.transplantmodels.com/lifetime).

Results: For the “base-case” potential donor (eGFR 90 ml/min/1.73 m², urine ACR 10 mg/g, systolic blood pressure 120 mmHg, and no adverse health characteristics), the predicted pre-donation lifetime incidence of ESRD varied by age, race, and sex: 2.7%, 1.1%, 0.9%, and 0.6% in 20-year-old black men, black women, white men, and white women, respectively, and 0.6%, 0.3%, 0.3%, and 0.2% in the corresponding 60-year-old candidates. The lifetime incidence of ESRD was higher with additional risk factors, particularly low eGFR or high ACR in young persons (Figure). The predicted lifetime incidence of ESRD before donation was <1% in 88% of recent US donors.

Conclusions: We suggest consideration of pre-donation lifetime ESRD risk in the evaluation and counseling of potential living kidney donors. Our equations estimate a person’s lifetime incidence of ESRD in the absence of donation according to multiple demographic and clinical characteristics.

Background: Prevalence of de novo hypertension after kidney donation appears to be similar to that in the general population. Factors associated with it development, however, have not been studied. Goals: 1) ascertain donors’ risk of developing HTN, 2) describe the impact of its development on death and renal function and 3) develop a HTN risk prediction model using pre-donation parameters.

Methods: Our donors are followed indefinitely through surveys inquiring about HTN, renal disease and also serial laboratory testing. Risk factors for post donation new onset hypertension were determined using stepwise proportional hazards regression.

Results: HTN status was ascertained in 3638 donors with a mean follow-up of 13±11 years. In total, 972 (27%) developed new onset hypertension. Pre-donation risk factors for development included older age, higher BMI, SBP, and serum glucose at donation (Table 1a). White donors were 40% less likely to develop hypertension, p<0.001 for all. HTN following donation was associated with a nearly 4 fold increased risk of death, proteinuria, and eGFR < 30 ml/min or ESRD (Table 1b). Coefficients from the regression model were then used to create a HTN risk calculator (C-statistic 0.65). A sample output for a 40 year old donor is shown in figure 1.

Funding: NIDDK Support

FR-OR069

Effect of Changing African American Race to Apolipoprotein L1 Genotype on Kidney Donor Risk Index | Bruce A. Julian,1 Robert S. Gaston,1 Barry I. Freedman,2 William Mark Brown,2 Amber M. Reeves-Daniel,2 Ajay K. Israni,3,4 David P. Schladt,1 Stephen O. Pastan,3 Sumit Mohan,3 Jasmin Divets.3 1Univ of Alabama at Birmingham; 2Wake Forest Univ School of Medicine; 3Minneapolis Medical Research Foundation; 4Hennepin County Medical Center, Univ of Minnesota; 5Emory Univ School of Medicine; 6Columbia Univ.

Background: Renal allografts from deceased African Americans (AAs) with 2 renal-risk variants in apolipoprotein L1 gene (APOL1) are lost sooner than kidneys from AAs with 0 or 1 variant. For the latter, allograft survival is similar to that for kidneys from European Americans. Kidney Donor Risk Index (KDRI) was developed recently, before APOL1 effect was described, to quantitatively estimate quality of deceased-donor kidneys; it assigns higher risk for all AA donors. We postulated that replacing AA race with APOL1 genotype in KDRI improves risk prediction for kidneys from deceased AA donors.

Methods: Using the effect size in retrospective studies, we calculated KDRI wherein only AAs with 2 APOL1 renal-risk variants received higher KDRI scoring. Weight of APOL1 risk variants was defined by 10-fold cross validation: 9/10 of available data was used to estimate parameter associated with APOL1 in Cox proportional hazard regression with other 9 KDRI variables as covariates. Revised KDRI scores were computed and tested on the last subset; predictive ability was measured by c-index. Cross-validation was done 100x for comparison with original KDRI.

Results: Retrospective analyses of 1,149 kidney transplantations from deceased AA donors (979 APOL1=0/1; 170 APOL1=2 renal-risk variants) showed mean donor age, serum creatinine, and KDRI of 35.4 yr, 1.25 mg/dL, and 1.45. Observed c-index with original KDRI tested with full data was 0.89; distribution of observed APOL1-revised KDRI c-indices had minimum 0.55 and maximum 0.98, median 0.87. APOL1-revised KDRI c-index was higher than observed KDRI c-index in 44% of cases.

Conclusions: For the 13% of general AA population with 2 APOL1 risk variants, KDRI did not change. However, for the other 87% of AAs, the revised KDRI improved by deleting AA race as a risk factor and better reflects the quality of these kidneys relative to current system.

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FR-OR070

Racial Disparities in Perioperative Complications After Live Kidney Donation | Krista L. Lentine,1 Ngan Lam,2 David A. Axelrod,3 Mark Schnitzler,1 Amit X. Garg,1 Jesse D. Schold,4 Daniel C. Brennan,1 Dorry L. Segev,4 1Saint Louis Univ; 2Western Univ; 3Dartmouth; 4Cleveland Clinic; 5Washington Univ; 6Johns Hopkins.

Background: The frequency and severity of perioperative complications after contemporary live kidney donation are not well-described.

Methods: We integrated national U.S. donor registry data with administrative records from an academic hospital consortium (98 centers, 2008-2012) to identify predonation comorbidity and perioperative complications captured in diagnostic, procedure and registry sources. Complication severity was graded by Clavien scoring. Correlates (adjusted odds ratio, aOR) of complications were examined with multivariate logistic regression.

Results: Among 14,964 donors, 11.6% were African American (AA) and 72.6% Caucasian; 93.8% of nephrectomies began as laparoscopic, 2.4% as robotic, and 3.7%
as open procedures. Compared with Caucasians, AA donors experienced higher rates of any complication (18.2% vs 15.5%, \(P=0.005\)), and those exceeding progressive severity thresholds including Clavien \(\geq 4\) (3.7% vs 2.2%, \(P=0.0002\) ) (Figure).

After adjustment for demographic, clinical (including comorbidity diagnoses), procedure and center factors, AA race was associated with increased risk of any complication (aOR 1.26, \(P<0.001\)), and Clavien \(\geq 2\) (aOR 1.39, \(P=0.0002\)), Clavien \(\geq 3\) (aOR 1.56, \(P<0.0001\)), and Clavien \(\geq 4\) (aOR 1.36, \(P=0.004\)) events. Other significant correlates of Clavien \(\geq 4\) events included obesity (aOR 1.55), predonation hematologic (aOR 2.78) and psychiatric (aOR 1.45) conditions, and robotic nephrectomy (aOR 2.07), while annual center volume >50 (aOR 0.45) predicted lower risk.

Conclusions: AA race is independently associated with increased frequency and severity of perioperative complications after live donor nephrectomy. Future work should seek to identify underlying mechanisms and approaches to reducing outcome disparities.

Funding: NIDDK Support

FR-OR072
Risk Prediction of End-Stage Renal Disease in Living Kidney Donors

Background: Recent studies have shown increased risk of end-stage renal disease (ESRD) in living kidney donors compared with healthy non-donors. Accurate risk prediction is paramount for informed consent for donation, but individual ESRD risk is unknown.

Methods: Using national donor registry data, we modeled ESRD in 122,773 donors via Cox regression, censoring for mortality. We performed multiple imputation with 50 replications to impute body mass index (BMI), unavailable prior to 1999. We used baseline hazard and hazard ratios to calculate individual risk of ESRD at 5, 10, 15, and 20 years post-donation.

Results: Male sex, African-American (AA) race, and higher BMI were associated with greater ESRD risk (all \(P<0.01\), Table 1). Older age was associated with increased risk in non-AA donors (HR per 10y \(= \times 1.40\), \(P=0.001\)), but decreased risk in AA donors (HR = \(0.76\) \(P=0.02\)).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.22</td>
</tr>
<tr>
<td>AA race (at age 40)</td>
<td>1.48</td>
</tr>
<tr>
<td>Age per 10y (non-AA donors)</td>
<td>1.40</td>
</tr>
<tr>
<td>Age per 10y (AA donors)</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI per 5 units</td>
<td>1.16</td>
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</table>

Overall cumulative incidence of ESRD at 5, 10, 15, and 20 years was 3.0, 11.6, 27.7, and 56.9 events per 10,000 donors, respectively (Figure 1). Predicted individual 20-year risk of ESRD ranged from 6.9 per 10,000 (0.07% chance) to 1240.4 per 10,000 (12.4% chance) of ESRD. Median (IQR) individual 20-year risk of ESRD was 49.8 (31.2-83.8) per 10,000 (Figure 1).

A web calculator of individual risk can be found at transplantmodels.com/donordrs.

Conclusions: Male gender and higher BMI are associated with greater ESRD risk in kidney donors. Old age is associated with greater ESRD risk among non-AA donors, but younger age is associated with greater risk among AA donors, likely due to donor selection. Greater permisiveness may be warranted for older AA donor candidates; younger AA candidates should be evaluated carefully and counseled about long-term ESRD risk.

Funding: NIDDK Support

FR-OR073
Factors Influencing Decision about Kidney Transplant: A Survey of Dialysis Patients
Fareeha Khalili, Ming Wang, Naman Trivedi, Eric Chang, Nasrollah Ghahramani. Pennsylvania State Univ College of Medicine, Hershey, PA.

Background: Kidney transplant (KT) is the treatment of choice for end stage renal disease (ESRD). The decision to pursue KT involves a complex interplay of disease-related, socioeconomic and ethnic factors. We explored factors influencing patients’ decision about KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants who fulfilled inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent variables were demographic factors, distance to dialysis unit, and modes of education about options. In multivariate analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of pursuing KT.

Results: Of 673 participants, 401 had been referred and 201 were listed for KT. Positive predictors of pursuing KT (n=268) included: received 3 or more modes of education about KT (OR=3.08;CI:1.62 to 5.87); nephrologist discussed the option of KT at least twice in previous year (OR=2.49;CI:1.43 to 4.32). The 2 most common reasons for not pursuing KT included satisfaction with current treatment (18%) and inadequate finances (14%). Urban residence (OR: 2.64;CI: 1.33 to 5.23) and > 5 years on dialysis (OR: 1.75;CI: 1.09 to 2.81) were associated with likelihood of indicating satisfaction with current treatment as a reason not to pursue KT. Age >60 (OR: 2.18;CI: 1.21 to 3.94) and proximity to dialysis unit (OR: 2.30;CI: 1.27 to 4.17) were associated with higher likelihood of indicating inadequate finances as reason not to pursue KT. Of those pursuing KT, 36% would not consider LDKT, most commonly citing unavailability of potential donor (28%). Positive predictors of pursuing LDKT were: ‘nephrologist discussed the option of transplant at least twice in last year’; and married status. Negative predictors of considering LDKT were regular attendance at religious service, age >60, being on dialysis >5 years.

Conclusions: Nephrologist-related factors (delivering diverse education) and patient characteristics (age, gender, race, health status perception, marital/socioeconomic status, duration/comfort with dialysis) are important drivers of the decision making process for choice of KT.

Funding: NIDDK Support

FR-OR074
A Propensity-Matched Analysis Comparing Rates of Post-Transplant Diabetes Mellitus (PTDM) in South Asian and Caucasian Renal Transplant Recipients
Javert Raj, Krashan Parekh, Charles Ferro, Richard Borowks, Adnan Sharif. Queen Elizabeth Hospital, Birmingham, United Kingdom.

Background: South Asians have increased risk for type 2 diabetes but the risk of post-transplantation diabetes mellitus (PTDM) is unknown. The aim of this study was to compare PTDM risk in South Asian versus Caucasian kidney allograft recipients in a propensity matched analysis.

Methods: In this retrospective analysis, data was extracted from electronic patient records at a single-centre (2004-2014). 354 Caucasian and 121 South Asians met the inclusion/exclusion criteria for this study. Caucasians were more likely to be older, male and have higher BMI compared to South Asians. Propensity score matching was therefore undertaken to remove their bias effect.

Results: Propensity matching resulted in 102 pairs of kidney allograft recipients. Median follow up was 51 months (range 3-130 months). Both groups had similar baseline

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.

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characteristics, although South Asians compared to Caucasians received more deceased-donor kidneys (74% vs. 43% respectively, p<0.001) and were more likely to be CMV positive (77% vs. 43% respectively, p<0.001). Five-year PTDM was higher in South Asians versus Caucasians (34% vs. 11% respectively, hazard ratio 4.3 [95% CI: 2.0-9.4, p=0.001]).

Donor type had significant interaction with ethnicity. While no difference in PTDM was observed in recipients of live kidneys, 5-year PTDM risk was 42% versus 5% for South Asian versus Caucasian deceased kidney recipients respectively (p<0.001). No difference was observed in allograft function, rejection episodes, adverse cardiovascular events or patient graft survival.

Conclusions: South Asian kidney allograft recipients have increased risk of PTDM, especially in the context of deceased kidney donation. It is important to recognize South Asians as high risk for PTDM to allow targeted screening and management strategies.

FR-OR075
Increased Circulating T-Lymphocytes Expressing HLA-DR in Kidney Transplant Recipients with Microcirculation Inflammation
Hye-Yeon Jeong, Chan-Duck Kim, Sukyung Lee, Ji-Young Choi, Se-Hee Yoon, Jang-Hee Cho, Sun-Hee Park, Yong-Lim Kim. Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; Internal Medicine, Konyang Univ, Republic of Ukraine.

Background: Despite the clinical impact of microcirculation inflammation (MI) and T-lymphocyte on antibody-mediated rejection in kidney transplant recipients (KTRs), the association between MI in allograft biopsy and activity of T-lymphocyte in the peripheral blood is not known. This study aimed to compare the histologic grading of renal allograft acute cellular rejection (ACR) and activity with serum T-lymphocyte subsets and HLA-DR positive monocytes in KTRs.

Methods: A total of 137 indication biopsies from renal allografts were performed from 117 KTRs. Among them, 24 biopsy specimens from KTRs who have data of serum T-lymphocyte subsets and HLA-DR positive monocytes at the time of biopsy were included in this study. The frequencies of serum HLA-DR(+)/CD4(+) and CD8(+) T cells, and HLA-DR positive monocytes were determined by flow cytometry. The histologic grading of renal allograft was classified according to the sum score of g+ptc (MI), i+t, ci+ct, and cv+ah. Analysis using the receiver-operating-characteristic curve showed that antibody-mediated rejection could be predicted with a sensitivity of 89.3% and a specificity of 58.3% using a cutoff value of 12.25% frequency of CD4(+)HLA-DR(+)/CD4(+) T cells.

Conclusions: MI was significantly associated with increased frequency of activated T-lymphocyte expressing HLA-DR in KTRs. Further large-scale studies are needed to confirm circulating CD4(+)HLA-DR(+)/CD4(+) T cells as a useful noninvasive immunologic monitoring tool for prediction of antibody-mediated rejection.

FR-OR076
Monitoring of Calcineurin Inhibitors by NFAT-Regulated Gene Expression in De Novo Renal Allograft Recipients
Claudia Sommerer, Martin G. Zeier, Stefan Meuer, Thomas Giese. Nephrology, Univ Hospital, Heidelberg, Germany; Immunology, Univ Hospital, Heidelberg, Germany.

Background: Calcineurin inhibitors are critical-dose drugs with a narrow therapeutic range and the optimal monitoring strategies are discussed in terms of safety and efficacy. A new pharmacodynamic monitoring tool – assessing the expression of nuclear factor of activated T cells (NFAT)-regulated genes – has been established to measure directly the function of calcineurin inhibitor (CsA) in an individual patient. Until now, only sparse data on NFAT-regulated gene expression within the early post-transplant period are available.

Methods: Altogether 80 de novo renal transplant patients were enrolled in this prospective observational trial. The immunosuppression consisted of IL-2 receptor antagonist induction, CsA, mycophenolic acid and steroids. The expression of the NFAT-regulated genes (interleukin 2, granulocyte-macrophage colony stimulating factor, Interferon γ) was determined by qRT-PCR at CsA C0 and C2 at regular follow-up visits within 6 months after transplantation.

Results: The median age of all patients was 47.9±13.7 years (54% male). Residual NFAT-regulated gene expression showed a high interindividual variability. Inversely to reduction of CsA and/or prescription of NFAT-regulated genes increased from 1.7±1.3% to 8.04±7.36% in month 1 to month 6. Despite of comparable CsA C0 levels NFAT-regulated gene expression was significantly less in patients with delayed rejection (2.0±1.2% vs. 2.0±1.7%, p=0.047). Patients with very low residual expression on NFAT-regulated genes were observed on increased risk of early infectious episodes. Residual expression of IFNγ and GM-CSF genes correlated most significantly with clinical outcome.

Conclusions: NFAT-regulated gene expression is highly inhibited in the early post-transplant period in renal allograft recipients on CsA treatment. High residual NFAT-regulated gene expression was related to acute rejection episodes but low residual expression with infectious complications. Thus, NFAT monitoring has the potential to support pharmacokinetic monitoring in the early post-transplant period.

FR-OR077
Proteomics of Urinary Exosomes to Identify Biomarkers of BK Virus Infection and Acute Rejection
Luk H. Hilbrands, Matthijs van der Vlag. Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Acute cellular rejection (ACR) and BK virus associated nephropathy (BKVAN) are frequent causes of graft dysfunction after renal transplantation with similar symptoms but requiring different treatments. We investigated whether patients with an ACR episode or BKVAN could be distinguished based on proteins present in urinary exosomes.

Methods: Urine samples (50 mL) were collected from renal transplant patients with ACR, BKVAN or stable graft function. Urinary exosomes were isolated by ultracentrifugation (110,000 g at 200,000×g). For each group (ACR, BKVAN, controls) we pooled equivalent amounts of exosome proteins of 4 patients (first set) and repeated this with 4 different patients in each group (second set). Subsequently, exosomes were lysed and Western blotting of protein was resolved by a 4-12% SDS-PAGE. After electrophoresis, gel lanes were cut into 5 pieces according to molecular mass. Proteins were in-gel digested with trypsin, and peptide mixtures were analysed using LC-MS/MS. Proteins were identified using the NCBI database. Partial least squares enhanced discriminant analysis was used to classify the patient groups based on exosomal protein content.

Results: A total of 340 individual proteins was detected in the first set of samples and 385 proteins in the second set, with 204 proteins overlapping between both sets. Our preliminary findings show a number of proteins for which the exosome content differed between ACR and BKVAN. Specific candidate proteins that can serve as urinary biomarkers include acid ceramidase, low density lipoprotein-related protein 2, copepepide VIII, alpha-1-acid glycoprotein 1 syndecan 4, and lactate dehydrogenase.

Conclusions: In this study we show that profiling of urinary exosomes is a promising technique to identify urinary proteins which allow differentiation between ACR and BKVAN in renal transplant patients.

FR-OR078
Identification of Signature Long Non-Coding RNAs in the Development of Diabetic Nephropathy
Jianping Long, Shawn S. Badal, Zengchun Ye, Bernard A. Ayanja, Farhad R. Danesh. Dept of Emergency Medicine, The Univ of Texas MD Anderson Cancer Center, Houston, TX.

Background: Long noncoding RNA (lncRNAs) have emerged as potent regulators of multiple cellular processes relevant to cellular homeostasis and differentiation. More recently, lncRNAs have also been implicated in the pathogenesis of a myriad of diseases, including cancer and heart diseases. However, the role of lncRNAs in diabetic nephropathy (DN) remains unclear.

Methods: Total RNA-Seq analysis was performed on glomeruli from Type 2 diabetic, db/db mice to explore differentially expressed lncRNAs. Following identification of a candidate IncRNA, Tug1 (Taurine-upregulated gene-1) we employed CRISPR/Cas9 genome editing to deplete Tug1 in cultured podocytes. Tug1 overexpression in podocytes was used for gain of function analysis. To understand the functional role of Tug1 in vivo and because Tug1 is reduced in diabetic podocytes, we generated podocyte-specific, Tug1 transgenic, db/db mice.

Results: RNA-Seq analysis revealed that expression of Tug1, a predicted antioxidant-responsive gene, is significantly reduced in the podocytes of db/db mice. Analysis of in vivo isolated podocytes from db/db mice demonstrated that downregulation of Tug1 over time is correlated with the progression of DN. To interrogate the functional relevance of Tug1, we performed transgenic and genome editing analysis in CRISPR/Cas9 genome editing to deplete Tug1 in cultured podocytes. Tug1 overexpression in podocytes was used for gain of function analysis. To understand the functional role of Tug1 in vivo and because Tug1 is reduced in diabetic podocytes, we generated podocyte-specific, Tug1 transgenic, db/db mice.

Conclusions: In this study we show that profiling of urinary exosomes is a promising technique to identify urinary proteins which allow differentiation between ACR and BKVAN in renal transplant patients.
**FR-OR079**

**Epigenetic Abnormalities Underlie Increased Expression of Nuclear Receptor PXR in Diabetic Kidney Disease**

**Atsushi Watanabe,1 Takashi Marumo,2 Wakako Kawarazaki,1 Mitsuhito Nishimoto,3 Nobuhiko Ayazawa,1 Daigoro Hirohama,7 Kohei Ueda,4 Hiroo Kumagai,7 Toshiro Fujita.**

1Dept of Nephrology and Endocrinology, National Defense Medical College, Tokorozawa, Japan; 2Div of Clinical Epidemiogenics, RCAST, Univ of Tokyo, Tokyo, Japan.

**Background:** Epigenetic abnormalities have been suggested to mediate the phenomenon of metabolic memory observed in diabetic complications. Because kidney is composed with various cell types, we investigated the epigenetic alterations in a cell type-specific manner and showed that epigenetic changes may induce persistent phenotypic changes of the proximal tubules in the diabetic kidney (JASN 2015 in press). PXR, a xenobiotic nuclear receptor, has recently been shown to play a critical role in metabolic changes of the proximal tubules in the diabetic kidney.

**Results:** Immunohistochemistry and quantitative RT-PCR analysis demonstrated that PXR is selectively expressed in the proximal tubules. Combined bisulfite restriction analysis and bisulfite sequencing revealed that the promoter region of Pxr of normal proximal tubules is significantly demethylated as compared to that of non-proximal tubular cells. In diabetic mice, significant increase in Pxr mRNA, demethylation of DNA and increased H3K4me3 in the promoter were also observed. Epigenetic changes are likely to play a causative role in PXR induction because DMNT inhibitor and HDAC inhibitor increased PXR expression in cultured human proximal tubular cells. To identify specific functions of PXR in proximal tubules, we treated mice with PXR agonist (PCN 100mg/kg once i.p.), and analyzed transcriptome of the kidney by microarray analysis. Significant increase of Rgs3, a molecule known to exert fibrotic effects in the kidney, was observed in the PCN-treated kidney.

**Conclusions:** We revealed that PXR, expressed selectively in the proximal tubules, is increased in the diabetic kidney. Abrupten expression of PXR may be maintained by epigenetic mechanisms and contribute to the progression of diabetic kidney disease through the novel PXR-RGC32 pathway.

**FR-OR080**

**Metabolic Control of Chromatin Remodeling by miR-93 in Diabetic Nephropathy**

**Shawn S. Badal,1 Yin Wang,1 Jiayin Long,1 Farah R. Danesh,1**

1Section of Nephrology, The Univ of Texas MD Anderson Cancer Center, Houston, TX; 2Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX.

**Background:** How podocytes respond to metabolic cues in their environment remains a central question in kidney research. This is relevant in the pathogenesis of diabetic nephropathy (DN), where recent evidence suggests that metabolic events in podocytes may play important roles in regulating chromatin structure. However, the molecular connection linking metabolic states in the cytoplasm to chromatin dynamics remains poorly understood.

**Methods:** We employed a combined in vivo and in vitro approach to understand the impact and mechanism of miR-93 overexpression in podocytes within the diabetic milieu. We generated triple transgenic, podocyte-specific, tamoxifen-inducible miR-93 transgenic mice on the Lepr<sup>db/db</sup> background (db/db db). We restored miR-93 expression in kidneys using systemically administered miR-93 mimics. Mechanistically, we employed RNA-Seq and DNase Hypersensitivity-Seq analysis to define novel targets of miR-93 in podocytes.

**Results:** Diabetes with forced expression of Pod-miR-93 exhibited a significant reduction in ACR and total albumin excretion when compared to non-induced, diabetic controls.Tamoxifen induced mice exhibited a significant reduction in mesangial expansion measured by PAS and podocyte injury measured by Desmin staining, compared to controls. Ultrastructure analysis revealed reduced podocyte effacement, and improved glomerular basement membrane thickness in miR-93 induced mice compared to controls. Restoring miR-93 expression via miR-93 mimics delivery in diabetic mice rescued the DN phenotype in a similar fashion. RNA-Seq and DNase-Seq analysis revealed a previously unrecognized role for miR-93 as regulator of chromatin dynamics through a novel target in DN, Msx2.

**Conclusions:** Our data suggest that miR-93 is a critical metabolic/epigenetic switch in the diabetic environment linking the metabolic state to chromatin remodeling through its modulatory effect on Msx2/H3S10 phosphorylation signaling pathway. We propose that low levels of miR-93, via chromatin remodeling, results in global changes to DN-related chromatin signature and transcriptome.

**FR-OR081**

**C-Reactive Protein Promotes Renal Fibrosis in Type 2 Diabetes via CD32- Smad3-mTOR Signaling Pathway**

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1Dept of Medicine & Therapeutics, Li Ka Shing Inst of Health Sciences, and Shenzhen Research Inst, The Chinese Univ of Hong Kong, Hong Kong, China.

**Background:** Increasing evidence shows that patients with type-2 diabetic nephropathy (T2DN) is associated with elevated serum levels of C-reactive protein (CRP). In this study, we tested a hypothesis that CRP may promote T2DN by impairing the mTOR pathway via the Smad3-dependent mechanism.

**Methods:** Human CRP-db/db mice and their littermate controls including db/db, db/m and CRP-db/db mice were generated by crossing db/db mice with CRP mice that overexpress human CRP. Blood fasting glucose, intraperitoneal glucose tolerance test (IPGTT), intraperitoneal insulin tolerance test (IPITT), 24-hour urinary microalbumin levels were measured every 4 weeks in groups of 8 mice over the 36-week period. To study the signaling mechanism, intraperitoneal TGF-beta3/mSmad3 and mTOR signaling were also studied in vivo and in vitro in HK-2 tubular epithelial cells.

**Results:** Compared with littermate db/db mice, CRP-db/db mice developed higher levels of blood fasting glucose and enhanced insulin resistance. This was associated with a marked increase in microalbuminuria and the development of more severe renal fibrosis in CRP-db/db mice was associated with a marked activation of TGF-beta3/mSmad3 and mTOR signaling. Further studies in cultured HK-2 TEC revealed that CRP acted through its receptor CD32 to promote high glucose-induced activation of Smad3 via both TGF-beta-dependent and NKp3/MAP kinase-crosstalk pathways, which was confirmed by the finding that addition of an neutralizing antibody against CD32 or TGF-beta1 and an inhibitor to ERK or p38 was capable of inhibiting CRP-induced Smad3 signaling. Furthermore, we also found that activated Smad3 then bound directly to mTOR as determined by a ChiP assay and stimulated fibrosis in response to CRP and high glucose, which was blocked by a Smad3 inhibitor (SIS3) and a mTOR inhibitor (rapacynin).

**Conclusions:** CRP promotes renal fibrosis in T2DN via the CD32-Smad3-mTOR signaling pathway.

**FR-OR082**

**NLRC4 Knockout Ameliorates the Development of Diabetic Nephropathy in Mice**

**Fang Ying,1 Yinghong You,2 Krohl Danesh,3 Takeyuki Nishimoto3,2**

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**Background:** Diabetic nephropathy is a growing health concern with characteristic sterile inflammation. An association of diabetic nephropathy with inflammasome activation has recently been shown, but the pathophysiological relevance of this finding remains unknown. In the current study, we aimed to study the role of NLRC4 inflammasome in the development of diabetic nephropathy in mice.

**Methods:** The expression of NLRC4 inflammasome and macrophage infiltration in renal tissues of patients with DN were detected by immunohistochemistry. Then, we used NLRC4<sup>−/−</sup> mice to test the hypothesis that diabetic nephropathy is associated with repressed NLRC4 inflammasome activation. We used the STZ-induced diabetes model, and followed the mice for up to 8 weeks. The mice were randomly divided into 3 groups: the normal control group; the wild-type diabetic group; NLRC4<sup>−/−</sup> diabetic group. After 8 weeks, serum biochemistry and urine albumin were measured. The kidneys were collected to test the macrophage by flow cytometric analysis and the renal pathology changes were observed by light microscopy. We also detected the level of IL-1β by ELISA and NLRC4 inflammasome activation by western blot. NF-KB, JNK signal transduction pathways and inflammatory cytokines in wild-type and NLRC4<sup>−/−</sup> mice were determined by western blot and real-time PCR.

**Results:** There were significantly increased NLRC4 expression and macrophage infiltration in the renal tubules and interstitium of DN patients compared with that of control patients, and the expression of NLRC4 was positive correlated with glomerular sclerosis. Inflammasome activation (caspase-1 and IL-1β) were detected in wild-type diabetic mice. Conversely, NLRC4 deficient mice were protected against diabetic nephropathy.Furthermore, inhibition of NLRC4 also suppressed NF-KB, JNK signal transduction pathways and decreased TNF-α, TGF-β and CTGF expression in STZ-diabetic mice.

**Conclusions:** Our study suggests that inhibition of NLRC4 inflammasome ameliorates the development of diabetic nephropathy in mice. Targeting the inflammasome may be a potential therapeutic approach to diabetic nephropathy.

**FR-OR083**

**Mitochondrial Lipid Overload in the Proximal Tubules Leads to Fibrosis**

**Kristian Studler, Claudia Kruger.**

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**Background:** While there is ample evidence for defective lipid metabolism in diabetes and insulin sensitive tissues, the role of lipid metabolism in renal disease is underappreciated. Mitochondrial lipid overload – overburdening β oxidation – is an important phenomenon in metabolic flexibility. This metabolic disturbance in the kidney has not been studied.

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

**Underline represents presenting author.**

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Proximal tubules almost exclusively use fat as their energy source, therefore it is important to understand what happens when they are overloaded with lipids. Tubular fibrosis seems to be a common pathway where all chronic kidney diseases culminate.

Methods: To test the relationship between mitochondrial lipid overload and tubular damage, we have developed a proximal tubule specific (GFP CRE) mouse strain lacking carboxylic anhydrase (CrAT). CrAT is responsible for the removal of excess fatty acid products from mitochondria. In its absence, incompletely oxidized fatty acids accumulate, pyruvate oxidation is compromised and a reducing environment conducive to superoxide formation created. This can lead to hydroxyl radical production which then will model lipid peroxidation. By deleting CrAT an ideal system can be created to specifically model lipid radical formation due to metabolic stress.

Results: Knockout mice developed fibrosis, protein casts and tubular injury as they aged when compared to I/R controls. This was accompanied with increased TGFβ expression, an increase in serum creatinine levels, increased expression of vimentin, collagen IV, Bax, and caspase-3. Similarly to other mice models of kidney disease, CrATGtg/- mice displayed phenotypic variations from minor to more severe injury. Kim-1 expression in CrATGtg/- mice correlated with the severity of fibrosis. Interestingly, mice also developed glomerular injury and FSGS-like lesions, suggesting tubulo-glomerular interactions when tubular mitochondria are overloaded. Challenging mice with high fat diet or uninephrectomy accelerated this phenotype.

Conclusions: Our studies suggest that mitochondrial lipid overload (deletion of CrAT) in the proximal tubules may lead to metabolic/redox disturbances and tubular apoptosis and fibrosis.

Funding: NIDDK Support

FR-OR084
Role of Neuropilin-1 in Glomerular Function and Disease Christina S. Bartlett, 1 Monika Lucyna Wnuk, 2 Vera Eremina, 1 Chengjin Li, 1 Yashpal S. Kanwar, 1 Jeffrey H. Miner, 1 Maria Pia Rastaldi, 1 Susan E. Quaggini. 1

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Background: Neuropilin-1 (NP-1), a co-receptor for a variety of growth factors (e.g. VEGF, PDGF, and TGF-b), is critical for development and patterning of vascular and nervous systems. Mesangial cells strongly express NP-1 yet the physiological relevance of this is unclear. To date, onset of proteinuria in humans following antibody blockade of NP-1 hints at the importance of NP-1 in glomerular function.

Methods: NP-1 expression was assessed by immunofluorescence in biopsy samples from normal nephrons, diabetic nephropathy (DN) and IgA nephropathy (IgAN) patients. Further investigations into the developmental function of NP-1, we analyzed mice with peripheral cell specific deletion of NP-1. Intrinsically cell behaviors affected by NP-1 were examined in primary human mesangial cultures.

Results: DN and IgAN biopsy samples have notably elevated mesangial expression of NP-1 indicating that NP-1 may have a role in glomerular dysfunction. In mice, deletion of NP-1 in the mesangium restricts glomerular maturation and causes dramatic mesangial expansion, marked GBM thickening and tubular dilatation. NP-1-deficient mutants develop severe proteinuria and succumb to renal insufficiency. In mutant glomeruli lacking NP-1 in the mesangium, VEGF/R2 phosphorylation is increased while podocyte ERK signaling is hyperactivated. In vitro, we showed that NP-1 mediates directed migration of mesangial cells towards PDGFβ. Inducible gene targeting of NP-1 is currently underway to delineate developmental versus maintenance functions of NP-1 in the glomerulus particularly within the context of DN.

Conclusions: NP-1 expression in the mesangium is needed for glomerular development. NP-1 regulates matrix production and its absence compromises glomerular filtration. Increased expression of NP-1 in DN and IgAN further suggests that glomerular function relies on a finely tuned balance of NP-1 signaling. Accordingly, NP-1 may be suitable as targets to ameliorate glomerular disease.

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FR-OR085
Protein S Protects Podocyte from Injury in Early Diabetic Nephropathy Fang Zhong, 1, 2 Kim Lee, 1 John C. He, 1

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Background: Elucidating mechanisms that mediate the early stage of diabetic nephropathy (DN) may help us identify novel preventive and therapeutic measures for patients with DN. Protein S (PS), a vitamin K-dependent protein, functions mainly as a cofactor for the formation of activated protein C (APC). APC is known to have podocyte protective effects in DN. However, the role of PS in DN has not been studied.

Methods: Proteomic analysis was performed in glomeruli isolated from STZ- and control rats. The podocyte cell-specific Prox1 homogenus knockout mice (KO) were developed to determine the role of PS in DN. Immortalized human podocytes (HPC) were used for in vitro studies. The expression of TMA receptors and podocyte-specific genes were examined by western blot and RT-PCR. The Protein S expression was examined in human kidney biopsies by immunostaining.

Results: Proteomic analysis of glomeruli revealed higher expression of PS in diabetic glomeruli. Then, we confirmed an increase of PS expression in the glomeruli of diabetic rats by RT-PCR and immunostaining. Interestingly, PS expression also increased in human kidneys with early DN but decreased in those with advanced DN. As a control, plasma concentrations of PS were not significantly different between diabetic and non-diabetic rats.

Conclusions: The findings in diabetic KO mice were more pronounced than in rats. In this study, we determined the role of PS in the development of diabetic kidney, we determined the role of PS in cultured human podocytes. We found that Knockdown of Prox1 enhanced high glucose-induced apoptosis while overexpression of Prox1 inhibited TNF-α-induced pro-inflammatory gene expression in podocytes likely through modulation of the TMA receptors. To further determine the role of PS in DN, we developed podocyte-specific Prox1 knockout mice (KO) and found that diabetic KO mice (KO-STZ) developed more proteinuria, mesangial expansion, and foot process effacement than diabetic wide-type mice (WT-STZ).

Funding: Our data support a protective role of PS against podocyte injury in early DN.

Funding: Other NIH Support - NIH R01DK078897, NIH R01DK088541, NIH P01-DK-56492

FR-OR086
Deletion of SHP-1 in Podocytes Prevents Diabetic Nephropathy Farah Lizotte, Benoît Denhez, Andréanne Guay, Pedro Miguel Geraldes. Medicine, Univ of Sherbrooke, Sherbrooke, QC, Canada.

Background: Both clinical and experimental data suggest that podocyte injury is involved in progression of diabetic nephropathy (DN) in the patients with type 1 diabetes. Although the mechanisms underlying the development of podocyte loss are not completely understood, insulin and neprilysin actions have been shown to play a major role in the podocyte survival and function. We have reported that SHP-1, a protein tyrosine phosphatase, is increased in podocytes of diabetic mice and inhibited insulin and neprilysin actions. However, the precise role of SHP-1 in the development of diabetic nephropathy remains to be investigated.

Methods: We have generated a non-diabetic (NDM) and diabetic Akita (DM; Ins2ΔC95Y) conditional podocyte specific SHP-1 knockout (podo-SHP-1KO) mice using the TetON-Cre fox system. Mice received or not dietoxin at 4 weeks of age and renal function (albuminuria and GFR) and pathology were examined at 7 months of age.

Results: Elevated albumin/creatinine ratio and GFR showed in DM mice are prevented by 86% and 100%, respectively in DM mice that lack SHP-1 gene specifically in podocytes. Mesangial cell expansion and glomerular hypertrophy is increased by 1.8 and 4.9 fold in DM mice and reduced by 78% and 72%, respectively in DM podo-SHP-1KO mice. Moreover, the expression of collagen type IV and TGF-β that is enhanced in DM mice compared to NDM was not increased in DM podo-SHP-1KO mice. Transmission electron microscopy analysis demonstrated podocyte foot process effacement in DM mice that is not observed in DM podo-SHP-1KO mice. Furthermore, inhibition of insulin-induced Akt and ERK phosphorylation showed in DM mice is completely prevented in DM podo-SHP-1KO mice. Similar to insulin, neprilisin phosphorylation is restored in DM podo-SHP-1KO mice compared to DM mice.

Conclusions: Our data indicate that the deletion of SHP-1 specifically in podocytes restored insulin and neprilysin actions and prevented renal pathology and dysfunction in diabetic mice.

Funding: Government Support - Non-U.S.

FR-OR087
Targeted Proximal Tubule Injury Promotes Progression of Diabetic Kidney Disease in Akita Mice Jae Hyung Chang, Takaharu Ichimura, Venkata Sabbisetti, Joseph V. Bonventre. Renal Div, Dept of Medicine, Brigham and Women’s Hospital, Boston, MA.

Background: Increasing evidence suggests that the kidney tubulointerstitial injury plays an important primary role in the pathophysiology of diabetes.

Methods: In the present studies, a mouse containing several epithelial cell-specific Sic2Cre allele was crossed with a mouse transgenic for a Cre-inducible simian diphtheria toxin receptor (DTR). The bигическое mouse was then bred with Akita mice as a genetic model of type 1 diabetes. Targeted tubule injury was induced in these animals (Akita DTRcre+/*;prox1-DTRcre+/*)) with injection of diphtheria toxin (DT).

Results: Male Akita mice developed sustained hyperglycemia. A single sublethal dose of DT in Akita DTRcre+/* mice resulted in a acute two-fold rise in urinary albumin excretion and progression of albuminuria over the study period. By 9 weeks after DT injection, Akita DTRcre+/* mice developed an almost five-fold increase in albuminuria, 40% increase in serum creatinine and 2-fold increase in blood urea nitrogen (BUN) level, and reduced kidney size when compared with Akita controls. Moderate glomerular mesangial expansion, and increased interstitial fibrosis and tubular atrophy (IFTA) and glomerulosclerosis was observed in Akita DTRcre+/* mice 20 weeks after DT injection. These pathologic changes were accompanied by increased levels of the major cytokine of proximal tubule injury, kidney injury molecule (KIM)-1, in both kidneys and urines of Akita DTRcre+/* animals. Increased proximal tubule DNA damage response (DDR) activation, pro-inflammatory and pro-fibrotic cells infiltration, and peritubular capillary rarefaction were observed in kidneys of DTR treated Akita DTRcre+/* mice.

Conclusions: In diabetes, proximal tubule injury, perhaps from glycosotins, can drive interstitial inflammation and fibrosis, capillary rarefaction, and secondary glomerular injury leading to progression of diabetic nephropathy. Our findings suggest novel therapeutic targets for the prevention and treatment of diabetic kidney disease.

Funding: Private Foundation Support

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Underline represents presenting author.

53A
FR-OR088

Wnt11 Signals from the Ureteric Bud Direct Organization of the Nephron Progenitor Niche Determining Nephron Endowment

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Background: Normal nephron endowment requires a balance of nephron progenitor (NP) self-renewal and differentiation during kidney development. Wnt11, a non-canonical Wnt signal produced by ureteric tip (UT), has been shown to positively regulate the Gdnf- Ret signaling axis and branching morphogenesis. Our current data identifies a new role for Wnt11 in organization of the NP niche.

Results: Wnt11+ NP cells are normally tightly associated with the UT, separating adjacent Foxd1+ interstitial progenitors from the UT. In Wnt11 mutants, inter-niche boundaries become less distinct and Six2+ and Foxd1+ cells intermix. RNA-seq of whole kidneys revealed minimal transcriptional changes within NPs suggesting Wnt11 primarily regulates cell behavior, as expected for a non-canonical Wnt. Single cell analysis of NPs in vivo and live imaging of kidney organ cultures shows that NPs normally make extensive membranous contacts with UTs. Long membrane projections extend to the UT from NPs that form layers above the UT. In contrast, NPs in Wnt11 mutants fail to exhibit elongated UT-directed membrane extensions. Wnt signal through Frizzled(Fzd) receptors: Fzd2 and Fzd7 are co-expressed within NPs. Fzd2-/−/−;Fzd7-/−/− mutants display a similar disorganization of the NPs, suggesting these two receptors likely mediate the non-canonical Wnt11 response.

Conclusion: Taken together, these data highlight the importance of non-canonical Wnt11 signals in maintaining NP behavior, and appropriate stratification and organization of distinct mesenchymal compartments in the UT niche, a prerequisite for generating a normal nephron complement in the developing mammalian kidney.

Funding: NIDDK Support, Private Foundation Support

FR-OR089

Bim Gene Dosage Is Critical in Modulating Nephron Progenitor Survival in the Absence of Dicer Activity During Kidney Development

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Background: We have previously demonstrated that conditional depletion of the miRNA-processing enzyme, Dicer, in nephron progenitors results in increased apoptosis and premature depletion of this cell population during kidney development. This is accompanied by increased expression of the pro-apoptotic protein, Bim.

Methods: To determine the functional significance of increased Bim, we generated a mouse model with depletion of both Bim and Dicer from nephron progenitors in the developing kidney. To this end, Six2-TGCre; Bimflx/flx mice were crossed with a conditionally floxed Bim allele generating the following genotypes: Six2-TGCre; Bim−/−; Dicer−/− (control), Six2-TGCre; Bim−/−; Dicer−/−; Bim−/− (mutant), Six2-TGCre; Bim−/−; Dicer−/−; Bim−/− (heterozygous rescue) and Six2-TGCre; Bim−/−; Dicer−/−; Bim−/− (homozygous rescue).

Results: Depleting the gene dosage of the number of nephron progenitors and improved nephron formation in Dicer-deficient kidneys. At the molecular level, the expression of the most abundant isoform of Bim (BimL), was increased, while the levels of the pro-survival protein Bcl-2 were reduced in mutant compared to control kidneys.

Conclusions: Together these data provide evidence for a model in which miRNA-mediated regulation of Bim controls the balance between apoptosis and survival during nephrogenesis, as one potential means of regulating nephron number.

Funding: NIDDK Support

FR-OR090

DGCR8-Dependent MicroRNA Biogenesis Is Essential to the Function of Pax8-Positive Epithelial Organs

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Background: miRNAs are small regulatory RNA molecules that have been shown to play an important role in physiology, development and function of many organs. As most organs our knowledge on the role of miRNAs depends on the use of Dicer-knockout models with this enzyme being a key component of the miRNA biogenesis machinery. However, the vast majority of these studies fulfill a number of other functions beyond the maturation of miRNAs. Furthermore a number of these small RNAs does not depend on Dicer in its maturation. Consequently, the phenotypes observed might well be due to miRNA-independent functions of Dicer.

Methods: We examined mice harboring a conditional knockout allele of Dgcr8. Dgcr8−/− mice show a strong increase in both cellular proliferation and apoptosis. Furthermore we did not reach a common dose and therefore lack confirmation that the phenotype observed is truly due to miRNA deficiency.

Results: The knockout mice develop a cystic kidney disease and hydropnephrosis. End-stage renal disease occurs by the age of 4-8 weeks. On the cellular level this phenotype is characterized by a strong increase in both cellular proliferation and apoptosis. Furthermore we did not reach a common dose and therefore lack confirmation that the phenotype observed is truly due to miRNA deficiency.

Conclusion: Together these data provides evidence for a model in which DGCR8-dependent miRNA biogenesis for both renal and thyroid function and can thus be the basis to future experiments addressing the role of specific microRNA sequences. Nonetheless, some aspects of the phenotype differ from the Dicer knockout model pointing towards miRNA-independent contributions of Dicer and Dgcr8 regarding the pathogenesis of these two organs in our mouse model.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR091

Oxygenation and Von Hippel-Lindau Regulate Nephron Progenitor Differentiation

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Background: During development, oxygenation plays a crucial role in kidney formation. Nephron progenitor (NP) differentiation is highly dependent on appropriate vasculature and subsequently oxygen concentration. Alterations in nephron differentiation lead to kidney malformations. The unperfused NP are hypoxic, which activates a hypoxia inducible factors (HIFs). The HIF gene are potential factors involved in tissue differentiation. Upon oxygenation the Von Hippel-Lindau gene (VHL), degrades the HIFs and allows for tissue differentiation. We previously showed in vitro that oxygenation drives NP differentiation. Thus, we hypothesize that stabilization of HIFs in the NP will cause congenital kidney defects.

Methods: To determine the role of VHL in the NP we utilized VHL floxed mice bred with the Six/TGPFcre line, to generate Six2creVHllox/−/− mutant mice. We performed a thorough histological assessment from early kidney development through to post natal ages. We coupled this with immunofluorescence (IF) and western blot analysis to analyze VHL and HIF expression.

Results: Histology revealed that Six2creVHllox/−/− mutant mice were underdeveloped from E11.5, with fewer differentiated NP derived structures. Postnatal mutant kidneys displayed significant pathology containing fewer nephrons, cystic tubules and proteinaceous casts. The mutant kidneys contained fewer proximal tubules, and remaining tubules were dilated. The mutant animals failed to thrive and were significantly smaller at weaning. IHC staining revealed a down regulation of VHL in the mutants coupled with an up-regulation of HIF1α in the NP, which was confirmed via western blot analysis. IF staining of mutant embryonic kidneys showed a delay in NP differentiation with ectopic Six2 remaining highly expressed in NCAM positive epithelialized structures of mutants.

Conclusions: In conclusion, VHL is critical in the NP to regulate the expression of HIFs. Inappropriate up regulation of HIFs causes alterations in NP differentiation, leading to kidney malformations.

FR-OR092

Interplay Between the Tbx2a and Tbx2a/b Transcription Factors and Notch Signaling Directs Nephron Segmentation

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Background: Nephron segment patterning remains an enigmatic process. The conservation of nephron segments across vertebrates enables insights acquired through work with animal models, and among these the zebrafish provides a simple system for developmental genetic studies of nephrogenesis. Zebrafish nephrons contain proximal and distal tubule segments, and the endothelial cells that encapsulate these tubule segments (the intermediate mesoderm) are situated between the distal tubule segments.

Methods: Here, we show that the T-box gene Tbx2a (tbx2a/b) orthologs are spatially restricted to the distal IM. Tbx2a and Tbx2b single and doubly deficient embryos, as well as tbx2a/b mutants, exhibited a modest expansion in the proximal segments accompanied by a reduction in the distal nephron, indicating that these genes have redundant roles in segment patterning.

Results: Abrogation of tbx2a/b expression was also associated with significantly expanded CS structures, coincident with increased expression of sim1a, a transcription factor that was recently demonstrated to be necessary and sufficient for CS formation. Further, we identified expression of the Notch pathway component her5 in the developing CS. In contrast, the expression between tbx2a and Notch, DAPT treatment was found to cause a moderate CS expansion in wildtypes, while DAPT induced further enlarged CS formation. In tbx2a/b deficient embryos, ectopic activation of Notch signaling in Tbx2a/b+/−/+4A4-UAS:NICD led to a reduced CS in wildtypes but not tbx2a/b deficient embryos, suggesting the tbx2a/b genes function downstream of Notch to inhibit the CS. In addition, ectopic Notch expression proximal tubule segments at the expense of distal, reducing tbx2 expression downstream and therefore suggesting that Notch promotes proximal segments in part by inhibiting tbx2 expression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only; Underline represents presenting author.
Critical Role of Talin in Cell-Cell Adhesion and Kidney Development

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Background: Interactions between cells and basement membranes are required for normal kidney development and function. These interactions are primarily mediated by the major cell surface integrin receptor protein integrins. Integrins are composed by α and β subunits and have two important functions: ligand binding and regulation of the cytoskeleton. The cytoskeletal protein, talin, is a key regulator of integrin function. Talin binds to and mediates the recruitment of integrins to focal adhesions and is required for the proper development of the kidney.

Methods: To determine the lineage of origin of the HCN3 (+) cells, we genetically labeled two different reporter mouse lines (Tg [msx2-GFP/GFP] and Tg [mrt-R26RLa1/2]) expressing GFP or R26RLa1/2 reporter mice were subjected to conditional lineage analysis identified DNp63 + cells as the progenitors of the HCN3 (+) cells.

Results: HCN3 (+) pacemaker cells (PMCs) in the pelvis-kidney junction (PKJ) were isolated using HCN3 antibodies and fluorescence activated cell sorting (FACS). These cells co-localized with HCN3 in the PKJ, demonstrating that HCN3 (+) PMCs arise from the metanephric mesenchyme, ureteric bud or renal stroma.

Conclusions: The pacemaker cells that generate intrinsic rhythmic activity in the bladder and ureteral musculature are derived from the metanephric mesenchyme.
Further outlining the NC origin of these cells. Analysis of isolated PTCs, compared to adjacent cells in the PKI, via RNA sequencing, revealed a 3-7-fold upregulation of genes associated with neuronal function.

**Conclusions:** We conclude that HCNC(+) urinary PTCs arise from the NC and express genes associated with neuronal function. These results provide a basis to identify molecular mechanisms that control PTC development.

**Funding:** Government Support - Non-U.S., Private Foundation Support

**FR-OR100**

**Tubular Regeneration After Acute Kidney Injury Is Limited and Only Driven by Tubular Progenitors**

**Elena Lazzeri,** Anna Julie Peired, Maria Lucia Angelotti, Francesca Becherucci, Duccio Lombardi, Laura Lasagni, Paola Romagnani. **Excellence Centre DENO TH, Univ of Florence, Italy.**

**Background:** Traditionally, AKI was considered as reversible because of the high regenerative capacity of the tubule. Despite this, AKI is associated with increased risk to develop CKD, suggesting an incomplete repair of the tubules. In addition, it is debated whether regeneration is mediated by differentiated tubular cells or a population of tubular progenitors.

**Methods:** We developed inducible transgenic Pax2–RtaA/tetO-cre/ROSA26-Confetti (Pax2/Confetti) mice to track all tubular cells and the Pax2xRtaA/tetO-cre/R26:Confetti mouse model (Pax2/Confetti) to track putative tubular progenitors. Administration of doxycycline at the 5th week of age drove the stochastic expression at single cell level of CFP, GFP, RFP, YFP, allowing to track Pax2+ or Pax8+ cells and their progeny. After 1 week of washout, mice underwent 30 min of unilateral ischemia followed by a 30 day repertition period. Tubules were collected, fixed and stained with CFP (Pax2/Fucci2) and Pax2xRtaA/ cre:R26:Fucci2 (Pax2/Fucci2) mouse models were used to study cell cycle (mCherry in G1 cells and mVenus in S/G2/M cells).

**Results:** Comparison of cholangiography in confetti mice demonstrated that Pax2+ progenitors is the only population that undergoes clonal expansion after tubular injury, excluding involvement of other tubular cells. However, regeneration was limited, and the majority of lost tubular cells was not replaced. In addition, confocal microscopy and DNA content analysis by flow cytometry in Pax8 and Pax2/Fucci2 mouse models demonstrated that only Pax2+ progenitors complete mitosis, while other tubular cells that entered the cell cycle do not complete cytokinesis and undergo death or growth arrest.

**Conclusions:** In summary: 1. The tubule displays limited regenerative capacity; 2. Differentiated tubular cells enter the cycle but do not complete mitosis; 3. Only tubular progenitors undergo a complete cell division providing regeneration after injury. Taken together, these results provide an innovative explanation of the mechanisms of tubular repair and a suggestive hypothesis to explain the occurrence of CKD after AKI.

**Funding:** Private Foundation Support

**FR-OR102**

**Early Activation of Fibroblasts Is Required for Renal Protection and Regeneration After Acute Kidney Injury**

**Dong Zhou,** Haiyan Fu, Roderick J. Tan, Youhua Liu. **1** Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; **2** Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

**Background:** Acute kidney injury (AKI) is responsible for about 2 million deaths each year worldwide, and its incidence is rising. While the role of vascular, tubular and interstitial inflammatory injury in the pathogenesis of AKI is elucidated, whether interstitial fibroblasts play any role in this process is poorly characterized.

**Results:** These results show that SS-31 can halt the progression of chronic kidney disease even when administered 4 weeks after the acute ischemic injury. SS-31® prevents progression of Chronic Kidney Injury After Acute Ischemia (Bendavia® Prevents Progression of Chronic Kidney Injury After Acute Ischemia)(Hazel H. Szeto, Shaoyi Liu, Yi Soong, Surya V. Seshan. *Pharmacology and Pathology, Well Cornell Medical College, New York, NY.*

**Conclusions:** It has been demonstrated that about 15% of patients who survive acute kidney injury (AKI) will advance to chronic kidney disease (CKD) characterized by tubulointerstitial fibrosis and glomerulosclerosis. We recently reported that mitochondria protection by SS-31 during ischemia mitigates microvascular rarefaction, inflammation and fibrosis (Am J Physiol 306:F970-F980, 2014). Here we report that delayed treatment with SS-31 can halt the progression of CKD.

**Methods:** Sprague-Dawley rats (n=40) were subjected to bilateral renal ischemia for 45 min followed by 4 weeks of recovery. Surviving animals (n=27) were then randomized to SS-31 (2 mg/kg/day) or saline by osmotic pump for 6 weeks. Kidneys were harvested for histopathology. Sham animals did not undergo ischemia.

**Results:** Despite recovery of renal function within 1 week after ischemia, pronounced tubulointerstitial fibrosis, interstitial inflammation, glomerulosclerosis, and tubulointerstitial fibrosis was seen at 4 weeks. Further increase in inflammation and fibrosis, accompanied by increase in TGFB and TNFα, were observed by 10 weeks in saline-treated rats. Pronounced changes were observed in glomeruli, with extensive fibrosis and peri-glomerular infiltration of inflammatory cells. Glomerular endothelial injury is suggested by the large increase in vWF expression. Electron microscopy revealed stressed vacuoles in podocytes and flattened foot processes. Rats that were treated with SS-31 from 4 weeks did not show any progression of glomerular or tubular injury, and prevented the upregulation of TGFB and TNFα.

**Funding:** Private Foundation Support

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

**Funding:** Government Support - Non-U.S., Private Foundation Support.
**Methods:** To address this issue, we established moderate (20 min) and severe (30 min) renal ischemia/reperfusion (IRI) models. Sonic hedgehog (Shh) signaling was rapidly induced at 1 hour after IRI and Shh induced fibroblast activation and proliferation. The effectiveness of CP-690550 was confirmed by decreased p-STAT3 levels 6 min after IRI and Shh induced fibroblast activation and injury repair, we generated tubule-specific Shh conditional knockout mice (Ksp-Shh−/−) by mating Shh−/− mice with Ksp-Cre mice. Mice with ablation of Shh in renal tubules exhibited normal phenotype under physiological conditions, but displayed an increased level of serum creatinine and morphological injury at 1 day after IRI, compared with controls. This agitated AKI in Ksp-Shh−/− mice was associated with a decreased vimentin and desmin expression, suggesting a beneficial role of fibroblast activation in this setting. Similarly, pharmacological blockade of Shh signaling by cyclopamine also aggravated serum creatinine and histological damages through inhibiting fibroblasts proliferation.

**Conclusions:** These studies suggest that fibroblast activation is an early event mediated by Shh signaling and plays an essential role in conferring renal-protection and injury repair in the setting of AKI.

**Funding:** NIDDK Support

**FR-OR105**

**Endothelial Sphingosine-1-Phosphate Receptor 1 (S1P1) Is Necessary for Recovery from Acute Kidney Injury (IRI) and Prevention of Fibrosis**

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**Background:** Fibrosis after AKI may result from maladaptive repair processes and can potentiate kidney dysfunction. The endothelium is the keystone of vascular homeostasis and vascular scaffolding after AKI may result in progressive fibrosis. S1P1, a G-protein coupled receptor, is important for endothelial function and we previously demonstrated that endothelial cell (EC) S1P1 is necessary for recovery from AKI and prevention of fibrosis.

**Methods:** Tamoxifen inducible, EC specific, S1P1 knockout mice (Tie2CreERT2S1P1floxflox/flox; S1P1Cre) or control (Tie2CreERT2S1P1floxflox/flox) were subject to unilateral IRI or sham operation for 24 hours and were allowed to recover for 3 days. Tamoxifen was then administered i.p. daily for 5d followed by a nephrectomy of the un-operated kidney and mice were euthanized on day 9. Plasmas were collected for creatinine (Cr) measurement and kidneys were prepared for histology to assess renal injury, fibrosis, by picro-sirus red, detection of αSMA+PDGFRβ+ myofibroblasts by IF, and neutrophils and macrophages by flow cytometry. Total kidney tissue mRNA was measured by RT-qPCR.

**Results:** S1P1−/− mice had higher Cr levels compared to control mice (1.24 vs. 0.18 mg/dl; p < 0.001 n = 5–6) on day 9 post IRI. S1P1 ECKO mice had increased tubular atrophy, a higher proportion of fibrotic area in the medulla and cortex (1.57 vs. 0.68% p < 0.05 n = 4–5), and increased density of interstitial myofibroblasts expressing COL1 and COL3 in IRI kidneys compared to controls. Leukocyte adhesion molecules Pecam-1, Icaml, E-selectin, and Vcam1 expression and the number of neutrophils and Ly6Clo macrophages were increased in IRI kidneys of S1P1 ECKO mice compared to control mice. 

**Conclusions:** During recovery from IRI, S1P1 suppresses endothelial cell activation of leukocyte adhesion molecules and subsequent inflammation to prevent maladaptive repair and tubular injury in protection against fibrosis. This data suggests that pharmacological activation of S1P1 and the preservation of EC function during a critical period of recovery after AKI may prevent the progression to fibrosis.

**Funding:** NIDDK Support

**FR-OR104**

**IL-4/13-Mediated Polarization and Proliferation of Renal Macrophages Are Essential for Recovery from Acute Kidney Injury**

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**Background:** Cytokines IL-4 and IL-13 play important roles in polarization of macrophages/dendritic cells to a M2 phenotype, which is important in the recovery process following acute kidney injury (AKI). Both IL-4 and IL-13 can activate JAK3/STAT6 signaling.

**Methods:** Mice with selective DTR expression in proximal tubule (“DTR mice”) were generated. Pericyte Ablation Leads to Acute Kidney Failure

Dario R. Lemos,1 Gabriela Campanholle,2 Ivan G. Gomez,3 Jeremy Stuart Duffield.1 Molecular Discovery, Biogen; Pfizer.

**Background:** Pericytes (PCs) are tissue-resident mesenchymal progenitor cells embedded within the basement membrane of blood vessels. We recently showed that during nephrogenesis pericytes are critical in both vascular and epithelial maturation and patterning. Those data indicate that PCs are important for the maintenance of kidney homeostasis postnatally.

**Methods:** Dipheria toxin was delivered in vivo, via intraperitoneal injection. Kidneys were collected and preserved for histology. Urine albumin was measured using Albuwell M kit (Roche Diagnostica, PA). Urine and plasma creatinine levels were measured using creatinine Liquid reagents Assay (DIAZYMEX, San Diego, CA). Plasma albumin was measured using a Olympus au640 Chemistry Analyzer. Gene expression was measured by Taqman PCR, using pre-made assays (Life Technologies, Palo Alto, CA).

**Results:** PDGFβR+ pericytes present in the adult kidney derive from FoxD1+ mesenchymal progenitor cells. Here we created a FoxD1-Cre;R26;−iDTR mouse model to study the effect of pericyte ablation in kidney homeostasis. We observed virtually complete depletion of PDGFβR+ cells in the kidney, compared to the control group, after two days of daily intraperitoneal dipheria toxin (DT) delivery without detectable variations in podocyte numbers or glomerular structure. Significant decrease in vascular density, increased vascular cell proliferation and endothelial swelling was detected. This was associated with aberrant vasoconstriction, lipid accumulation, and injury of the proximal tubule epithelial cell dysfunction. These observations were supported by finding elevated levels of plasma creatinine, blood urea nitrogen and albuminuria, markers of organ failure. Mice lacking pericytes progressed to rapid health deterioration and death by three days. Importantly, neither the number of macrophages nor the levels of inflammatory cytokines changed significantly during the treatment, ruling out a role for inflammation-induced damage as the cause for progressive loss of kidney integrity.

**Conclusions:** Our data show that by supporting homeostasis, pericytes are essential for proper kidney function.

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

Underline represents presenting author.

57A
FR-OR107
Preferential Proliferation in Response to Injury by an Interstitial-Derived Collecting Duct Subpopulation
Joan Li, Jinjin Guo, Jill A. McMahan, Andrew P. McMahan, Melissa H. Little.1,34 1Univ of Queensland, Brisbane, QLD, Australia; 2Keck School of Medicine of the Univ of Southern California, Los Angeles, CA; 3Murdoch Childrens Research Inst, Melbourne, VIC, Australia; 3Univ of Melbourne, Melbourne, VIC, Australia; 4Univ of Southern California Keck School of Medicine, Los Angeles, CA.

Background: We have reported the incorporation of Wnt4-expressing interstitial cells into the developing collecting duct (CD) during early postnatal development. These cells, representing a distinct CD subpopulation, may play a specific role in CD repair.

Methods: Time-mated Wnt4+/-; R26tdTomato females received Tamoxifen injection (25mg/kg bw) at E17.5. Male offspring (8-12 wks) were subjected to Unilateral Ureteral Obstruction (UUO) for 3 or 7 days. Mice were euthanized 3 or 7 days after UUO. Kidneys were collected and processed for immunofluorescence studies. Confocal images were analyzed and quantified using Imaris software.

Results: At 7 days after UUO the cortical CDs were severely dilated. This was accompanied by down-regulation and misdistribution of Aqp2 protein as well as up-regulation of Wnt4 expression. An interstitial-derived, Wnt4 expressing cell population was identified which comprised 20% of cortical CD cells present at E17.5. At 7 days after UUO the percentage of Tdtomato+ cells within the CD increased significantly compared to control (37% vs 14%, p= 0.0001), while pHH3 + cells increased significantly compared to control (37% vs 14%, p=0.00001). The number of Tdtomato+ cells within the CD and the proliferation rate of those CD cells were not significantly different at 3 days after UUO compared to control.

Conclusions: In response to UUO damage, CD epithelial cell turnover is augmented by the incorporation of Wnt4 expressing interstitial cells into the developing CDs. This provides further evidence supporting the importance of reduced eGFR in mediating the acid retention.

FR-OR108
Net Acid Excretion and Progression of CKD: Results from the Chronic Renal Insufficiency Cohort Study
Julia J. Scialla,1 John R. Aspinl,2 Mirela A. Dobre,3 Alex R. Chang,3 James P. Lash,4 Chi-yan Hsu,5 Radhakrishna Reddy Kallem,6 L. Lee Hamm,7 Harold I. Feldman,1 Jing Chen,7 Lawrence J. Appel,8 Cheryl A. Anderson,6 Myes S. Wolf,9 1Duke Univ; 2Litholik Corp; 3Case Western Reserve; 4Geisinger Health System; 5Univ of Illinois Chicago; 6Univ of California San Francisco; 7Tulane Univ; 8Johns Hopkins Univ; 9Univ of California San Diego; 10Northwestern Univ.

Background: Higher diet-dependent acid load has been associated with faster CKD progression, but not using gold-standard measurements [net acid excretion (NAE)].

Methods: We measured NAE in 24 urines from 1000 CKD participants as urinary ammonia + titratable acid (calculated from urinary phosphorus, creatinine and pH). Urinary bicarbonate (HCO3-) was negligible. 19 samples with urine pH ≥7.4 were excluded. Urinary creatinine and phosphorus (P) were used to calculate net endogenous acid production (NEAP), as previously published. We modeled risk of ESRD or 50% reduction in GFR (NGF-230 events) over a median of 5 years using Cox models with stratification by diabetes (DM).

Results: Higher NAE associated with greater intake of meat/fish/poultry and calories by questionnaires (each p<0.01) and independently with higher NEAP (p<0.01) and lower serum HCO3- (p=0.01). Higher NEAP associated with lower fruits and vegetables (p<0.01), but not meat/fish/poultry (p=0.7) or calories (p=0.2). Higher NEAP independently associated with lower HCO3- (p<0.01) but not eGFR (p=0.8). Unexpectedly, higher NEAP associated with lower fruits and vegetables (p<0.01), but not meat/fish/poultry (p=0.7) or calories (p=0.2). Higher NEAP independently associated with lower HCO3- (p<0.01) but not eGFR (p=0.8). Unexpectedly, higher NEAP associated with lower fruits and vegetables (p<0.01), but not meat/fish/poultry (p=0.7) or calories (p=0.2).

Conclusions: Higher NAE, but not NEAP, associated with lower risk of renal events in CKD. This risk may be due to changes in renal ammoniagenesis, particularly in diabetic CKD. Funding: NIDDK Support.
FR-OR11

Urinary Sodium and Potassium Excretion and Risk of Developing Chronic Kidney Disease
Lyanne M. Kieneker,1 Ron T. Gansevoort,2 Rudolf A. de Boer,2 Gerjan Navis,3 Stephan J.L. Bakker,1,4 Michel M. Joosten.1 1 Internal Medicine, Nephrology, UMC Groningen, Netherlands; 2 Cardiology, UMC Groningen, Netherlands.

Background: It is unclear whether urinary sodium and potassium intake are relevant to the development of chronic kidney disease (CKD) in the general population. Our aim was to examine the associations of urinary sodium and potassium excretion (UNaV and UKV resp.), as estimates of intake, with risk of developing CKD in the general population.

Methods: We studied 5,315 subjects free of CKD at baseline of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study; a prospective, population-based cohort of Dutch men and women aged 28-75 years. UNaV and UKV were measured in two 24-hour urine specimens at baseline (1997-1998) and midway during follow-up (2001-2003). Incident CKD was defined as de novo development of creatinine or cystatin C-based estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2 and/or albuminuria >30 mg/24h.

Results: Baseline UNaV and UKV were 135 mmol/24h (interquartile range [IQR]: 106-169 mmol/24h) and 70 mmol/24h (IQR: 57-85 mmol/24h), respectively. During a median follow-up of 10.3 years (IQR: 6.2-11.4 years), 872 subjects developed CKD. After multivariable adjustment for important covariates, no association was observed between UNaV and risk of CKD (hazard ratio per 50 mmol/24h decrease [1 standard deviation], 1.03; 95% confidence interval, 0.93-1.13). Each 21 mmol/24h (1 standard deviation) decrement in UKV was significantly associated with a 16% higher risk of developing CKD (multivariable adjusted hazard ratio, 1.16; 95% confidence interval, 1.05-1.29; Figure 1). Sensitivity analyses in which CKD was defined by either eGFR or albuminuria alone, rendered essentially similar results.

Conclusions: Low potassium intake and not high sodium intake was associated with an increased risk of developing CKD in the general population.

Funding: Private Foundation Support

FR-OR112

Sedentary Behavior as a Risk Factor for CKD
Dominique Ferrante,1 Kate Lyden,1 Xiaoru Chen,1 Robert E. Boucher,1 G. Wei,1 Srinivasa Bedhu,1,2 ‘U of Utah; 1 VA SLC; 2 UC Denver.

Background: Sedentary behavior (engaging in activities in the seated or lying position) that barely raise the energy expenditure above resting level is commonly confused with physical inactivity (lack of moderate/vigorous physical activity (MVPA)). Sedentary behavior is an important risk factor for DM, HTN and obesity. It is unclear whether sedentary behavior is an independent risk factor for CKD. Therefore, we examined this in 5873 participants in whom intensity and duration of physical activities were measured objectively with an Actigraph accelerometer in the 2003-2006 National Health & Nutrition Examination Survey (NHANES) data.

Methods: Based on the number of counts/min recorded, sedentary (<100/min) and moderate/vigorous (~2000/min) activity durations were defined and normalized to 60 min. Logistic regression models adjusted for age, gender, race, education, smoking, alcohol use, lung disease and mobility limitations were used to examine the associations of sedentary and MVPA durations with the presence of CKD (defined as CKD-EPI eGFR <60 ml/min/1.73 m2).

Results: The mean age was 49 ± 13 yrs. 52% were women and 9.5% were black. 7.4% had CKD. The mean sedentary duration was 34.0 ± 5.6 min/hr. MVPA duration was highly skewed with median (25th - 75th percentile) of 1.2 (0.5 - 2.3) min/hr. Prevalence of CKD by sedentary and MVPA durations are summarized in the figure.

Conclusions: Metabolically healthy obesity is associated with eGFR decline >= 30% but not kidney failure.

Funding: Private Foundation Support

FR-OR113

The Metabolically Healthy Obesity Phenotype and Risk of Incident Kidney Failure
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Background: Little data exist on the association between obesity in the absence of metabolic abnormalities (metabolically healthy obesity) and renal outcomes.

Methods: Using data from 86,004 patients in the Geisinger Health System from 2004-2014, we examined the risk of kidney failure (dialysis, transplant, or eGFR <15 ml/min/1.73m2) and eGFR decline ≥30% by categories of body mass index (normal 18.5-24.9, overweight 25-29.9, obesity ≥30) and metabolic health (<2 of the following: triglycerides ≥150, HDL cholesterol <40 in men, <50 in women, blood pressure ≥130/85, and glucose ≥100). Cox regression analyses were adjusted for demographics, smoking status, history of cardiovascular disease, and baseline eGFR.

Results: Only 10.6% of patients had normal BMI with 30.0% overweight, and 54.3% obese. Proportions of metabolically healthy individuals in normal, overweight, and obesity groups were 67.9%, 30.0%, and 20.0%, respectively. Over a median follow-up time of 6.0 years, 1,376 patients developed kidney failure and 17,668 developed eGFR decline ≥30%. Compared to metabolically healthy persons of normal BMI, metabolically healthy overweight and obese individuals had similar or lower risk for ESRD (overweight HR 0.75, 95% CI: 0.47-1.19; obese HR 0.77, 95% CI: 0.48-1.25). When examining eGFR decline ≥30% as the outcome, metabolically healthy overweight and obese individuals were at increased risk (overweight HR 1.08, 95% CI: 0.98-1.19; obese HR 1.45, 95% CI: 1.32-1.59). Metabolically unhealthy persons had higher risk for ESRD and eGFR decline ≥30%, with a similar risk regardless of BMI (Figure) Relationships were similar using a competing risks model accounting for risk of death.

Conclusions: Metabolically healthy obesity is associated with eGFR decline ≥30% but not kidney failure.

Funding: NIDDK Support
The Metabolomic Signature of Diabetic Kidney Disease Predicts Diabetic Renal Disease Progression  

Manjula Dardu,1,2 Loki Natrarajan,2,3 Minya Pu,2,3 Rintaro Saito,1,2 Kumar Sharma,2,4 Center for Renal Translational Medicine, Univ of California, San Diego, La Jolla, CA; 1Inst of Metabolomic Medicine, Univ of California, San Diego, La Jolla, CA; 4Moores Cancer Center, Univ of California, San Diego, CA; 3Veterans Administration, San Diego Healthcare System, La Jolla, CA.

Background: We recently published a metabolomic signature of diabetic kidney disease (MSDKD), indicative of mitochondrial dysfunction. Presently we determined the prognostic value for chronic kidney disease progression in diabetic patients from the longitudinal FinnDiane cohort.

Methods: 60 patients with mean 55 years (SD=9.6) age and mean diabetes duration 27 years (SD = 11 years) were analyzed to predict eGFR. Predictors included baseline (BL) metabolites and clinicalvariables, BL eGFR, HbA1c, UACR, and diabetes duration. Principal component weights obtained from the MSDKD were designated as PCA score 1 and PCA score 2. Linear (for continuous eGFR) and logistic (for dichotomous eGFR: > vs <= 3ml/min/1.73m² per year) regression models were examined to determine associations between the PCA scores and eGFR outcomes.

Results: Baseline mean eGFR levels were 86.23 (26.67) mL/min/1.73m², HbA1c were 8.3% (SD 1.1), and UACR were 11 (SD 34.1) and follow up was 6.6 (SD 3.5) yrs. eGFR levels at follow up were 81.96 (SD 24.69) mL/min/1.73m², and 25% (N=15) declined more than 3 ml/min/1.73m² per year. Statistical modeling revealed that, after adjustment for baseline eGFR and follow-up interval, the PCA Score 2 (mean =0.4, SD=0.64) was a significant predictor of worse (i.e. lower) eGFR (coef.= -12.4, p=0). For dichotomized for baseline eGFR and follow-up interval, the

Conclusions: We demonstrate that MSDKD is a strong independent predictor for kidney disease progression in type I and type II diabetes patients, and hence may serve as prognostic biomarker for CKD.

Funding: NIDDK Support, Veterans Administration Support

SA-OR002

Association Between Mitochondria DNA Copy Number and Incident Chronic Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study  


Background: Mitochondria play a key role in cellular energy production. Higher mitochondrial DNA copy number (mtDNA-CN) in peripheral blood has been associated with lower risk of diabetes and lower prevalence of microalbuminuria, both risk factors of chronic kidney disease (CKD). It is unknown whether mtDNA-CN is associated with incident CKD.

Methods: We estimated mtDNA-CN from 119 mtDNA single nucleotide polymorphisms (SNPs) genotyped using the Affymetrix 6.0 microarray. Incident CKD was defined as a composite outcome of (a) baseline estimated glomerular filtration rate (eGFR) ≥ 60ml/min/1.73m² with a 25% drop to < 60ml/min/1.73m², (b) CKD-related hospitalization, or (c) end-stage renal disease (ESRD) based on linkage to the US Renal Data System (USRDS). The association between quartiles of mtDNA-CN and incident CKD was evaluated using Cox regression.

Results: Among 9060 participants, those with higher mtDNA-CN had significantly lower prevalence of coronary heart disease and diabetes, and lower levels of C-reactive protein and white blood cell count. Baseline eGFR did not differ significantly by mtDNA-CN quartiles. Over a median follow-up period of 19 years, 1459 participants developed CKD. Higher mtDNA-CN was associated with lower risk of incident CKD adjusted for age, gender, and race (quartile 4 vs. 1: hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.66-0.87, p for trend < 0.0001). This association persisted with some attenuation after adjustment for other renal risk factors, including diabetes, hypertension, and coronary heart disease, smoking, high sensitive C-reactive protein and white blood cell count (quartile 4 vs. 1: HR 0.89, 95% CI: 0.76-1.03, p for trend 0.03).

Conclusion: Higher mtDNA-CN is associated with lower risk of incident CKD independent of known risk factors of CKD and inflammation biomarker levels. Further research on modifiable factors influencing mtDNA-CN may lead to insight on the pathogenesis and prevention of CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR003

Urinary EGF Predicts Composite Endpoints in Three Independent Chronic Kidney Disease Cohorts  

Viji Nair, Li Zhu, Peter X.K. Song, Laura H. Mariani,1 Susan P. Steigerwald, Jicheng Lv, Jennifer Joyce Hawkins,1 Hong Zhang,1 Matthias Kretzler,1 Wenjun Ju,1 Medicine, Univ of Michigan, Ann Arbor, MI; 1Medicine, Peking University First Hospital, PKU, Inst of Nephrology, Peking, China; 2Biostatistics, Univ of Michigan, Ann Arbor, MI; 1Arbor Research Collaborative for Health, Ann Arbor, MI; 1St. John Hospital and Medical Center, Detroit, MI.

Background: The nephropathy community is in need of non-invasive biomarkers that can predict CKD progression and identify patients for targeted treatment better than estimated glomerular filtration rate (eGFR) and proteinuria. Our previously identified and validated epidermal growth factor (EGF) as an independent risk predictor of CKD.

Methods: We tested the association of FMO3 158K, the most common allelic variant, with plasma TMAO concentration in 3 prospective cohorts. A model to predict follow-up eGFR using clinical variables alone was validated by the LASSO model. A model to predict follow-up eGFR using clinical variables alone was validated by the LASSO model. A model to predict follow-up eGFR using clinical variables alone was validated by the LASSO model. A model to predict follow-up eGFR using clinical variables alone was validated by the LASSO model.

Results: Each additional minor allele at the 158K locus was associated with a 0.35 µg/mL higher serum TMAO concentration (1.42, 1.97, 2.10 µg/mL for 0, 1, 2 minor alleles, respectively; p=0.02) and a 0.20 unit higher TMAO/beta-tube rate (p=0.05). A greater number of minor alleles at the 158K locus was associated with faster rates of eGFR decline. Participants who had 0, 1 and 2 minor alleles at the 158K locus experienced average eGFR losses of 9%/year, 12%/year, and 14%/year, respectively (p for trend 0.05). Compared to participants with the homozygous dominant genotype (G/G), heterozygous (G/A) and homozygous recessive (A/A) participants had a 1.94-fold and 2.24-fold higher risk of mortality (p for trend 0.04).

Conclusions: In summary, we demonstrate that common genetic variation within the FMO3 gene is associated with change in eGFR and mortality among CKD patients. Further elucidation of these relationships could have implications for personalized recommendations for diet modification in patients with CKD.

Funding: Other NIH Support - NCATS IKL2R020515-01, Private Foundation Support

SA-OR004

Normalization of Biomarkers to Urine Creatinine: Impact on CRIC Study Findings  


Background: There is no standard approach to the reporting of urine biomarkers; some studies normalize to urine creatinine concentration and others do not. Whether this influences findings is not well understood.

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

Underline represents presenting author.
Methods: Urine kidney injury molecule-1 [KIM-1], neutrophil gelatinase associated lipocalin [NGAL], N-acetyl-beta-D-glucosaminidase [NAG], and liver fatty acid-binding protein [LFABP] were measured in 2466 Chronic Renal Insufficiency Cohort participants. Cox models were used to examine the association between biomarkers and CKD progression, defined as halving of eGFR or incident ESRD. We compared results with and without normalization of biomarkers to UCr.

Results: Baseline mean eGFR was 44.8±18 mL/min/1.73 m²; median albuminuria was 53 mg/g UCr (6-503). After adjustment for eGFR, albuminuria, as well as socio-demographic and clinical covariates, non-normalized KIM-1 and NAG were independently associated with CKD progression by quintile (Table) and continuous biomarker value analysis [HR per SD 1.16 (1.05-1.28) and 1.14 (1.04-1.25), respectively] but KIM-1/Cr and NAG/Cr were not. There were no independent associations between NGAL or LFABP and outcomes regardless of normalization.

Conclusions: Normalization for Ucr influences the associations of biomarkers with CKD outcomes. In theory, normalization controls for differences in urine concentration, but more studies are needed to better understand the impact on a variety of clinical outcomes. At minimum, researchers should state their approach a priori, measure Ucr, and perform sensitivity analyses where the alternate approach is tested.

Funding: NIDDK Support

SA-OR005

Proton Pump Inhibitor Use Is Associated with Incident Chronic Kidney Disease

Benjamin Lazarus,1,2,3 Yuan Chen,1 Francis Perry Wilson,4 Josef Coresh,4,5 Morgan Gramp,1,6,7

1 Johns Hopkins Univ, Baltimore, MD; 2 Royal Brisbane and Women’s Hospital, Queensland, Australia; 3 Yale Univ School of Medicine, New Haven, CT

Background: Proton pump inhibitors (PPIs) are one of the most commonly used drugs worldwide, and have been linked to acute kidney injury and interstitial nephritis. We hypothesized that PPI use may also be associated with chronic kidney disease (CKD).

Methods: We followed 10,482 participants in the Atherosclerosis Risk in Communities Study with an eGFR of ≥60mL/min/1.73m²; median albuminuria was 53 mg/g Ucr (6-503). After adjustment for eGFR, albuminuria, as well as socio-demographic and clinical covariates, non-normalized KIM-1 and NAG were independently associated with CKD progression by quintile (Table) and continuous biomarker value analysis [HR per SD 1.16 (1.05-1.28) and 1.14 (1.04-1.25), respectively] but KIM-1/Cr and NAG/Cr were not. There were no independent associations between NGAL or LFABP and outcomes regardless of normalization.

Conclusions: Normalization for Ucr influences the associations of biomarkers with CKD outcomes. In theory, normalization controls for differences in urine concentration, but more studies are needed to better understand the impact on a variety of clinical outcomes. At minimum, researchers should state their approach a priori, measure Ucr, and perform sensitivity analyses where the alternate approach is tested.

Funding: NIDDK Support

SA-OR006

Underuse of Renin Angiotensin System Inhibitors and Other Medications in U.S. Patients with Advanced Chronic Kidney Disease Receiving Nephrologist Care: Results from the International CKDopp

Elodie Speyer,1 Laura H. Mariani,1 Charlotte Tu,1 Lindsay Zepel,2 Celine Langle,3 Brian Bieber,2 Christian Combe,1 Antonio Alberto Lopes,1 Ziad Massy,4,5 Roberto Peces-Filho,4 Ronald L. Pisoni,1 Helmut Reichel,1 Benedicte Stengel,1 Bruce M. Robinson,2 1 Arbor Research Collaborative for Health, USA; 2 Biomedical Agency, France; 3 CHU Bordeaux, Univ de Bordeaux, France; 4 Federal Univ of Bahia, Brazil; 5 Ambroise Pare Univ Hospital, UTSQ, France; 6 Pontificia Univ Catolica do Parana, Brazil; 7 Nephrological Center Villingen Schwenningen, Germany; 8 Inserm UMR1018, France

Background: In the US, ~86% of incident ESRD cases are attributable to hypertension or diabetes. Guideline-directed medication use may help to slow CKD progression and lower ESRD incidence. We report early findings on use of key medication classes by CKD stage in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopp).

Methods: CKDopps is a prospective cohort study of patients with eGFR ≤60 in random national samples of nephrology clinics in Brazil, France, Germany, and the US. Early data from CKDopps (excluding Brazil and Germany for now) were used to characterize medication usage.

Results: 2,621 patients were included from 39 French, and 17 US clinics. The median number of prescriptions ranged from 7-9. Statin use was 52% and aspirin use was 31-48%. RASI (ACEI or ARB) use for CKD Stage 3 and 4 patients was 72 and 77% in France, and 51 and 55% in the US, respectively. Aldosterone blockade use was 3-6%. Among diabetics, insulin use was lower in US (32%) than in France (48 and 57% for stage 3 and 4 patients, respectively), as was metformin use which was 30 and 7%, and 10 and 1%. For stage 4 patients, sulfonylurea use was higher in the US (21%) than in France (8%).

Conclusions: These early results show large international differences in medication usage for diabetes and cardiovascular disease amongst CKD patients. Patients in US were much less likely to use RASIs, metformin or insulin than in France. Early data from Germany and Brazil will be available by mid 2015. Further investigation should determine the reasons for these practice variations and their impact on CKD progression, survival, and other outcomes.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

SA-OR007

Albuminuria Changes and Subsequent Risk of End-Stage Renal Disease and Mortality

Juan Jesus Carrero,1 Yingying Song,2 Alessandro Gasparini,1 Abdul Rashid Tony Qureshi,3 Kunhiro Matsushita,4 Johan Amlot,5 Marie Evans,1 Peter F. Barany,6 Bengt Lindholm,7 Morgan Gramp,8 Shoshana Ballew,9 Carl Gustaf Elinder,1 Josef Coresh,2 1 Renal Medicine and Baxter Novum, Karolinska Inst, Sweden; 2 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 3 Medical Sciences, Uppsala Univ, Sweden

Background: Albuminuria is used to stage chronic kidney disease (CKD). Changes in albuminuria during the course of disease may serve as early indicators of CKD progression and complications beyond eGFR, but the risk implications are not well understood in large clinical studies.

Methods: Observational study based on the Stockholm CREAtineine Measurements (SCREAM) project, a laboratory data extraction of all citizens from the region of Stockholm, Sweden, with at least one serum creatinine during 2006-2011; 39802 individuals with repeated albumin to creatinine ratio (ACR) measurements were followed up until 12/31/2012. ESRD risk after baseline (908 events) was related to fold-change in ACR during a baseline window of 1, 2 or 3 years. The secondary outcome was death (3890 events). Adjustment variables included demographics, comorbid history, laboratory assessments and medication, as well as first eGFR and ACR.

Results: The association between ACR changes and ESRD risk was strong and showed a largely linear dose-response relationship (Figure for 2-3 year baseline period). For example, 8-fold increase in ACR (e.g., from normal of 5 mg/g to microalbuminuria of 40 mg/g) conferred ~5 fold higher risk of ESRD compared to stable ACR. The association was weaker for mortality but significant for ACR increases. The observed risk estimates were similar and consistent at 1, 2- and 3-year time-window.

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

Underline represents presenting author.
Conclusions: Increases in albuminuria were strongly and consistently associated with the risk of ESRD and mortality, suggesting their usefulness as a kidney outcome in clinical studies of CKD progression.

SA-OR008

Prevalence of Chronic Kidney Disease, Diabetes and Hypertension in Rural Tanzania Based of Different Methodologies

Background: Studies were conducted to explore the hypothesis that there are previously underappreciated and interrelated epidemics of chronic kidney disease (CKD), diabetes (DM), and hypertension (HTN) in rural Tanzania.

Methods: We initially assessed prevalence in a probability-based sample of 740 subjects randomly sampled from households in Kisinga District, TZ. Prevalence of DM was obtained by measuring HbA1c. Blood pressure was measured by AHA guidelines, and kidney function by serum creatinine in blood samples obtained at home interview. Estimation of glomerular filtration rate (eGFR) was computed with the CKD-EPI equation.

Results:

<table>
<thead>
<tr>
<th>NCD</th>
<th>Diabetes</th>
<th>Pre-Diabetes</th>
<th>CKD Stage 3-5</th>
<th>Pre-HTN</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>HbA1c &lt; 6.5%</td>
<td>HbA1c &gt; 5.9 to &lt; 6.5</td>
<td>eGFR &lt; 60 ml/min/1.73 m²</td>
<td>BP &gt; 130/80-89 mmHg</td>
<td>BP &gt; 140/90</td>
</tr>
<tr>
<td>Prevalence</td>
<td>14.7%</td>
<td>30.5%</td>
<td>12.6%</td>
<td>40.0%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

Following the probability based screening of households, we assessed the same NCD’s in individuals who voluntarily presented for healthcare assessment in a community prevention center we established. We measured BP and assessed urine for glycosuria and proteinuria with dipsticks in 685 subjects self-selected from the community. We observed glycosuria in 3.6%, proteinuria in 8.1% and glycosuria and proteinuria in 1.8%.

Conclusions: In summary we observed unexpectedly high and similar prevalence of hypertension, diabetes, and obesity in rural Tanzania. These findings will likely contribute to rapidly accelerating rates of cardiovascular morbidity and mortality in these areas. Additional studies are desperately needed to address this problem.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc, Nashville, TN

SA-OR009

Race and the Association of Blood Pressure with Clinical Outcomes in U.S. Veterans with Chronic Kidney Disease

Background: We examined the association of pre-dialysis eGFR slopes with all-cause, cardiovascular (CV), and infectious mortality during two years after dialysis start in 19,254 U.S. veterans who transitioned to ESRD between October 1, 2007-September 30, 2011. eGFR slopes were categorized into four groups (<10, -10-<-5, and 0/1 ml/min/1.73m²/year). Associations were examined in Cox models with adjustment for age, gender, race, comorbidities, and last pre-dialysis eGFR.

Results:

<table>
<thead>
<tr>
<th>eGFR slopes (ml/min/1.73m²/year)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P Value</th>
<th>Age, sex, race-Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>Fully Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; -10</td>
<td>0.67 (0.63-0.72)</td>
<td>&lt;0.001</td>
<td>1.17 (1.09-1.25)</td>
<td>&lt;0.001</td>
<td>1.26 (1.17-1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-10 - &lt; -5</td>
<td>0.88 (0.76-0.95)</td>
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<td>1.00 (reference)</td>
<td>N/A</td>
<td>1.00 (reference)</td>
<td>N/A</td>
<td>1.00 (reference)</td>
<td>N/A</td>
</tr>
<tr>
<td>0</td>
<td>1.42 (1.29-1.57)</td>
<td>&lt;0.001</td>
<td>1.53 (1.39-1.69)</td>
<td>&lt;0.001</td>
<td>1.04 (0.93-1.16)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Conclusions: Patients with rapid pre-dialysis eGFR decline have higher mortality risk in the first two years after dialysis start. The rate of eGFR decline in late CKD stages can be an additional predictor of mortality in incident dialysis patients.

Funding: NIDDK Support, Veterans Administration Support

SA-OR011

A Randomized Controlled Trial of Rituximab for Severe Idiopathic Membranous Nephropathy (IMN)

Background: IMN is a common cause of nephrotic syndrome. Anti-PLA2R antibodies occur in 70% of patients. No randomized controlled trial has evaluated rituximab efficacy and safety.

Adjusted hazard/odds ratios (95%CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.40 (1.27-1.55)</td>
<td>1.44 (1.36-1.54)</td>
</tr>
<tr>
<td>Incident ESRD</td>
<td>10.69 (8.94-12.78)</td>
<td>6.09 (5.07-7.30)</td>
</tr>
<tr>
<td>Steeper slopes of eGFR (&lt; -5 ml/min/1.73m²/year)</td>
<td>3.51 (3.13-3.93)</td>
<td>2.20 (2.04-2.38)</td>
</tr>
<tr>
<td>Incident ischemic stroke</td>
<td>1.96 (1.82-2.36)</td>
<td>1.86 (1.82-2.15)</td>
</tr>
<tr>
<td>Incident CHD</td>
<td>1.46 (1.15-1.91)</td>
<td>1.81 (1.48-2.20)</td>
</tr>
</tbody>
</table>

Conclusions: Hypertension is associated with higher incidence of mortality, vascular events and ESRD in both AA and white patients with CKD. Elevated SBP may affect the progression of CKD more in AA patients.

Funding: NIDDK Support, Veterans Administration Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Patients with biopsy proven IMN and persistent nephrotic syndrome after 6 months despite Non Immunosuppressive Antiproteinocic Treatment (NIAT) were randomly assigned to 6-month therapy with NIAT and 375 mg/m^2 of rituximab on days 1 and 8, or NIAT alone. At month 6, the primary end point was the rate of remission; the composite end point was defined as reduction of proteinuria >50% and increase of serum albumin >30%; secondary outcome parameters were total serum albumin, serum creatinine, and PLA2R-Ab.

Results: 37 and 38 patients received NIAT with rituximab and NIAT alone. At month 3, rituximab decreased PLAR-Ab rate and titer (P<0.001), and induced PLA2R-Ab depletion in 56 of 59 patients (P<0.001). At month 6, 13 (35 %) patients in the NIAT-rituximab group and 8 (21 %) in the NIAT group reached the primary end point (P=0.17); 15 (41 %) patients in the NIAT-rituximab group and 5 (13 %) in the NIAT group reached the composite end point (OR=0.22, 95% CI= [0.07; 0.70]; P=0.007). Serum albumin increased more with rituximab (P=0.029), without difference in proteinuria. Number of SAEs was comparable in both groups.

Conclusions: Rituximab induced immunological and clinical remission defined by a composite end point with a high safety profile (GEIMITRUXClinicalTrials.gov number).

Funding: Pharmaceutical Company Support - Hoffmann-La Roche, Private Foundation Support, Government Support - Non-U.S.

SA-OR102  Two-Year Outcomes of Patients with Idiopathic Membranous Nephropathy, Previously Randomized to Either Modified Punticelli Regimen or to a Combination of Tacrolimus and Steroids  

Background: The patients with idiopathic membranous nephropathy (IMN) followed for 1 year are known to relapse more often with Tacrolimus than with cyclophosphamide (CP) therapy, either given with oral steroids. The present study aimed at finding the clinical outcome in patients randomized to a combination of Tacrolimus and oral prednisolone (TAC*) or Modified Punticelli regimen (MPR) (cyclophosphamide and steroids) at 2 years.

Methods: IMN patients (n=70) with persisting nephrotic syndrome after at least 6 months of ACEIs or ARBs or with complications of nephrotic syndrome were randomized to receive TAC* or MPR. The outcome of the study was remission at the end of 18 and 24 months of initiating therapy. Definition: Complete remission (CR): 24-hour urine protein <0.5 gm on 3 occasions with normal serum albumin. Partial remission (PR): 24 hour urine protein <500 mg/day but <2 gm/day or <50% of baseline with normal serum albumin (³5.0 gm/dl) and serum creatinine. Partial remission had negative PLA2R antibodies, and its association with clinical response to therapy.

Results: Of the 70 randomized patients followed for 18 months, 54 had follow-up for 24 months. Intention-to-treat analysis and remission at the end of 12 (n=70), 18 (n=67) and 24 (n=54) months are mentioned in Table 1. At the end of 18 and 24 months response rate with TAC* was lower compared to subjects treated with MPR (p=0.05). The adverse events were comparable in both the groups. PLAR2R antibodies titers rose in all patients with relapse of nephrotic range proteinuria.

Conclusions: Preliminary analysis suggests that at 2 years post randomization, TAC* is inferior to MPR in maintaining remission of NS (The total follow-up of 70 cases will be presented at ASN).

SA-OR103  Antibody Guided Therapy with Cyclophosphamide and Prednisone in Patients with Idiopathic Membranous Nephropathy  

Background: The discovery of anti-PLA2R antibodies provides options for individualized therapy in patients with idiopathic membranous nephropathy (IMN). We previously showed that the level of anti-PLA2R antibodies (aPLA2R) after 6-12 months of corticosteroids predicted long-term outcomes (Bech, CJASN 2014). We present the first data of antibody guided therapy.

Methods: CP-therapy (combined with steroids) is started in patients with idiopathic membranous nephropathy (IMN). We previously showed that the level of anti-PLA2R antibodies (aPLA2R) after 6-12 months of corticosteroids predicted long-term outcomes (Bech, CJASN 2014). We present the first data of antibody guided therapy.

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remission of proteinuria. In 3 patients THSD7A-Ab persisted. 2 of them achieved remission of proteinuria, 1 had a relapse 3 months afterwards. The third patient had no remission of proteinuria during follow-up.

Conclusions: In this cohort of patients with MN the new IFT showed 97% sensitivity and 100% specificity for the detection of THSD7A-Ab compared to WB. We compared the adverse effects of PP (osteoporosis, hypertension and diabetes mellitus) between the first rituximab infusion (baseline) and the end of the 24-month observation period. In addition, we examined the adverse effects of rituximab during the same period.

Results: The PP dose was significantly lower at 24 months than at the baseline. The bone density was significantly higher at 24 months as compared to the baseline value (Z-score: -1.8 vs. -1.1; p < 0.05). Blood pressure at 24 months was significantly lower than that at the baseline (120.9/74.4 vs. 111.8/70.3 mmHg, p < 0.05). Eight patients with diabetes mellitus showed improved glycemic control at 24 months as compared to that at the baseline. There were no adverse effects of PP. However, mild infusion reactions occurred in 31 patients (57%). The frequency of the infusion reactions decreased significantly with every successive infusion.

Conclusions: Rituximab treatment was effective and safe in patients with steroid-dependent nephrotic syndrome, allowing reduction of the PP dose, and ameliorated the adverse effects of PP. It may be preferentially used in patients at a risk of the adverse effect of PP.

SA-OR018

Amelioration of the Adverse Effects of Prednisolone by Rituximab Treatment in Adults with Steroid-Dependent Minimal-Chaange Nephrotic Syndrome

Yoei Miyabe, Takashi Takei, Yuko Iwabuchi, Takahito Moriyama, Kosaku Nitta. Tokyo Women's Medical Univ, Japan.

Background: We previously demonstrated the efficacy of single-dose 6-monthly rituximab infusions in 25 adults with steroid-dependent minimal-change nephrotic syndrome. Herein, we assessed the safety of rituximab treatment and its effect in ameliorating the adverse effects of prednisolone (PP) in a larger study sample.

Methods: We treated 54 adult patients with four a single-dose 6-monthly infusions of rituximab (375 mg/m² BSA per dose). We compared the adverse effects of PP (osteoporosis, hypertension and diabetes mellitus) between the first rituximab infusion (baseline) and the end of the 24-month observation period. In addition, we examined the adverse effects of rituximab during the same period.

Results: The PP dose was significantly lower at 24 months than at the baseline. The bone density was significantly higher at 24 months as compared to the baseline value (Z-score: -1.8 vs. -1.1; p < 0.05). Blood pressure at 24 months was significantly lower than that at the baseline (120.9/74.4 vs. 111.8/70.3 mmHg, p < 0.05). Eight patients with diabetes mellitus showed improved glycemic control at 24 months as compared to that at the baseline. There were no adverse effects of PP. However, mild infusion reactions occurred in 31 patients (57%). The frequency of the infusion reactions decreased significantly with every successive infusion.

Conclusions: Rituximab treatment was effective and safe in patients with steroid-dependent nephrotic syndrome, allowing reduction of the PP dose, and ameliorated the adverse effects of PP. It may be preferentially used in patients at a risk of the adverse effect of PP.
Conclusions: This unique statistical approach identified clusters which describe individual eGFR trajectories. Non-linear trajectory groups had more young patients, higher eGFR and upcr. Further work is needed to determine whether trajectory clusters represent different underlying disease pathophysiology and to identify cluster predictors at the time of biopsy.

Funding: NIDDK Support, Other NIH Support - NCATS, ORDR

SA-OR020
The Role of Calcineurin Inhibitors in Early Treatment of Primary FSGS
Louis-Philippe Laurin,1 Bethany J. Foster,1 A. Gasim,2 Caroline J. Poulton,2 J. Charles J. Bennett,2 Ronald J. Falk,3 Patrick H. Nachman.2
1Div of Nephrology, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 2Dept of Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 3Div of Nephropathy and Hypertension, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 4Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada.

Background: In primary focal segmental glomerulosclerosis (FSGS), calcineurin inhibitors (CNIs) have primarily been studied in patients deemed resistant to glucocorticoid (GC) therapy. Little data is available about their use early in the treatment of FSGS. We sought to estimate the association between choice of therapy and end-stage kidney disease (ESKD) in idiopathic FSGS.

Methods: An inception cohort of patients with biopsy-proven primary FSGS diagnosed between 1980 and 2012. Time to ESKD between different early therapies was reported with time-dependent Cox regression hazard ratio (HR) with 95% confidence interval (CI).

Results: 458 patients were studied (332 NOS, 64 Tip, 62 Collapsing): age 40.7 ± 9.4 years. 45.6% Black; 48.7% female; follow-up time 92±94 months. 183 patients received no immunosuppression, 173 received GC alone, 90 were treated with CNIs and/or GC. Baseline eGFR <30 mL/min/1.73m², baseline proteinuria ≥3.5 g/d and baseline serum albumin (per g/dL higher) were associated with a lower likelihood of ESKD compared to GC alone [HR 0.42 (95% CI 0.15, 1.18)]. Little data is available about their use early in the treatment of FSGS. We sought to estimate the association between choice of therapy and end-stage kidney disease (ESKD) in idiopathic FSGS.

Methods: Data were obtained from the UK Transplant Registry on all PRTR who received a donation after brain death (DBD) or living donor (LD) kidney-only transplant between 2000 and 2011. HLA,A, B and DR mismatch were categorised into four levels and two groups. Data were fully anonymised and ethical principles adhered to.

Results: 1,389 paediatric renal transplant recipients were analysed; 807 (58%) received a DBD donor kidney. Using Cox proportional hazard regression modelling of renal allograft survival, the risk of graft failure is 1.55 times as likely in children who receive a well HLA-matched DBD kidney compared to those that receive a poorly HLA-mismatched LD kidney (p=0.01, 95% CI 1.11-2.18). This analysis accounts for survival improvements across transplant years. In both DBD and LD grafts, there was no difference in renal allograft survival in children who received a good or poorer HLA-mismatched transplant (p=0.16 for DBD graft, p=0.55 for LD graft).

Conclusions: In children, well HLA-matched DBD renal transplants have inferior graft outcomes when compared with poorly HLA-matched LD grafts. It is difficult to justify preferentially waiting for an improved HLA-matched DBD kidney even when a poorer HLA-mismatched LD kidney transplant is available.

Funding: Government Support - Non-U.S.

SA-OR022
UK National Registry Study of Kidney Donation After Circulatory Death for Pediatric Recipients
Matko Maraj,1 Laura Anne Pankhurst,2 Alex J. Hudson,2 Khalid Sharif,3 Stephen D. Marks.3
1Univ College London, United Kingdom; 2NHS Blood and Transplant, United Kingdom; 3Great Ormond Street Hospital NHS Foundation Trust, United Kingdom.

Background: Donation after circulatory death (DCD) is an important source of organs for kidney transplantation and evidence in adults suggests that similar graft outcomes are achieved to donation after brain death (DBD) kidney transplantation. There is very little evidence reporting the use of DCD kidneys in children. The aim of this study was to determine graft outcomes for children in the UK who have received a DCD kidney and compare these to outcomes for all renal transplants.

Methods: Data was collected on all kidney transplants performed for paediatric recipients (age <18 years) in the UK from the NHS Blood and Transplant registry from 2000-2014 and separated into DCD, DBD and living donor kidney transplants. Data obtained included donor and recipient characteristics with 3-year graft survival and overall patient survival. All data were fully anonymised and ethical principles adhered to.

Results: 1773 kidney transplants were performed in children in the UK from 2000-2014. 22 (1.2%) of these were from DCD donors, 955 (53.9%) were from DBD donors and 796 (44.9%) were from living donors. 3-year graft survival was 95.5% in the DCD group, 87.1% in the DBD group and 92.9% in the living donor group. Overall patient survival is 100% in the DBD group, 98.7% in the DCD group and 98.8% in the living donor group.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Multivariate determinants of ESKD HR (95% CI)
Immunosuppression None 1
CNIs and/or GC 0.49 (0.28-0.86)
Age 1.00 (0.99-1.01)
Male sex 1.15 (0.76-1.73)
FSGS variant None 1
NOS 0.21 (0.09-0.48)
Tip 1.71 (0.99-2.95)
Collapsing 4.28 (2.81-6.48)
Baseline eGFR <30 mL/min/1.73m² 1.25 (0.68-2.29)
Baseline proteinuria ≥3.5 g/d 0.69 (0.53-0.90)
Baseline hypertension 1.33 (0.81-2.20)

Although not statistically significant, CNIs ± GC were associated with a lower likelihood of ESKD compared to GC alone (HR 0.42 (95% CI 0.15, 1.18)).

Conclusions: The use of CNIs as part of the early immunosuppressive regimen in primary FSGS may be associated with improved outcome, but their superiority over GC alone remains unproven.

SA-OR021
Living Donation Has a Greater Impact on Allograft Survival Than HLA Matching in Pediatric Renal Transplant Recipients
Matko Maraj,1 Alex J. Hudson,2 Laura Anne Pankhurst,2 Susan V. Fuggle,1 Stephen D. Marks.3
1Univ College London, United Kingdom; 2NHS Blood and Transplant, United Kingdom; 3Great Ormond Street Hospital NHS Foundation Trust, United Kingdom.

Background: Living donor kidney transplantation accounts for around half of all paediatric (<18 years) renal transplant recipients (PRTR) and results in improved renal allograft survival, although there are no data comparing the effect of HLA-mismatching on outcomes. The UK 2006 Kidney Allocation Scheme prioritises children with good HLA mismatching (Level 1: 2.000 A,B,DR or 0 DR & £1 B). The aim of this study was to determine the effect of HLA mismatching on deceased and living donor renal allograft outcomes in paediatric recipients.

Methods: Data were obtained from the UK Transplant Registry on all PRTR who received a donation after brain death (DBD) or living donor (LD) kidney-only transplant between 2000 and 2011. HLA,A, B and DR mismatch were categorised into four levels and two groups. Data were fully anonymised and ethical principles adhered to.

Results: 1,389 paediatric renal transplant recipients were analysed; 807 (58%) received a DBD donor kidney. Using Cox proportional hazard regression modelling of renal allograft survival, the risk of graft failure is 1.55 times as likely in children who receive a well HLA-matched DBD kidney compared to those that receive a poorly HLA-mismatched LD kidney (p=0.01, 95% CI 1.11-2.18). This analysis accounts for survival improvements across transplant years. In both DBD and LD grafts, there was no difference in renal allograft survival in children who received a good or poorer HLA-mismatched transplant (p=0.16 for DBD graft, p=0.55 for LD graft).

Conclusions: In children, well HLA-matched DBD renal transplants have inferior graft outcomes when compared with poorly HLA-matched LD grafts. It is difficult to justify preferentially waiting for an improved HLA-matched DBD kidney even when a poorer HLA-mismatched LD kidney transplant is available.

Funding: Government Support - Non-U.S.
In the DCD group the median time to asystole was 12.5 minutes and the median standard deviation of heart rate time was 13 minutes. In the DCD group there was 1 case of primary non-function and 5 cases of delayed graft function.

**Conclusions:** This is one of the largest studies reporting outcomes in children who receive DCD kidney transplants. In the post-2000 era children receiving a DCD kidney transplant have good graft survival at 3-year follow up, comparable to those receiving a kidney from a DBD donor or a living donor. This limited evidence encourages the use of selected DCD kidneys in paediatric transplantation as favourable graft outcomes can be achieved, and national DCD allocation algorithms may need to be amended in view of this.

**Funding:** Government Support - Non-U.S.

SA-OR023

**Longitudinal Change in Neurocognitive Functioning in Pediatric Chronic Kidney Disease**

**Stephen R. Hooper,1 Matthew Matheson,2 Rebecca J. Johnson,2 Arlene C. Gerson,3 Marc Lande,1 Susan R. Mendley,4 S. Shimmin,2 Debbie S. Gipson,2 Susan L. Firth,2 Bradley Warady,5 UNC-CKID Study Group.

**Background:** Few longitudinal data exist on the cognitive functioning of children with mild to moderate chronic kidney disease (CKD). We report longitudinal findings for the neurocognitive functioning of participants with mild to moderate CKD from the 48-site CKID Study, with a particular focus on identifying CKD-related variables predictive of change in cognition over time and progression to renal replacement therapy (RRT).

**Methods:** The sample comprised 2,009 assessments over a span of approximately 12 years. Measures of IQ, attention, and parent ratings of executive functions were obtained. Joint longitudinal mixed models and time-to-event models with a shared random effect were used to examine the predictive value of CKD-related variables at study entry (glomerular diagnosis, age of CKD onset, iGFR, nephrotic proteinuria, elevated blood pressure, anemia) and over time (duration of disease, iGFR annual percent change) adjusting for baseline covariates (e.g., gender, maternal education), while simultaneously examining the association of neurocognitive decline with RRT.

**Results:** Median chronological age at study entry was 11.3 years; 56% Caucasian; 62% male. 33% had maternal education of a college degree. The median duration of CKD was 7.9 years, with 62% of children having disease onset at birth. 21% had a glomerular diagnosis; average iohexol-based GFR was 52.3 ml/min/1.73m². After adjusting, lower iGFR and elevated blood pressure at study entry were associated with declining Performance IQ. Lower iGFR and annual percent change in iGFR were associated with worse parent ratings of executive functioning. The shared parameter associating declining neurocognitive abilities with RRT showed Attention Variability to be related to progression to RRT.

**Conclusions:** Findings suggest that selected disease-related variables should trigger referral for neurocognitive assessment as children with lower iGFR and elevated blood pressure, and those with larger annual iGFR change may be at greatest risk for neurocognitive declines. Attention variability also was significantly associated with CKD disease progression to RRT.

**Funding:** NIDDK Support

SA-OR024

**Biomarkers and Urinary Tract Infection in Infants**

**Sinrid Valdimarsson, Sverker Hansson, Ulf J. Jodal, Pediatric Urotheprologic Center, The Queen Silvia Children’s Hospital, Sahlgrenska Academy, Univ of Gothenburg, Gotteborg, Sweden.

**Background:** Urine culture is needed to diagnose infants with urinary tract infection (UTI). Symptoms are nonspecific and urine biomarkers are a possible tool to improve the diagnostic accuracy minimizing the need for investigations and invasive procedures. The aim was to evaluate if urine biomarkers can aid in the diagnosis of UTI.

**Methods:** This is a prospective study of infants with first UTI. Urine biomarkers were measured in infants with UTI and in a control group of children with fever from other causes. Measured urine biomarkers were Kidney injury molecule 1, Clara cell protein, Retinol binding protein, Neutrophil gelatinase associated lipocalin, high sensitive C-reactive protein, Interleukin-1b, Interleukin-6 and Interleukin-8 (IL-8); all were adjusted for urine creatinine/cre). The area under the ROC curve (AUC) for each biomarker was compared for children with UTI versus children with fever without UTI; the optimal cutoff level for equal weight on sensitivity and specificity was determined.

**Results:** 108 infants with UTI, 59 boys (mean age 2.7 months) and 49 girls (mean age 4.0 months) and a control group of 64 patients with fever without UTI (23 girls and 41 boys) were included. The biomarkers NGAL/cr and IL-8/cr were superior in differentiating children with UTI and without UTI. AUC for NGAL/cr was 0.98 and a cutoff value of 233 had 96.3% sensitivity and 100% specificity. AUC for IL-8/cr was 0.97 and a cutoff value of 466 had 91.7% sensitivity and 95.3% specificity.

**Conclusions:** This prospective study shows that the urine biomarkers NGAL and IL-8 had high sensitivity and specificity for the diagnosis of UTI in infants. Infants with fever and a low NGAL/cr value were highly unlikely to have a UTI.

**Funding:** Government Support - Non-U.S.

SA-OR025

**Phospholipase A2 Receptor Autoantibodies in Pediatric Membranous Nephropathy**

**Rebecca Kirkwood-Wilson,1 Maryline Fresquet,1 Nicholas J. Webb,2 Paul E. Brenchley,3 Rachel Lennon,4,5 Welcome Trust Centre for Cell-Matrix Research, Univ of Manchester, United Kingdom; 6Dept of Paediatric Nephrology, Royal Manchester Children’s Hospital, United Kingdom; 7Manchester Inst of Nephrology and Transplantation, United Kingdom.

**Background:** Membranous nephropathy (MN) is the commonest cause of nephrotic syndrome in adults, with most cases being primary, or autoimmune in nature. Understanding of MN advanced with the discovery of phospholipase A2 receptor (PLA2R) as the target autoantigen and with the detection of circulating autoantibodies in the sera of adult patients. In the pediatric population, MN is rare and often presents with persistent, steroid-resistant, proteinuria and is diagnosed by typical histological features on renal biopsy. In this study, we describe the clinical phenotype, renal histological analysis, anti-PLA2R status, and autoantibody binding in children with biopsy-proven PMN treated at the Royal Manchester Children’s Hospital over the past 7 years.

**Methods:** We carried out phenotypic characterisation of patients, determination of anti-PLA2R status by ELISA, anti-PLA2R Ig subclass analysis and histological characterisation of renal biopsies. Anti-PLA2R binding was determined by comparing autoantibody reactivity to recombinant fragments of the PLA2R under denatured and native conditions.

**Results:** Determination of anti-PLA2R status revealed 50% of children were seropositive. Seropositivity was associated with a severe clinical phenotype with nephrotic syndrome with renal impairment and IgG4 was the predominant subclass. Seronegative patients presented with asymptomatic proteinuria. Autoantibody reactivity patterns to recombinant fragments of the PLA2R, differed with clinical phenotype at presentation.

**Conclusions:** Here we report, for the first time, a series of 6 children with biopsy-proven MN. We demonstrate a correlation between clinical phenotype and anti-PLA2R status and evaluate autoantibody-PLA2R binding in the paediatric MN population. Our results suggest that minor, or alternative, epitopes exist within the PLA2R which may be responsible for autoantibody binding in paediatric MN.

**APOL1-Associated Glomerular Disease in African-American Children in the CKiD and NEPTUNE Cohorts**

**Derek Ng,1 C. Robertson,2 C. Gillies,2 Sophie Limou,2 Robert Woroniecki,3 Kimberly J. Reidy,4 Sangeeta R. Hingorani,6 Keisha L. Gibson,7 Christine B. Sethna,7 Cheryl Ann Winkler,7 Jeffrey B. Kopp,7 Susan L. Firth,2 Bradley Warady,5 John R. Sedor,2 Frederick J. Kaskel,7 M. Sampson.2 1Johns Hopkins; 2U of Michigan; 3NICI; 4Stony Brook Univ; 5Montefiore Med. Center; 6U of Washington; 7U of North Carolina; 8Cohen Children’s Med Center; 9NIDDK; 10Children’s Hosp of Philadelphia; 11Children’s Mercy Hosp; 12Case Western Reserve.

**Background:** Little is known about APOL1 associated nephropathy in children. This study aimed to describe characteristics and longitudinal outcomes in African-American children with glomerular disease, stratified by APOL1 risk genotype in the Chronic Kidney Disease in Children cohort (CKiD) & the Nephrotic Syndrome Study Network (NEPTUNE).

**Methods:** Enrollment criteria for CKiD was age 1-16, diagnosis of CKD, & estimated glomerular filtration rate (GFR) of 30-90 ml/min. NEPTUNE subjects were enrolled with suspected primary nephrotic syndrome, proteinuria, >0.5g/day, & clinically indicated biopsy. 56 CKiD subjects with glomerular disease & 48 NEPTUNE pediatric subjects were included here (all African-American). APOL1 was directly genotyped and subjects were classified as low risk (LR, 0 or risk alleles) or high risk (HR, 2 risk alleles). All analyses were performed under the recessive model; LR vs HR subjects. By APOL1 genotype, odds of premature and eGFR & proteinuria over time were modeled.

**Conclusions:** This is one of the largest studies reporting outcomes in children who receive DCD kidney transplants. In the post-2000 era children receiving a DCD kidney transplant have good graft survival at 3-year follow up, comparable to those receiving a kidney from a DBD donor or a living donor. This limited evidence encourages the use of selected DCD kidneys in paediatric transplantation as favourable graft outcomes can be achieved, and national DCD allocation algorithms may need to be amended in view of this.

**Funding:** Government Support - Non-U.S.

SA-OR026

**APOL1-Associated Glomerular Disease in African-American Children in the CKiD and NEPTUNE Cohorts**

**Derek Ng,1 C. Robertson,2 C. Gillies,2 Sophie Limou,2 Robert Woroniecki,3 Kimberly J. Reidy,4 Sangeeta R. Hingorani,6 Keisha L. Gibson,7 Christine B. Sethna,7 Cheryl Ann Winkler,7 Jeffrey B. Kopp,7 Susan L. Firth,2 Bradley Warady,5 John R. Sedor,2 Frederick J. Kaskel,7 M. Sampson.2 1Johns Hopkins; 2U of Michigan; 3NICI; 4Stony Brook Univ; 5Montefiore Med. Center; 6U of Washington; 7U of North Carolina; 8Cohen Children’s Med Center; 9NIDDK; 10Children’s Hosp of Philadelphia; 11Children’s Mercy Hosp; 12Case Western Reserve.

**Background:** Little is known about APOL1 associated nephropathy in children. This study aimed to describe characteristics and longitudinal outcomes in African-American children with glomerular disease, stratified by APOL1 risk genotype in the Chronic Kidney Disease in Children cohort (CKiD) & the Nephrotic Syndrome Study Network (NEPTUNE).

**Methods:** Enrollment criteria for CKiD was age 1-16, diagnosis of CKD, & estimated glomerular filtration rate (GFR) of 30-90 ml/min. NEPTUNE subjects were enrolled with suspected primary nephrotic syndrome, proteinuria, >0.5g/day, & clinically indicated biopsy. 56 CKiD subjects with glomerular disease & 48 NEPTUNE pediatric subjects were included here (all African-American). APOL1 was directly genotyped and subjects were classified as low risk (LR, 0 or risk alleles) or high risk (HR, 2 risk alleles). All analyses were performed under the recessive model; LR vs HR subjects. By APOL1 genotype, odds of premature and eGFR & proteinuria over time were modeled.
SA-OR027

Comprehensive Approach to Understand Human Renal Development Based on the Identification of Responsible Genes for CAKUT

A Randomized Study of Cholecalciferol Supplementation in Incident Hemodialysis Patients – Preliminary Evaluation After 2 Years

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Background: Studies have shown that vitamin D deficiency is associated with cardiovascular (CV) risk factors, mobility and mortality in uremic patients (pts). Our aim is to prospectively assess the safety and efficacy of vitamin D (cholecalciferol) supplementation in incident HD pts and to compare the clinical results with a control group supplemented with placebo.

Methods: We evaluated 108 (66% M) pts in group A (GA) under VIT D 20 000 U/wk, and 95 (67% M) pts in Group B (GB) on placebo, matched in age, (mean 66 and 65 years), BMI (mean 25.7 and 26.3 kg/m2 respectively), etiology of renal disease and the prevalence of comorbidities such as HTN, arthritism, peripheral vascular disease and cancer. The prevalence of DM (42 vs 57%), ischemic heart disease (18 vs 32%) and cerebrovascular disease (5 vs 14%) were analyzed by the next-generation sequencing (Illumina exome and Agilent custom panels) in combination with the conventional Sanger sequencing and/or the DNA microarray subsequent to the phenotype classification based on the clinical manifestations.

Results: Responsible genes in 62 cases from 44 families were identified. The phenotype classification assisted to detect the reported responsible genes including PAX2, EYA1, HNF1B, UMOD, OFD1, SALL1 and CHD7 by Sanger sequencing, and the next-generation sequencing powerfully enabled us to identify responsible/candidate genes including PAX2, UPCA, RET, FRAS1 and EPFO which were unpredictable from the clinical phenotype.

Conclusions: To clarify the molecular mechanisms of candidate genes, further experiments including in vitro and in silico assays would be required.

SA-OR028

A Randomized Study of Cholecalciferol Supplementation in Incident Hemodialysis Patients – Preliminary Evaluation After 2 Years

Cristina Jorge,1,2,3 Patricia Matias,1,2 Pedro Bravo,1 Clara Mil-homens,4 Cecilia Silva,4 Pedro M. Ponce,4 Carlos M.P. Oliveira,4 Célia Gil,1,2 Manuel A. Ferreira,1,2,5 Nephrology, Vila Franca de Xira, Portugal; Dialiper, Vila Franca de Almadã, Portugal; Nephrology, Lumiar, Portugal; NIDAN, Portugal.

Background: Although regenerative medicine using the pluripotent stem cells holds promise for the treatment for the renal failure, the complexity of the structure composed of diverse cell types makes the difficulty in the establishment of the differentiation protocol into renal nephron. Towards the comprehensive understanding of the molecular network underlying human renal development, this study aims to identify responsible genes for congenital anomalies and the kidney and urinary tract (CART) and reveal the molecular mechanism of pathogenesis.

Methods: Two hundred six CAKUT cases including 115 cases from 105 families of syndromic CAKUT and 91 cases from 82 families of non-syndromic CAKUT together with some sporadic cases were enrolled in GA. CAKUT was confirmed in agreement with the criteria which was approved by the ethical committee at Kobe University. Genomic DNA samples were analyzed by the next-generation sequencing (Illumina exome and Agilent custom panels) in combination with the conventional Sanger sequencing and/or the DNA microarray subsequent to the phenotype classification based on the clinical manifestations.

Results: Responsible genes in 62 cases from 44 families were identified. The phenotype classification assisted to detect the reported responsible genes including PAX2, EYA1, HNF1B, UMOD, OFD1, SALL1 and CHD7 by Sanger sequencing, and the next-generation sequencing powerfully enabled us to identify responsible/candidate genes including PAX2, UPCA, RET, FRAS1 and EPFO which were unpredictable from the clinical phenotype.

Conclusions: To clarify the molecular mechanisms of candidate genes, further experiments including in vitro and in silico assays would be required.

SA-OR029

Levocarnitine Improves Cardiovascular Function in Hemodialysis Patients with Left Ventricular Hypertrophy

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Background: Levocarnitine deficiency in hemodialysis (HD) patients is common. This may contribute to clinical disorders, including cachexia, erythropoiesis stimulating agent resistant anemia, and glucose intolerance, muscle weakness, and myopathy as well as to intradialytic symptoms such as muscle cramps, hypotension, and cardiac arrhythmia. Although the effect of levocarnitine therapy on uremic anemia has been studied in small trials, its effects on cardiac function remain unclear.

Methods: This prospective, open-label, randomized, parallel, controlled, multi-center trial, enrolled 282 HD patients who were randomly assigned to an oral levocarnitine therapy group (n = 110) or a control (no levocarnitine therapy) group (n = 112). Patients were monitored for 12 months during levocarnitine treatment (administered orally 20 mg/kg/day) or control. The primary endpoint was cardiac function measured by echocardiography. The secondary endpoints were clinical parameters and identification of factors that predict a favorable response to levocarnitine therapy. Echocardiographic parameters were measured at baseline and after 6 and 12 months of therapy.

Results: A total of 222 patients were randomly assigned, of whom 148 patients (levocarnitine group, n = 75; control group, n = 73) were analyzed. The ejection fraction values increased from 54.0 ± 5.8% at baseline to 56.0 ± 6.1% after 6 months (p < 0.001) to 58.1 ± 5.6% after 12 months (p < 0.001) in the levocarnitine group, while no significant changes in ejection fraction were observed in the control group. Furthermore, left ventricular mass index (LVMI) and N-terminal probrain natriuretic peptide levels were significantly decreased throughout the study in the le vocarnitine group. Multivariate analysis revealed that LVMI was an independent predictor of improvement in ejection fraction following levocarnitine therapy. Subgroup analysis revealed that responders to levocarnitine were patients with lower left ventricular mass index (LVMI).

Conclusions: Levocarnitine therapy is useful for hemodialysis patients with LVH; these patients may benefit from such therapy, with amelioration of cardiac function and mitigation of LVMI.

SA-OR030

Predictive Ability of Self-Rated Health and Symptom Burden for Mortality in Hemodialysis

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Background: Little is known about the ability of self-rated health to predict mortality in hemodialysis.

Methods: A prospective cohort study in hemodialysis (N=362). The Euro Quality of Life Questionnaire (EQSD), the Palliative Care Outcome Scale Renal (POS-S Renal) and the participant self-rated health (EQ visual analogue scale: EQVAS) were used to assess HRQL, symptom burden and self-rated health. Participants were followed from instrument completion to death or study end.

Results: Over a median (25th-75th centile) of 2.6 (1.4-3.3) years, 32% (N=116) of participants died. With competing risks survival analysis factors most notably associated with mortality were: adjusted hazard ratio (95%CI) included: higher symptom burden 2.4 (1.3, 3.0) P < 0.004 (highest tertile), lower HRQOL 2.6 (1.3, 5.3) P = 0.01 (lowest tertile), lower self-rated health 2.7 (1.4, 5.2) P = 0.004 (lowest tertile). Answering “Yes” to the questions: “problems with mobility?” 2 (1.1, 3.3) P = 0.01, or “problems with usual activities?” 2.1 (1.5, 3.0) P < 0.001. 55% of those aged > 60 years reporting problems with either self care, mobility or daily activities in this study died over a mean (SD) of 2.1 (1.1) years, compared to 18% over 2.5 (1) years in those reporting ‘no’ to these questions, P < 0.001. After age adjustment area under the receiver operating curves (AUC) (95%CI) for mortality were: 0.71 (0.63, 0.80) for symptom burden, 0.76 (0.65, 0.84) for HRQOL and 0.71 (0.62, 0.79) for self-rated health.

Conclusions: Age adjusted participant-related health and predictive models based on combinations of individual elements from the POS S Renal and EQ5D instruments could possibly aid in mortality discrimination and subsequent advance care planning in hemodialysis.

SA-OR031

Isonatric Dialysis Biofeedback in Hemodiafiltration with Online Regeneration of Ultrafiltrate in Hypertensive Hemodialysis Patients: A Randomized Controlled Study

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Background: Biofeedback in hemodiafiltration with online regeneration of ultrafiltrate (HFR) could improve arterial hypertension by using an isonatric mode maintaining a homonatric (HFR) could improve arterial hypertension by using an isonatric mode maintaining a homonatric dialysis pressure. This trial was designed as a randomized controlled study to find out if isonatric dialysis is more effective than conventional dialysis.

Methods: 47 hemodialysis patients having an arterial pressure > 140/90 mmHg were randomized (ratio 2/1) HFR iso versus HFR during 24 dialysis sessions. The course from S1 to S24 of the predialytic systolic (SBP) and diastolic (DBP) blood pressure, the defined

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daily dose (DDD) of antihypertensive treatment and of the dry weight were compared by a paired t-test and by mixed model for repeated measurements adjusted for treatment x time interaction. The impact of age, diabetes and cardiovascular co-morbidities on response to treatment was evaluated. Tolerance was evaluated by the number of sessions complicated by symptomatic hypotension.

Results: In the Isometric HFR group (N=32), the predialysis SBP decreased from S1 to S4 of 9 ± 20 mmHg (-0.12 ± 0.08 mmHg/ day) and increased of 5 ± 24 mmHg (+0.13 ± 0.05 mmHg/ day) in the HFR group (N=15), variation that differed between the 2 groups (DS1-S4, p = 0.035; interaction treatment*time, p=0.012). The DHP (HFRiso: -3 ± 14 mmHg; p=0.038), the DDD of antihypertensive treatment (HFRiso: -0.1 ± 0.9 vs HFR: -0.3 ± 1.1, p=0.7) and the dry weight (HFRiso 0.2 ± 1 vs HFR 0.2 ± 1.5 kg, p=0.9) did not vary during the study. Age influenced the PAS course independently of the treatment group (interaction age*time, p=0.05). The number of symptomatic hypotension was similar in both groups.

Conclusions: Isometric HFR improved blood pressure control without increasing dialysis hypotension episodes.

Funding: Pharmaceutical Company Support - Bello

SA-OR032

Relevance of B-Lines on Lung Ultrasound in Volume Overload and Pulmonary Congestion: Clinical and Therapeutic Correlations in Hemodialysis Patients

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Background: Volume overload in patients on hemodialysis (HD) is an independent risk factor for death from cardiovascular events. The role of lung ultrasound (US) in predicting physical performance, morbidity and mortality, and its potential advantage in its utility for assessing volume status in patients on HD.

Methods: ESRD patients on HD at Island Rehab center older than 18 were screened. Those with chronic lung disease and pregnant women were excluded. Patients achieving their dry weight (DW) had a lung US in a supine position. Residents were trained to visualize BL, and recorded scores in real time. Clips were reviewed by blinded certified physicians. Scores were classified as mild (0-14), moderate (15-30) and severe (≥30) for pulmonary congestion, as validated by Zoccali et al.

Results: 81 patients on HD were recruited. 58 were males, mean age 59.7 years, hemoglobin 10.6 g/dL, 44 had NYHA Class 1, 24 had class 2, and 13 had class 3. In univariate analysis, NYHA class had significant correlation with BL scores and classes (<0.001), and diastolic dysfunction (0.002). In multivariate analysis, NYHA grade strongly correlates with BL-Lines classification (0.01) but not with heart function (0.95). The mean difference between physicians and residents scoring was 3.7 (0.048). However, this difference was not significant after classification and scores were in agreement (Kappa 0.56).

Conclusions: At DW, NYHA grading tightly corresponded to BL classification irrespective of cardiac function. Pulmonary congestion is common among patients on HD; NYHA score is mainly driven by the extravascular water and not by heart dysfunction. These results render fluid overload estimated by a BL a better predictor for ESRD patient’s performance and a reliable indicator for their volume status assessment. Moreover, moderate lung congestion noted in patients with NYHA class 1 outline the importance of lung US in identifying subtle lung congestion opening a new concept for achieving DW.

SA-OR033

Combined Target Ranges for Blood Pressure and Fluid Overload

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Background: Recent research has revealed areas of increased mortality risk in the combination of systolic blood pressure (BPsys) and fluid overload (FO) (Fig 1a). It was the aim of this retrospective analysis to assess whether classifying patients according to a dedicated flow chart taking into account BP, FO and antihypertensive therapy (AHT) may indicate improved survival compared with a BP target range alone.

Methods: Pre-dialysis FO and BPsys were measured monthly in 31,349 patients from the Fresenius NephroCare Clinic Network. Patients were classified as being on/off target in January 2013 according to the flow chart in Figure 1b, which combines a BPsys target range of 130 to 160 mmHg with information about AHT and FO [L] (Target1). FO was measured by bioimpedance spectroscopy. Normohydration was defined as FO normalized range of 130 to 160 mmHg with information about AHT and FO [L] (Target1). FO was calculated over 2 yrs follow-up time using COX analysis adjusting for 31 different co-morbidities and laboratory parameters.

Results: Unadjusted Kaplan Meier curves revealed a 2yr survival of 82% for patients on Target1, and 75% for being not on Target1 (<0.0001). Fig 1c. Adjusted HR for patients being on Target1 was 0.74 [95% CI: 0.70 - 0.78]; the adjusted HR for being on Target2 was 0.84 [0.79 - 0.88]. At time of classification 66% of patients were on Target1, while 61% were on Target2.

Conclusions: Combining information on BPsys, AHT and FO indicates survival advantages compared with using only a BP target.

Fig 1. (a) Mortality risk of BPsys and FO. (b) Classification tree based on BPsys, AHT and FO. (c) Kaplan Meier curves for 31,349 patients being on/off target according to classification in Figure 1b.

SA-OR034

Volume Status Assessed by Bioimpedance in Hemodialysis Predicts Mortality

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Background: Mortality rates average over 20% in the End-Stage Renal Disease (ESRD) US population with cardiovascular disease being the leading cause of death. Accurate intravascular volume assessment is critical in the treatment of patients who receive chronic hemodialysis (HD) therapy due to its deleterious effects on the heart and blood pressure (BP). Clinically assessed dry weight and interdialytic weight gain (IDWG) are often used as surrogates of volume status. Bioimpedance has emerged as an effective tool for volume management but is not readily available in clinical practice. Thus we examined the association of volume status determined by bioimpedance with mortality, compared to the association of IDWG and BP with mortality in ESRD patients.

Methods: ACTIVE ADIPOSE (A Cohort Study to Investigate the Value of Exercise in ESRD/Analyses Designed to Investigate the Paradox of Obesity and Survival) was a multicenter study of prevalent HD patients coordinated by the United States Renal Data System in 2009-2011. The data collection sites were 14 outpatient dialysis clinics in Atlanta and San Francisco. Volume status by bioimpedance defined by calculation of extracellular fluid (ECF): total body water (TBW) ratio. Associations by quartiles of ECF:TBW, IDWG, and BP with 1-year mortality were estimated using Cox proportional hazards regression models.

Results: 660 patients were included in this analysis, with 36 total deaths at 1 year. After adjustments, each increase of 0.01 in ECF:TBW (range, 0.39-0.57) in quartiles was associated with a >30% increased risk of mortality, (HR-1.32, 95% CI, 1.15-1.52) p<0.001. In comparison, quartiles of IDWG (HR-0.96, 95% CI, 0.78-1.17) and BP (per 10 mmHg, systolic, HR-0.99, 95% CI, 0.82-1.19; diastolic (HR-0.90, 95% CI, 0.64-1.25), were not associated with mortality. Further, the associations of ECF:TBW with mortality were independent of BP, IDWG, and BMI.

Conclusions: Volume status by bioimpedance, but not IDWG or BP, was significantly and independently associated with greater mortality in this HD cohort. These findings question the common clinical practice of using IDWG as a surrogate of volume status in the HD population as it may not correlate with clinical outcomes.

Funding: NIDDK Support

SA-OR035

Abnormal Global Longitudinal Strain Is Associated with All-Cause Mortality in Hemodialysis Patients

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Background: Cardiovascular mortality is high in hemodialysis (HD) patients. Early detection of cardiac dysfunction is important. Left ventricular global longitudinal strain (GLS) measures the maximal shortening of myocardial longitudinal length during systole compared to the resting length in diastole. Reduced GLS may reflect abnormal systolic function before loss of ejection fraction (EF) becomes apparent. We aimed to determine the prevalence, clinical correlates and prognostic value of abnormal GLS in stable HD patients.

Methods: Clinical and echocardiographic data were obtained in a prospective study of HD patients at one centre. Survival analysis for GLS was performed using Cox regression adjusted for age, co-morbidities, dialysis chronology, laboratory data, left ventricular mass index adjusted for height (LVMH1.75) and Teicholz EF.

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Results: The mean age was 62±14 years; 69% were male, 39% had diabetes, 29% heart failure, 17% coronary artery disease. The mean GLS was -13.4±3.3%. LV ejection fraction (LVEF) was 63.8±12.9% and LVMIIHt was 53.6±17.2 g/m². 98% of patients had abnormal GLS (>20%), compared with 14% with reduced LVEF (<50%) and 55% with LV hypertrophy. Factors associated with an abnormal GLS included LVMIIHt (OR 1.06, 95% CI 1.04-1.09, P=0.01), LVEF (OR 0.96, 95% CI 0.94-0.99, P=0.01) and diabetes (OR 2.04, 95% CI 1.08-3.9; p=0.03). Median follow-up was 24 (17-30) months, during which there were 41 deaths (21%). After adjustment for age, diabetes, coronary artery disease, LVEF, LVMIIHt, a 3-month-averaged serum potassium and albumin, a less negative GLS remained an independent predictor of all-cause mortality (HR 1.18 for each 1% worsening change in GLS, 95% CI 1.03-1.35, P=0.02).

Figure 1. Survival in < median versus median GLS (median = -13.7%)

Conclusions: Abnormal GLS is highly prevalent amongst HD patients, and appears to be a better marker of all-cause mortality in stable HD patients than the "standard" echocardiographic parameters LVEF and LVMIIHt.

SA-OR363
Trimethylamine-N-Oxide (TMAO) and Cardiovascular Events in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study
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Background: Uremic toxins that contribute to cardiovascular (CV) disease and observed higher mortality in whites vs. blacks remain undefined. TMAO, a highly dialyzable metabolite, is associated with accelerated atherosclerosis and CV events in non-dialysis patients but previous studies in dialysis patients have been equivocal.

Methods: We measured TMAO in 1232 patients of the Hemodialysis (HEMO) Trial, 3-6 months after randomization and analyzed its association with CV mortality, sudden cardiac death (SCD) and first CV event, using Cox models adjusted for demographics, clinical characteristics, comorbidities, albumin and residual urea clearance.

Results: Mean age of the patients was 58 years, 34% white and 42% male. Median TMAO level was 88 µM (IQR, 62 to 124) and did not differ by race (p=0.9). The association of TMAO with outcomes differed by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with a 45% higher risk of TMAO with outcomes differed by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with a 45% higher risk of TMAO with outcomes differed by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with a 45% higher risk of TMAO with outcomes differed by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with a 45% higher risk of TMAO with outcomes differed by race (Figure) and was associated with outcomes only in whites. In whites, each 2-fold increase in TMAO was associated with a 45% higher risk (Table). TMAO levels decreased in the higher Kt/V group but did not have an effect on outcomes (p>0.1).

<table>
<thead>
<tr>
<th>Events</th>
<th>IR*</th>
<th>ADMA</th>
<th>SDMA</th>
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<tr>
<td></td>
<td><strong>HR</strong> (95% CI)</td>
<td>P</td>
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<tr>
<td>Cardiovascular Mortality</td>
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<td>Sudden Cardiac Death</td>
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<td>38</td>
<td>1.79 (1.19-2.69)</td>
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<tr>
<td>First Cardiovascular Event</td>
<td>644</td>
<td>274</td>
<td>1.50 (1.20-1.87)</td>
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* IR, Incidence Rate; **HR per 2-fold increase in solute

Conclusions: The association between TMAO and CV events differs among white and black hemodialysis patients.

Funding: NIDDK Support

SA-OR357
Serum Asymmetric (ADMA) and Symmetric (SDMA) Dimethylarginine and Morbidity and Mortality in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study
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Background: ADMA, an endogenous nitric oxide synthase inhibitor, and SDMA, a promoter of oxidative stress, accumulate in dialysis patients and may contribute to uremic toxicity.

Methods: We measured predialysis levels of ADMA and SDMA in 1276 patients of the Hemodialysis (HEMO) Trial, 3-6 months after randomization and analyzed its association with all-cause and cardiovascular (CV) mortality, sudden cardiac death (SCD) and first CV event, using Cox model adjusted for potential confounders (demographics, clinical characteristics, comorbidities, albumin, residual urea clearance).

Results: Mean age of the patients was 58 years, 65% black and 42% male. Median (interquartile range) for ADMA was 0.9 µM (0.8, 1.0) and SDMA was 4.1 µM (3.3, 5.0). In fully adjusted models, ADMA was associated with all outcomes whereas SDMA was only associated with CV mortality (Table). Subgroup analyses did not show significant interactions with race or HEMO interventions.

Funding: NIDDK Support

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Underline represents presenting author.
Conclusions: ADMA and SDMA are uremic solutes associated with morbidity and mortality in hemodialysis patients.

Funding: NIDDK Support

SA-OR038
Glomerular on-a-Chip as a Model to Study the Glomerular Filtration Barrier In Vitro
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Background: The glomerular filtration barrier (GFB) has three major components: the podocyte with the "slit diaphragm", the glomerular basement membrane and the fenestrated glomerular endothelial cell (hGEC); each of them is essential for the correct blood filtration. Damage to any of these components often leads to a severe, irreversible GFB disruption with onset of chronic damage requiring drug treatment and eventually dialysis and transplantation. Development of alternative therapeutic approaches is limited by our poor understanding of the complex cell-matrix interactions and cellular cross-talk in vivo and the absence of in vitro GFB models. Therefore, an in vitro system that mimics the complex GFB architecture and that can be used to better study glomerular (patho-)physiology is urgently needed.

Methods: We have generated a population of renal progenitors from human amniotic fluid (hAKPC-P) that can differentiate into podocyte-like cells. Taking advantage of the peculiar characteristics of available microfluidic systems, we have developed an innovative Glomerulus-on-a-Chip system by co-culturing hAKPC-P and hGEC cells in OrganoPlate® microfluidic plates. Evaluation of culture conditions, immunostainings and qPCR were performed to characterize the 3D culture.

Results: We have successfully established the conditions for in vitro co-culture of hAKPC-P-hGEC in a microfluidic plate for up to 21 days. Apoptosis and proliferation were assessed by TUNEL and PCNA. Vessel formation by hGEC was confirmed along with expression of endothelial marker VE-Cadherin while hAKPC-P-derived podocytes were positive for nephrin and podocin. De novo deposition of collagen IV in the 3D microfluidic plates was confirmed by immunostaining.

Conclusions: Our preliminary results suggest the feasibility of OrganoPlates for co-culture of podocytes and hGEC in a 3D environment that more closely mimics the structure of the GFB. If successful this system might prove useful for the assessment of several aspects of cell-cell and cell-matrix interaction, thus helping to understand podocytes/endothelial crosstalk (or its perturbations) and how this might affects glomerular homeostasis.

Funding: Private Foundation Support

SA-OR039
Pharmacokinetic Model for Screening Nephrotoxicity Using Kidney on a Chip
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Background: Animal renal clearance is usually higher than human renal clearance, which may underestimate nephrotoxicity. We developed a microfluidic device lined with kidney epithelial cells to mimic in vivo-like microenvironment. We evaluated the nephrotoxicity of two different gentamicin regimens using this kidney on-a-chip and human pharmacokinetic data.

Methods: The microfluidic device had top channels like luminal spaces and bottom channels like interstitial spaces. MDCK cells on the porous membranes between the two channels were exposed with a fluid shear stress (1.0 dyn/cm²). D1 regimen was 19.2 mM underling represents presenting author.

Reduced nutrient and waste clearance was observed in the static condition. For the next 24 hours, D1 and D2 regimens were applied under shear-stress condition. Although the junctional protein immunoreactivity was decreased in both regimens, ZO-1 and occludin immunoreactivity showed a higher in the D1 regimen than in the D2 regimen (P < 0.05).

Conclusions: These data suggest that gentamicin may interrupt junctional protein complex and membrane permeability, and that single dose alleviate the nephrotoxicity, compared to the continuous infused regimen. Microfluidic devices can be one of novel pharmacokinetic models for evaluating nephrotoxicity.

Funding: Other NIH Support - NIH GM096040, Government Support - Non-U.S.
SA-OR042
Non-Invasive Measurement of Renal Blood Flow (RBF) in Rat by Magnetic Resonance Imaging (MRI) 
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Background: Quantitative measurement of RBF provides important information on renal physiology, nephropathies and kidney viability in different animal models. Arterial Spin Labeling–MRI (ASL-MRI) is a non-invasive method to measure blood flow without exogenous contrast media, using arterial water protons labeled by radiofrequency as an endogenous tracer. However, the low signal/noise ratio and the motion artifacts pose a challenge when acquiring RBF in small animals. Our objective is to evaluate the feasibility and reproducibility of the RBF measurement by ASL-MRI under basal conditions and in a high RBF state in rats.

Methods: ASL-MRI images were obtained in seven male Sprague-dawley rats (200-300g) under the inhalatory anesthesia (isoflurane 2%). Rectal temperature probe was used to control the body temperature. After 4 days the MRI studies were repeated in 3 rats (6 kidneys) to evaluate reproducibility, using paired sample T-test and the test-retest reliability (TR) by the equation TR=(1-SDn/Mn)x100 were M and SD are the mean and standard deviation of the RBF in “n” different sessions. RBF was also measured in a set of animals that underwent unilateral nephrectomy 24 hours before and after the surgery. MRI was acquired using a 7 Tesla Varian MRI system with a spin echo imaging sequence using respiratory triggering and navigator correction to reduce motion artifacts. The sequence was averaged 16 times and the total scan time for the entire series of ~20 minutes. In house software was used to analyze the postprocessing imaging.

Results: The mean cortical RBF was 30 5±59 and 271.8±39 ml/min/100g tissue in right and left kidney, respectively. Re-test analysis showed no differences, with the means of differences 9.4±35ml/min/100g tissue (p=0.58). The TR was 92.4±6%. The RBF before and after the nephrectomy was 270±30 and 456.6±34 ml/min/100g tissue (p=0.004), respectively, showing a relative increase of 69.1%.

Conclusions: ASL-MRI performed with navigator correction and respiratory gating is feasible and reliable non-invasive method to measure RBF in rats.

SA-OR043
Intravoxel Incoherent Motion Analysis of Diffusion Weighted Imaging to Glomerular Filtration Rate – Proof of Concept René van der Bel,1 Oliver J. Gurney-Champion,2 Wouter V. Potters,2 Hein J. Verberne,3 Liifert Vogt,1 Erik Stroes,1 Aart J. Nederveen,2 C.T.P. (Paul) Krediet,1 1Internal Medicine, AMC, Univ of Amsterdam, Netherlands; 2Radiology, AMC, Univ of Amsterdam, Netherlands; 3Nuclear Medicine, AMC, Univ of Amsterdam, Netherlands.

Background: Glomerular filtration fraction (FF) can be calculated from the 21H-thalamate clearance (glomerular filtration rate (GFR)) and 1H-piuran clearance (effective renal plasma flow (ERPF)). This technique is costly and time consuming. Intravoxel Incoherent Motion (IVIM) analysis provides an assessment of diffusion weighted imaging (DWI) for fractions of blood and (pre-)urine within kidney tissue. This could serve as a surrogate for filtration fraction. With this study we a proof of concept for an MRI derived kidney function measurement.

Methods: After a baseline phase, 6 healthy volunteers (age 18-24 yrs) were subjected to continuous Angiotensin II (Ang-II) infusion at 3.0 ng/kg/min. Blood and (pre-)urine fractions and FF were measured during a similar infusion protocol.

Results: Ang-IIdo increased both GFR and ERPF (10±7.1%, p=0.016; 24±4.5%, p=0.001), resulting in an increase in FF of 19.4% (p=0.001). RBF decreased from 11±1.2±0.7 to 8.05±1.02 ml/s (by 27%, p=0.001). Renal IVIM imaging showed an increase in the urine fraction of 24.6±1.14% (p=0.002) and a decrease of the perfusion fraction by 12±21.8% (p=0.096). Renal IVIM measures (pre-)urine fractions and FF were correlated (R=0.44, p=0.033). RBF correlated to the gold standard ERPF (R=0.75, p=0.001).

Conclusions: These data suggest that a combination of IVIM and phase contrast kidney imaging could provide reliable and fast noninvasive FF and ERPF measurement.

SA-OR044
Visualization of Kidney Fibrosis in Diabetic Nephropathy by DTI MRI Jun-Ya Kajimori1, Yoshihata Isaka,2 Masaki Hatanaoka,2 Satoko Yamamoto,2 Hiroshi Shibata,4 Akira Fujimori,4 Akihiko Fujikawa,4 Sosuke Miyoshi,4 Naotsugu Ichimaru,1 Toshiki Mortyama,1 Hiromi Rakugi,2 Shiro Takahara.1 1Dept of Advanced Technology of Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 2Dept of Geriatrics & Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; 3Osaka Univ Health Care Center, Osaka Univ, Toyonaka, Osaka, Japan; 4Drug Discovery Res Inst, Astellas Pharma Inc, Tsukuba, Ibaraki, Japan.

Background: Renal fibrosis (RF) is a well-known marker for chronic kidney disease (CKD) progression. However, an available examination for evaluation of RF is invasive biopsy. Diffusion MRI was once recognized as a promising option for RF. But now it is controversial and it could not be applied to diabetic nephropathy (DN).

Methods: To seek an optimal imaging method applicable even for fibrosis in DN, we tried series of MRI imaging methods, including proton density weighted imaging (PDWI), T1 weighted imaging (T1WI), T2 weighted imaging (T2WI), diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI).

Results: We identified DTI MRI by spin echo sequence plus a special kidney attachment as the best option for evaluation of UO fibrosis, compared with normal kidney in the opposite side. To confirm these results, we applied this technique to rat UO therapeutic model with anti-fibrotic reagent, Fasudil. FA values calculated form DTI MRI showed statistically significant linear correlation with RF area measured by Sirius Red or Masson trichrome staining positive area. Next, by using SHIRIDmcr-cp/ep/cp rat with or without telmisartan as a RF model of DN, we finally succeeded in visualization and evaluation of fibrosis accumulated in outer stripe of outer medulla region by FA map.

Conclusions: By DTI MRI with spin echo sequence, it may be possible to accurately evaluate RF in CKD including even DN.


SA-OR045
Super-Resolution Microscopy Reveals the Formation of a Mat of Contractile Fibers as Part of the Podocyte Foot Process Effacement Phenomenon Han Suleiman,1 Jeffrey H. Miner,1 Andrey S. Shaw.1 1Pathology and Immunology, Washington Univ in Saint Louis, Saint Louis, MO; 2Pathology and Immunology, Washington Univ in Saint Louis, Saint Louis, MO; 3Renal Division, Washington Univ in Saint Louis, Saint Louis, MO.

Background: The ~200 nm resolution of traditional microscopes is limited by the wave-length of light. Imaging structures smaller than 200 nm, such as podocyte foot processes and slit diaphragms, has required electron microscopy (EM). New super-resolution imaging techniques can break the diffraction barrier of light, thus allowing us to easily image and resolve the molecular composition of structures in a nanometer range.

Methods: We used an array of antibodies for Stochastic Optical Resolution Microscopy (STORM) to study the spatial distribution of key molecules of the podocyte cytoskeleton and slit diaphragm in healthy and injured glomeruli. We also developed a novel technique that allows us to image podocyte actin cables by EM.

Results: In healthy glomeruli, synaptopodin is localized to the center of each foot process, while nephrin is at the slit diaphragm. As foot processes efface, nephrin redistributes apically away from the base of foot processes. We confirmed this in 3 different injury models. After podocyte injury the positions of synaptopodin and α-actinin-4 clusters did not change, but there was robust recruitment of mossy Ila, normally only in primary processes, to the bases of foot processes. The pattern of mossy Ila staining, in alternating stripes with synaptopodin and α-actinin-4, indicates the formation of contractile actin fibers during effacement. Using our new EM method, we observed a dramatic change in the morphology of actin fibers during effacement.
Conclusions: We demonstrate the utility of super-resolution microscopy to visualize podocyte foot processes and cytoskeleton organization in situ. Our results show that podocytes in live mice are in primary processes, while only non-contractile actin filaments are in foot processes. After foot process effacement, the contractile cables fall to the bottom of the podocyte and form a sarcomere-like contractile network adjacent to the GBM.

Funding: NIDDK Support, Private Foundation Support

SA-OR046

Intravital and Organ Slice Imaging of Podocyte Membrane Dynamics
Sebastian Braehler, 1 Haiyang Yu, 2 Gokul Murali Krishnan, 1 Hani Suleiman, 2 Jeffrey H. Min, 1 Bernd H. Zinsselmeyer, 1 Andrew S. Shaw, 1 Dept of Pathology and Immunology, Washington Univ School of Medicine, St. Louis, MO; 2 Renal Div, Washington Univ School of Medicine, St. Louis, MO.

Background: The elaborate network of podocyte foot processes, which is stabilized by the actin cytoskeleton, is one of the key components of the glomerular filtration barrier. The question of whether podocytes change their shape under physiological conditions or in response to injury has been vigorously debated. The Rho-family of small GTPases is at the center of this debate, as these molecular switches control assembly and disassembly of the actin cytoskeleton. Evidence as to whether and how small GTPases change podocyte shape and dynamics is largely circumstantial, as all studies to date have been conducted in vitro.

Methods: Here we use intravital two-photon imaging of fluorescently labeled podocytes to answer these questions. Rosa26-confetti/Pod-Cre mice were used as reference and compared with mice expressing eGFP-labeled, constitutively active Rac1 (eGFPCA-Rac1) in podocytes. To achieve a higher resolution we also imaged freshly isolated kidney slices to answer these questions. Rosa26-confetti/Podo-Cre mice were used as reference and Immunofluorescence stainings, western blotting and live Ca
2+ imaging were performed on isolated glomeruli from WT, TRPC6 transgenic (TG), and TRPC6 knockout (KO) mice.

Results: Podocytes in Rosa26-confetti/Pod-Cre mice showed a stable network of foot processes, which remained unchanged with time in the absence of significant membrane movement. eGFPCA-Rac1 podocytes lost their characteristic shape and showed increased membrane dynamics and podocyte shedding. Shed podocytes seemed viable, as they were observed migrating in the tubular system. Organ slice imaging resembled the intravital results but yielded a higher temporal-resolution, which validates this approach as a suitable technique to capture intravital imaging. With this approach, we were also able to show that increased membrane dynamics is a feature of injured podocytes in a glomerular disease model.

Conclusions: We show in vivo for the first time that Rac1 converts podocytes from a state of immobility to one with greatly increased membrane dynamics and blunted foot processes, which also occurs in a model of glomerular injury. This suggests that foot process effacement is the end result of a highly dynamic state, and that foot process instability could contribute to proteinuria itself.

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

SA-OR047

Intravital Multiphoton Imaging of Podocyte Ca2+ Confirms the Important Role and Mechanism of TRPC6 in Glomerular Pathology
Kengo Kidokoro, Anne Riquier-brison, Janos Peti-Peterdi. Physiology and Biophysics, and Medicine, Univ of Southern, Los Angeles, CA.

Background: TRPC6 channels in podocytes are important Ca
2+ influx pathways involved in the modulation of the actin cytoskeleton and in the actions of angiotensin II (ANG II). TRPC6 overactivity by gain-of-function mutations and high ANGII leads to albuminuria and chronic kidney disease (CKD). However, the regulation of podocyte Ca
2+ dynamics by TRPC6 and the mechanism of the resulting glomerular dysfunction in vivo and in response to injury have been elusive. We aimed to directly and quantitatively visualize and study the dynamic effects of TRPC6 on podocyte and glomerular function during the development of glomerular injury.

Methods: Serial multiphoton microscopy of the intact living kidney of the same wild type (WT), TRPC6 transgenic (TG), and TRPC6 knockout (KO) mice was performed over two weeks of high ANGII treatment (1000 ng/kg/min). All mice expressed the intensely green and calcium sensitive fluorescent protein GCaMP3 only in podocytes. Changes in single cell GCaMP3 fluorescence intensity were measured and served as readout for podocyte (Ca
2+) changes.

Results: Systolic blood pressure increased from baseline 106.4±145.5 mmHg after ANGII treatment for two weeks in mice with WT, similarly in TRPC6 TG and KO mice. In WT mice, normalized GCaMP3 fluorescence intensity in podocytes (Ca
2+) increased >2-fold in TG, while in non-podocytes, with no change in untreated mice. In KO mice, normalized GCaMP3 fluorescence intensity was decreased compared to WT mice. In TRPC6 TG mice, normalized GCaMP3 fluorescence intensity increased >2-fold, but remained below 20%, at baseline in TRPC6 TG and KO mice, respectively. Glomerular functional parameters after ANGII treatment were examined in TRPC6 TG mice, while improved in TRPC6 KO mice. Podocytes with high GCaMP3 fluorescence intensity appeared migrating to the parietal Bowman’s capsule after ANGII in WT and TRPC6 TG, but not in TRPC6KO mice.

Conclusions: This study demonstrated in vivo direct visual evidence of the critically important pathogenic role of TRPC6 in the development and progression of glomerular disease. Podocyte TRPC6 is a promising therapeutic target for the prevention of CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Amgen

SA-OR048

Mesangial Filopodial Invasion of Glomerular Capillaries in Alport Syndrome
Dominic E. Cosgrove, Daniel T. Meehan, Brianna M. Dufek, Duane C. Delimont. Genetics, Boys Town National Research Hospital, Omaha, NE.

Background: Recent work shows mesangial cell fillopodia invade the glomerular capillaries in Alport mice and humans. Filopodia progressively deposit laminin 211 and likely other mesangial matrix proteins in the GBM. Laminin 211 activates focal adhesion kinase in podocytes, which results in up-regulation of metalloproteinases and pro-inflammatory cytokines. These novel observations, which are key to glomerular disease initiation, have been met with some skepticism, which incentivized the current study.

Methods: Three color structured illumination microscopy (SIM, an ultra-high resolution confocal) was used to label mesangial cells and results in the formation of drebrin-immunopositive actin microspikes (filopodia).

Results: SA-OR046

The elaborate network of podocyte foot processes, which is stabilized by the actin cytoskeleton, is one of the key components of the glomerular filtration barrier. The question of whether podocytes change their shape under physiological conditions or in response to injury has been vigorously debated. The Rho-family of small GTPases is at the center of this debate, as these molecular switches control assembly and disassembly of the actin cytoskeleton. Evidence as to whether and how small GTPases change podocyte shape and dynamics is largely circumstantial, as all studies to date have been conducted in vitro.

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Conclusions: We show in vivo for the first time that Rac1 converts podocytes from a state of immobility to one with greatly increased membrane dynamics and blunted foot processes, which also occurs in a model of glomerular injury. This suggests that foot process effacement is the end result of a highly dynamic state, and that foot process instability could contribute to proteinuria itself.

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

SA-OR049

The DREADD Concept: A Novel In Vivo Tool for Kidney Research Questioning the Role of Ca
2+ on Actin Dynamics in Podocytes
Sybille Köhler, 1,2 Sebastian Braehler, 1 Julia Binz, 1,2 Matthias Hackl, 1,2 Frank Schwaeda, 1,2 Thomas Benzing, 1,2 Bernhard Schermmer, 1,2 Paul T. Brinkkoetter, 1,2 Dept II of Internal Medicine and Center for Molecular Medicine, Univ Hospital Cologne, Germany; 1 Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Germany; 2 Dept of Physiology, Univ of Regensburg, Germany; 2 Dept of Pathology and Immunology, Washington Univ School of Medicine.

Background: The close homology between the slit diaphragm of the kidney glomerulus and the mechanosensor in C. elegans led to the hypothesis that the slit diaphragm is part of a conserved mechanosensor that is closely linked to an actin-based, contractile cytoskeleton regulated by Ca
2+.

Methods: We generated a transgenic mouse line with specific expression of a mutated (Y149C/A239G) G protein-coupled human muscarinic type 3 receptor transgene (hM3) in the ROSA26 locus. This receptor is exclusively activated by the synthetic compound CNO and not by the endogenous M
2+/-agonist acetylcholine. We mated the hM3-DSTOP_CRE-mouse with the podocin:cre mouse to achieve podocyte specific expression. We tested receptor expression and function both, in vitro and in vivo using immunofluorescence stainings, western blotting and live Ca
2+ imaging using 2-photon microscopy.

Results: Here, we applied the DREADD (designer receptor exclusively activated by a designer drug, Conklin et al. 1998) concept to further test this hypothesis and to investigate the effects of an intracellular Ca
2+ increase on the podocyte actin cytoskeleton. Even though we observed a strong Ca
2+ increase in podocytes after CNO-administration no effects on the actin based cytoskeleton, glomerular perfusion or filtration were observed. Even administration of CNO over a prolonged period (4 wks) did not induce glomerular disease.

Conclusions: In conclusion, increasing Ca
2+ levels in podocytes alone are not sufficient to induce podocyte rearrangements and to affect glomerular perfusion and filtration. Hence, these results challenge our current view on actin dynamics in podocytes and their role in glomerular perfusion and filtration.

Funding: Government Support - Non-U.S.

SA-OR050

Loss of Epithelial Membrane Protein 2 Aggravates Podocyte Injury via Uregulation of Caveolin-1
Weimin Zhou, 1 Xiaoyang Wan, 1 Zhao-hong Chen, 1 Won- II Choi, 1 Heon Yung Gee, 2 Friedhelm Hildebrandt, 1-3, 4 Pediatrics and Cardiogenic Disease, Univ of Michigan, Ann Arbor MI; 1 Research Inst of Nephrology, Jinling Hospital, Nanjing, China; 2 Boston Children’s Hospital, Boston, MA; 3 Howard Hughes Medical Inst.

Background: Nephrotic syndrome is a chronic kidney disease defined by proteinuria with subsequent hypoalbuminemia, hyperlipidemia and edema, due to impaired renal glomerular filtration barrier function. Glomerular podocytes have been proposed to play a critical role in the maintenance of glomerular filtration barrier and the pathogenesis of

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

Underline represents presenting author.
nephrotic syndrome. We have previously identified mutations in EMP2 (epithelial membrane protein 2) as a cause of this disease. In this study, we have confirmed that TNFα upregulation in podocytes plays a fundamental role in regulating the progression of podocyte injury when compared to total deletion of Agtr1a in Dnm 1, 2 KO podocytes.

Conclusions: Our results demonstrate that deletion of Dynamin 1, 2 in podocytes results in increased AT1aR signaling. Inhibition of AT1aR signaling in podocytes plays a fundamental role in regulating the progression of podocyte injury when compared to total deletion of Agtr1a in Dnm 1, 2 KO podocytes.

SA-OR053

The Spectrum of Nephrotic Syndrome from Minimal Change Disease to FSGS Correlates with Rac1 Activation


Nephrology, McGill Univ, Montreal, Quebec, Canada.

Background: Within podocytes, cytoskeletal organization is regulated by Rho-family GTPases including Rac1. Clinical and animal studies suggest that Rac1 activation within podocytes contributes to the pathogenesis of nephrotic syndrome (NS). We hypothesize that Rac1 activity is increased in clinical NS and podocyte-specific activation of Rac1 will result in NS in mice.

Methods: Kidney biopsies from patients with minimal change disease (MCD) and idiopathic focal segmental glomerulosclerosis (FSGS) were immunostained for active Rac1. Serum from FSGS patients was used to treat isolated podocytes. Mice carrying the tetracycline-inducible constitutively active Rac1 mutant (L61, CA-Rac1, Flag-tagged) were bred with mice with the podocin-driven reverse tetracycline trans-activator to generate double transgenic mice (DTG). Podocin was targeted with Dox. When Dox was withdrawn after 5 days, low responders returned to near-normal levels after 4 weeks. When Dox was withdrawn after 2 weeks in high responders, podocin was not resolved. After 1 month, high responders displayed severe glomerulosclerosis.

Conclusions: Active Rac1 staining is increased in patients with NS. FSGS sera promote Rac1 activation in cultured podocytes. In mice, the amount of Rac1 activation within podocytes determines severity of foot process effacement, podocinuria, and degree of reversibility upon Dox withdrawal. The amount of Rac1 activation may be a critical factor determining whether MCD or FSGS arises within the NS spectrum.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

73A
SA-OR055

Novel Score to Predict Post-Transplant Outcomes  Miklos Zsolt Molnar,1 Danh V. Nguyen,2 Vanessa A. Ravel,2 Elani Streja,3 Mahesh Krishnan,4 Yanjun Chen,2 Csaba P. Kovacsdy,1 Kamary Kalantar-Zadeh,2 1Univ of Tennessee Health Science Center, Memphis, TN; 2Univ of California, Irvine, CA; 3DaVita Healthcare Partners, VA.

Background: Several previous studies have developed scoring tools to predict the allograft and patients’ survival in kidney transplant patients using information, which was not available at the time of transplantation. We developed a score to predict post-transplant outcomes using pre-transplant information including routine laboratory data available at the time of transplantation.

Methods: Linking the 5-year patient data of a large dialysis organization to the SRTR, we identified 15,125 hemodialysis patients who underwent first kidney transplantation. Prediction models were developed using Cox models for (a)mortality, (b)transplant failure(death censored) and (c)combined death or transplant failure. The cohort was divided into a two-thirds development set and a one-third validation set. We used backward-selection based on Akaike’s information criterion to avoid arbitrary and ineffective selection rules based on p-values. We used the bootstrap method to assess model overfitting and calibration using the development dataset. Model predictive discrimination was assessed using the index of concordance, or C statistic, which accounts for censoring in time-to-event(a-c).

Results: Patients were 50±13 years old and included 39% women, 15% African-American and 36% diabetics. For prediction of post-transplant mortality and graft loss 10-10 predictors were used (recipients’ age, cause and length of ESRD, hgb, albumin, comorbidities, race and type of insurance as well as donor characteristics such as donor age, diabetes, number of HLA mismatches). The new model showed the overall best C-statistics comparing to the currently used EPTS score.

Discrimination C (95%CI)

<table>
<thead>
<tr>
<th>Current model</th>
<th>Model based on EPTS predictors</th>
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<tbody>
<tr>
<td>Combined</td>
<td>0.63 (0.62-0.65)</td>
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<td>Mortality</td>
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Conclusions: The new prediction tool, using exclusively data available prior to the time of transplantation, performs better to predict outcomes than currently used tool such as EPTS.

Funding: Other NIH Support - R21AG047306 and R01DK59668

SA-OR056

Long-Term Deceased Donor Kidney Graft Survival Has Improved in the Last Decade  Douglas Scott Keith, Gayle M. Vranic, Anggie G. Nishio-Lucar. Medicine, UVA, Charlottesville, VA.

Background: Long-term graft survival did not improve significantly in the 1990s. We sought to determine if long-term graft survival is improving in the last decade.

Methods: All adults deceased donor renal transplant recipients in the SRTR database between 2000 and 2010 were included in the study. K-M survival analysis was carried out based on year of transplantation in all recipients who had at least 6 months of graft survival. Graft survival, death censored graft survival and death with graft function were analyzed. Cox modeling was carried out to determine if the year of transplant affected the outcomes. Graft survival, death censored graft survival and death with graft function were analyzed.

Results: Patients were 50±13 years old and included 39% women, 15% African-American and 36% diabetics. For prediction of post-transplant mortality and graft loss 10-10 predictors were used (recipients’ age, cause and length of ESRD, hgb, albumin, comorbidities, race and type of insurance as well as donor characteristics such as donor age, diabetes, number of HLA mismatches). The new model showed the overall best C-statistics comparing to the currently used EPTS score.

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Funding: Other NIH Support - R21AG047306 and R01DK59668

Improve Outcomes in Transplant Recipients

This occurred in spite of the decreasing quality of kidneys based on KDPI. The improvement in graft survival was exclusively due to improved death censored graft survival. The rate of death with graft function did not change. This steady improvement in graft survival occurred during a transition in maintenance immunosuppression from cyclosporine based regimens to tacrolimus. Cox analysis confirmed the improvement in graft survival and death censored graft survival but also showed that the rate of death with graft function was decreasing when adjusted for the covariates.

<table>
<thead>
<tr>
<th>Transplant Year</th>
<th>H.R of Graft Failure (C.I.)</th>
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<tbody>
<tr>
<td>Reference: 2000</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>0.97 (0.93-1.03)</td>
</tr>
<tr>
<td>2002</td>
<td>0.94 (0.89-0.98)</td>
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<tr>
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<tr>
<td>2007</td>
<td>0.79 (0.75-0.83)</td>
</tr>
<tr>
<td>2008</td>
<td>0.71 (0.67-0.75)</td>
</tr>
<tr>
<td>2009</td>
<td>0.73 (0.68-0.78)</td>
</tr>
<tr>
<td>2010</td>
<td>0.70 (0.63-0.75)</td>
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</table>

Covariates: Age, Race, Gender, Acute Rejection, DGF, KDPI, HLA mismatch, Dialysis Duration, PRA, and Retransplant

Conclusions: Long-term graft survival has improved in the last decade in spite of declining donor quality. This improvement was associated with a shift in maintenance immunosuppression to tacrolimus.

SA-OR057

Characteristics Associated with Greater Than 5 Year Kidney Graft Survival Among HIV+ Recipients  Laura Panarey, Alden Michael Doyle, Karthik M. Rangan. Nephrology and Hypertension, Drexel Univ Hahnemann Hospital, Philadelphia, PA.

Background: We have previously reported that donor factors have direct influence on the incidence of peri-operative delayed graft function (DGF), decreased time to acute cell-mediated rejection (ACR), and affect graft outcomes.

Methods: Our aim was to identify donor and recipient risk factors associated with > 5 year kidney allograft survival among HIV+ recipients by conducting a retrospective chart analysis of all HIV + transplants performed at our center with at least 5 years of follow up (N=94).

Results: In our HIV + kidney transplant cohort, greater than 5 year allograft survival was significantly associated with modifiable risk factors including: living donor allografts (LRT), minimizing cold ischemia time, and pre-transplant diagnosis of HCV. Non-modifiable demographics not associated with at least 5 year survival included: Age, Sex, BMI, and the history of CAD or DM. Implicated elsewhere; neither ethnicity nor gender mismatch of allograft appeared to significantly affect our HIV + transplant outcomes at 5yars. While cellular and humoral rejection are known to affect the HIV + transplant cohort; time to ACR was significantly different, inferior graft survival experienced an earlier first cell-mediated rejection (ACR), and affect graft outcomes.

Discrimination C (95%CI)

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Conclusions: Our data suggest that optimization of HIV+ kidney transplant outcomes is associated with modifiable factors such as HCV (encouraging data for new treatment); addendum of donor quality (LRT preferable) and avoidance of DGF.

Recipient Factors  p-Value  <5 year allograft survival  > 5 year allograft survival

| Diabetes Mellitus (DM) | 0.0126 | 11/73 | 6/14 |
| Cardiovascular (CAD/PVD/UA) | 0.0298 | 14/73 | 6/14 |
| Hepatitis C Virus (HCV) | 0.0025 | 10/73 | 4/20 |
| Protease Inhibitors (HIV treatment) | 0.05 | 44/56 | 12/56 |
| Non-Protease Inhibitor (HIV treatment) | 0.85 | 28/38 | 16/28 |

Donor Factors  p-Value  <5 year allograft survival  > 5 year allograft survival

| KDRI (kidney donor risk index) | 0.004 | 1.44 ± 0.5 | 1.38 ± 0.6 |
| Cold Ischemia Time (CIT) | 0.07 | 15/72 | 12/20 |
| Non-Cadaveric Transplant (LRT) | 0.0056 | 3/73 | 4/20 |
| DGF | 0.0013 | 40/73 | 11/20 |

Figure 1: Risk factors high risk (HIV+) Kidney Transplant Cohort

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR058

Identifying the Two Specific Types of Antibody-Mediated Rejection and Their Outcomes in Kidney Recipients  Olivier Aubert,1 Alexandre Lourdy,1 Luis G. Hidalgo,2 Jeff Reeve,2 Denis Glotz,2 Christophe M. Legendre,1 Carmen Lefaucheur,3 Philip F. Halloran,4 INSERM,4 ATAGIC.

Background: Antibody-mediated rejection (ABMR) can be related to preformed/recurrent anti-HLA DSA or de novo anti-HLA DSA.

Methods: We included 965 kidney biopsies taken from two North American and five European centers and assessed patients with ABMR. We compared patients with preformed/recurrent DSA (Type-1 ABMR) to patients with de novo DSA (Type-2 ABMR). Microarray-based gene expression was assessed in biopsies. Patients with type-1 were managed in two centers with aggressive standardized treatment protocols; type-2 ABMR was managed as standard-of-care.

Results: We identified 278 patients with ABMR: 153 (55%) type-1 and 125 (45%) type-2. The mean time from transplantation to rejection was 10.1±18.8 vs 84.9±71.1 months for the type-1 and 2 ABMR. The mean eGFR at the time of biopsy was lower in type-1 ABMR (38±18) vs type-2 (46±20 mL/min/1.73m²) (p<0.0012). Kidney biopsies with type-1 ABMR presented with higher microcirculation injury (p=0.04 vs. 2.4±1.5) and less transplant glomerulopathy score (0.5±0.9 vs. 1.6±1.1) (p<0.0001). C4d PTC deposition was similar (32% vs 34%). Using the gene expression assessment, type-1 ABMR exhibited a higher expression of global disturbance transcripts, injury-repair response associated transcripts (IRRATS), endothelial cell associated transcripts (ENDAT), injury-induced transcripts (IRIT3) (p<0.0001) but a lower expression of NK cell transcript burden (NKB) (p=0.0147). Type-1 and Type-2 ABMR exhibited similar high expression of transcripts reflecting γ-IFN response (GRIT1), T cell transcript burden (TCB) and macrophage-associated transcripts (QCMAT). Kidney allograft survival at 4 and 8 years after rejection was superior in type-1 ABMR (72% and 58%) compared to type-2 (51% and 35%) (p<0.0001).

Conclusions: Type-1 and type-2 ABMR present with distinct phenotypes and outcomes. The fact that type-1 ABMR is treated with aggressive defined protocols and has superior outcomes despite lower GFRs and more molecular injury at the time of biopsy suggests that between Fibrolast Growth Factor 23 (FGF-23) concentrations and the evolution of cardiac morphology following transplant.

SA-OR060

Longitudinal Assessment of Cardiac Morphology and Function following Kidney Transplantation Clark David Kensing1, Antonio Hernandez,2 Megan Fairchild,4 Guanhua Chen,4 Loren Lipworth,4 Talat Alp Ikizler,4 Kelly A. Birdwell,4 Dept of Surgery, Vanderbilt Univ Medical Center; 3Dept of Anesthesiology, Vanderbilt Univ Medical Center; 4Dept of Biostatistics, Vanderbilt Univ Medical Center; 4Dept of Medicine, Vanderbilt Univ Medical Center.

Background: Despite improvement in traditional cardiovascular (CV) risk factors following renal transplantation, the death rate from CV disease remains high. Our aim was to evaluate the longitudinal change of cardiac morphology and function in a cohort of patients following renal transplantation, as well as to evaluate the association between Fibrolast Growth Factor 23 (FGF-23) concentrations and the evolution of cardiac morphology following transplant.

Methods: We performed a longitudinal prospective cohort study of 145 kidney transplant recipients, measuring left ventricular mass index (LVMi), left atrial volume index (LAVi) and ejection fraction (EF) by echocardiography at months 1 (baseline), 12, and 24 post-transplant. FGF-23 levels were measured at months 1 and 24 post-transplant. A linear mixed effects model was used to assess each outcome adjusting for age, race, gender, time on dialysis, CV disease, glomerular filtration rate, diabetes, and body mass index.

Results: The cohort (mean age 49±13 years) was 74% male and 75% white. LVMi (P<0.001), LAVi (P<0.001), and EF (P<0.009) decreased significantly over time following transplant. Results from the multivariate models can be reviewed in Table 1. A one-unit decrease in FGF-23 was significantly associated with a 5.83 grams/meter² decrease in LVMi (P=0.04).

Conclusions: LVMi, LAVi and EF improved significantly over 12 and 24 months post-transplant. There was also a significant association between FGF-23 and LVMi following transplant. This study is funded by NIDDK, Nephrology, and Renal Transplantation, and University Hospitals Leuven, Belgium.

SA-OR059

Serum Dickkopf-1, Renal Allograft Fibrosis and the Risk of Graft Failure After Kidney Transplantation Martin H. De Borsse1, Charlotte A. Keyzer,1 Jelmer K. Hulmala,2 Thomas Vanhove,3 Gerjan Navis,1 Dirk R. Kuypers,2 Stephanie J.L. Bakker,1 Dept of Nephrology, Univ Medical Center Groningen, Netherlands; 2Dept of Nephrology and Renal Transplantation, Univ Hospitals Leuven, Belgium.

Background: Renal fibrosis is a final common pathway contributing to graft failure after kidney transplantation (KTs). Aberrant Wnt/β-catenin signaling contributes to progressive renal fibrosis. Dickkopf-related protein 1 (Dkk-1) is a soluble endogenous inhibitor of the Wnt signaling pathway, and is induced in response to tissue injury in animal studies. We investigated whether serum Dkk-1 is associated with renal interstitial fibrosis and graft failure in renal transplant recipients (RTR).

Methods: Serum Dkk-1 was measured by ELISA (R&D) in two cohorts of outpatient RTR. In a cross-sectional cohort we analyzed the relationship between Dkk-1 and prevalent renal fibrosis using logistic regression. In a longitudinal cohort we studied the association with graft failure using Cox regression.

Results: In the cross-sectional cohort (n=225, 60% male, age 54±13 years) serum Dkk-1 was associated with renal fibrosis at two years post-KTx independent of age, sex, proteinuria and eGFR (odds ratio 2.10 [95% CI 1.11-3.95], P=0.02). In the longitudinal cohort (n=700, 57% male, age 53±13 years, 5.4±1.9-12.0 years after KTx) Dkk-1 was associated with graft failure during 3.1±2.8-3.8 years of follow-up. Serum Dkk-1 was inversely associated with graft failure (HR 0.45 [95% CI 0.27-0.76], P=0.003 per doubling of Dkk-1), independent of known risk factors for graft failure or Dkk-1 correlates. The association persisted in sensitivity analyses restricted to patients with interstitial fibrosis/hyaluronic atrophy.

Conclusions: We present the first human data connecting serum Dkk-1, an endogenous inhibitor of the pro-fibrotic Wnt/β-catenin signaling, with prevalent renal allograft fibrosis, and with long-term protection against graft failure in RTR. These findings are in line with preclinical studies suggesting that Dkk-1 is induced upon tissue injury and serves as an endogenous anti-fibrotic factor, and position Dkk-1 as a potential target for anti-fibrotic therapy after KTx.

Funding: Pharmaceutical Company Support - The generation of the cohort was made possible by a grant from the Dutch Top Institute Food and Nutrition. M.H.J.B. and C.A.K are supported by a consortium grant from the Dutch Kidney Foundation (NIGRAM consortium, grant no. C10.11). This study was funded by a grant from De Cock-Hadders Foundation (grant no. 2015-44).

SA-OR061


Background: Over 10 years we have studied the safety and efficacy of tolerance induction using hematopoietic cell transplantation in combination with kidney transplantation.

Methods: Twenty-two patients underwent HLA-matched living donor kidney transplantation followed by a conditioning regimen of 10 fractions of total lymphoid irradiation (12 Gy total) and 5 doses of ATG. Inclusion of purified donor CD34+ hematopoietic progenitor cells and T cells was on day 11 post-kidney transplant. Fifty-three patients contemporaneously underwent HLA-matched living donor kidney transplantation under conventional immunosuppression.

Results: Seventeen patients developed mixed chimerism of 6 months duration or longer and have now been off immunosuppression from 1 to 7 years. Their outcomes at two years post-transplant are compared to those of the 52 (one graft was lost to thrombosis on day 1) conventionally treated patients.
Conventionally Treated, 2006-13 | Tolerance Induction, 2005-13
---|---
Number | 52 | 17
Immunosuppressants (monoch/duo/triple) | 2 / 34 / 16 | Off drug 4 to 18 mo (of 24 mo)
Age at transplant (years) | 38 +/- 11.2 | 40 +/- 10.5
Sex (M/F) | 26/26 | 9/8
Cause of ESRD (DM/NG/other) | 4 / 17 / 31 | 1 / 6 / 10
Infection (N of episodes) | 8 (1 CMV, 2 v. zoster) | 6 (1 CMV, 4 v. zoster)
Cancer | 0 | 1 (breast, at 23 mos)
Acute rejection (N of patients) | 3 (5.9%) | 0
Creatinine (mg/dL) | 1.2 +/- 0.35 | 1.2 +/- 0.26
Weight gain (kg) | 5.2 +/- 7.36 | 7.4 +/- 8.39
Hypertension | 27 (52%) | 9 (55%)
Antihypertensives drugs (1/2/3) | 15 / 9 / 36 | 6 / 3 / 0
Hyperlipidemia | 20 (39%) | 3 (18%)
Post-transplant diabetes mellitus | 4 (7.8%) | 0

Death-censored graft survival is shown (p=0.10).

Conclusions: Transplantation under this protocol is safe, achieves tolerance eliminating risk of acute rejection, and offers a better metabolic profile and better graft survival with time.

Funding: Other NIH Support - NHLBI, Private Foundation Support

SA-OR062

Better Renal Function Preservation with Early Conversion to Everolimus in De Novo Renal Transplant Recipients: 24-Month Results from the ELEVATE Study

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Background: Long-term exposure to calcineurin inhibitors (CNIs) is one of the key factors contributing to progressive deterioration of renal function and graft loss. We present the 24 month (M) renal outcomes from the ELEVATE study which determined whether early CNI to everolimus (EVR) conversion in renal transplant recipients (RTxRs) provides better preserved renal function compared to continuation of standard CNIs.

Methods: The ELEVATE (NCT01114529) was a 24M, multicenter, open-label study, in which de novo RTxRs were randomized (RND) at 10-14 weeks post-transplant to convert from CNI to EVR (n=360; C, 6-10 ng/mL) or continue standard CNI (n=357; C; tacrolimus: 5-10 ng/mL, cyclosporine: 100-250 ng/mL) all received enteric-coated mycophenolate sodium + steroids. The primary end point was change in estimated glomerular filtration rate (eGFR; MDRD-4) from RND to M12.

Results: A total of 717 patients were RND; 229 (65%) and 283 (79%) patients completed on study drug in EVR and CNI groups, respectively. The least squares (LS) mean change in eGFR for EVR vs CNI from RND to M12 was 0.25 vs 1.45 (diff: 1.70; p=0.134) and 0.74 vs -1.07 (diff: 1.80; p=0.017) mL/min/1.73 m² for intent-to-treat (ITT) and on-treatment (OT) analysis, respectively. Up to M24, mean eGFR was significantly higher at all time-points after RND in EVR vs CNI group for OT analysis. At M24, mean eGFR in EVR vs CNI groups was 62.5 vs 57.4 mL/min/1.73 m² (ITT: p=0.006) and 66.1 vs 59 mL/min/1.73 m² (OT: p=0.001), respectively. The difference in eGFR at M24 between EVR and CNI groups was 5.1 (ITT) and 7.1 mL/min/1.73 m² (OT), respectively, in favor of EVR. Pretreatment (3 day) was reported in three patients in the EVR group and two in the CNI group.

Conclusions: Early conversion to EVR therapy 3M post-transplant vs continued CNI resulted in better preserved renal function up to 2-years of follow-up.

Funding: Pharmaceutical Company Support - Novartis

SA-OR063

Month 48 Follow-Up Results of the HERAKLES Study: Superior Renal Function After Early Conversion to an Everolimus-Based Calcineurin Inhibitor Free Regimen Kiemens Ruud,1 Oliver Witzke,1 Thomas Rath,2 Peter Wellens,1 Johannes Jacobs1,2 Bertil Wennemars1,2,3,4 A. Hauser,1 RoFa.5 G.1,1 Petra Reinke,1 Martina Portner,1 Martin G. Zeier,1 Frank Lehner,1 Wolfgang Arns,1 Claudia Sommerer,1 HERAKLES Study Group, Germany; HERAKLES Study Group, Switzerland; Novartis Pharma, Germany.

Background: To follow up on renal function (GFR) at month (mo) 48 after kidney transplantation (Tx) in patients (pts) on immunosuppressive regimen with different calcineurin inhibitor (CNI) exposures.

Methods: 802 pts were included in this prospective, open-label, randomized multi-center study. After induction with basiliximab all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 mo post Tx 499 pts were randomized: 1) to continue standard (STD) CsA (100-180ng/ml) with EC-MPS (n=166), b) to a CNI-free regimen with everolimus (EVR, 5-10ng/ml) + EC-MPS (n=171) or c) to convert to CNI-reduced CsA (50-75ng/ml) with ECVR (EC-3.8ng/ml) (n=162).

Results: GFR (Nankivell, ITT) was similar at randomization 3 mo post Tx and had significantly improved at mo 12 by -1.56mL/min (95%CI [-2.92; -0.83]; p=0.001) and remained significantly improved by -6.8mL/min in favor of CNI-free from mo 12 (89p=0.02). 34% of CNI-free, 36% of CNI-reduced and 44% of STD pts had an improvement in GFR at mo 48 (p=0.09 CNI-free vs STD). All 3 groups had similar rejection rate since randomization (13% CsA-free, 16% CNI-free, 16% CNI-reduced) and overall comparable safety profile. Mean trough levels at mo 48 were for CsA 111ng/ml in STD and 86ng/ml in CNI-reduced pts and for EVR 5.9ng/ml in CNI-free and 5.5ng/ml in CNI-reduced pts.

Conclusions: CNI-free as well as reduced CNI in combination with EVR represent both efficacious and safe regimen. CNI-reduced group had higher CsA levels than anticipated. The fact that CNI reduction was not fully accomplished might have prevented GFR differences compared to STD in this randomized treatment group. However, CNI-free regimen was associated with better GFR maintained for 4 years post Tx. The results of this large trial confirm previous reports of improved GFR after Csa withdrawal with EVR in combination with EC-MPS.

Funding: Pharmaceutical Company Support - Novartis Pharma

SA-OR064

Belatacept pts Had Superior Graft Survival versus CsA pts: Final Results from BENEFIT Flavio Vincenti,1 J. Grinyo,2 R. Bray,3 L. Rostaing,4 B. Bresnahan,5 K. Rice,6 S.M. Steinberg,7 H. Gebel,8 M. Polinsky,8 U. Meier-Kriesche,9 S. Munier,10 R. Townsend,11 C.P. Larsen,12 University of California, San Francisco; 13University of Bellvitge, Barcelona, Spain; 14Emory Univ, Atlanta; 15University and INSERM U563, IFR-BMT, Toulouse, France; 16Medical College of Wisconsin, Milwaukee; 17Baylor Univ Medical Center, Dallas; 18Sharp Memorial Hospital, San Diego; 19BMS, Lawrenceville.

Background: At 3 and 5 yrs post-transplant in BENEFIT, renal function was improved in kidney transplant recipients administered belatacept (bela) vs CsA. We report final 7-yr results.

Methods: Pts were randomized to more (MI) or less intensive (LI) bela or CsA regimens. Outcomes were assessed for all randomized, transplanted pts at yr 7. In a prospective analysis, time to death or death-censored graft loss was compared using Cox regression. Presence of DSAs was established centrally (FlowPRA). Kaplan–Meier estimates for the cumulative rate of de novo (DN) DSAs were derived. Mean calculated GFR (cgGFR) was estimated from mos 1–84 using a repeated measures model with an unspecified covariance matrix. Differences in GFR at each timepoint were also estimated.

Results: In total, 153/219 of bela MI, 163/226 of bela LI and 131/221 of CsA pts were evaluable. HRs comparing time to death/graft loss were 0.573 for bela MI vs CsA (P=0.02) and 0.570 for bela LI vs CsA (P=0.02)—a 43% risk reduction in death/graft loss for bela MI vs CsA. Cumulative event rates of DN DSAs at yr 7 for bela MI, bela LI, and CsA were 1.86, 4.64, and 17.81, respectively. Serious AE rate was similar at 71% (bela MI; 69%, bela LI; 76%, CsA). Mean cgGFR increased slightly over 7 yrs for both bela regimens but declined for CsA. Differences in mean cgGFR at yr 7 were 25.6 mL/min/1.73 m² for bela MI vs CsA and 23.7 mL/min/1.73 m² for bela LI vs CsA differences favored each bela regimen vs CsA at all time points (P<=0.001).

Conclusions: In this 7-yr analysis, bela conferred statistically better graft survival and renal function vs CsA, with a reduced incidence of DN DSAs. The bela safety profile was consistent with previous reports.

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Underline represents presenting author.

76A
SA-OR065

Differential Expression of MicroRNA in Urinary Exosomes of Preeclampsia Patients
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Background: Urinary exosomes are low density membrane vesicles originating from the multiple cellular bodies of upstream renal epithelial cells. The exosomes contain molecules, such as microRNA (miRNA), which may serve as potential biomarkers for kidney disease, and, in particular, preeclampsia, a systemic disease with renal manifestations that affects 5-8% of pregnant women in the world.

Methods: We recruited 10 preeclamptic pregnant women and 9 healthy pregnant controls; each submitted a 50 mL spot urine sample for exosome isolation. Exosomes were isolated by sequential centrifugation and ultracentrifugation, and the exosomal miRNAs purified using mirNeasy kit (Qiagen). After isolation of miRNA from urinary exosomes, we used the Nanostring nCounter system to assess miRNA expression. Analysis of Variance (ANOVA) was performed to test for differences in exosomal miRNA expression (log2) between cases (n=10) and controls (n=9). Statistical significance was defined at p<0.05

Results: After adjusting for maternal age and experimental batch, two miRNAs remained statistically significant. miR-544a was upregulated among cases compared to controls, whereas and miR-495 was downregulated. Enrichment analysis of the 624 and 913 highly predicted downstream mRNA targets showed that miR-544a targets were enriched for cardiovascular system diseases including arterial pressure (p=6.6x10-4) and vasocostriction (p=1.2x10-3); whereas the targets of miR-495 were associated with renal and urological system development (p=2.8x10-6).

Conclusions: We believe that these pilot results demonstrate the potential to identify a biomarker for preeclampsia that may be mechanistically plausible. Larger studies are presently being conducted.

SA-OR066

Functional Testing of Human Epithelial Na+ Channel Missense Variants Identified in the GenSalt Study
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Background: In Liddle syndrome, epithelial Na+ channel (ENaC) mutations that result in increased cell-surface expression are associated with early-onset hypertension, underscoring the importance of this channel in modulating blood pressure. Whether genetic variants that result in subler increases in channel function contribute to salt-sensitive hypertension remains unclear.

Methods: A number of human ENaC variants were identified in 300 Genetic Epidemiology Network of Salt Sensitivity (GenSalt) participants with salt-sensitive hypertension and 300 with salt-independent hypertension. We used the Xenopus oocyte expression system to examine the functional properties of missense ENaC variants identified in the GenSalt study.

Results: Among 6 SCN11A (encoding the ENaC α subunit) variants, 3 (s115N, r476W and a481M) showed significantly greater, and one (a334T) showed significantly lower ENaC currents than wild type. Among 3 SCN11B (ENaC β subunit) variants, J3D1N showed a significant reduction in ENaC currents; b6635N showed a significant increase in ENaC currents. Both β subunit variants substitute amino acids in intracellular domains. Among 5 SCN11G (ENaC γ subunit) variants, one (γL438Q) had significantly greater ENaC currents than wild type. Each of the variants located in ENaC’s extracellular domain that altered channel activity also altered Na+ self-inhibition, a process wherein extracellular Na+ suppresses channel open-probability.

Conclusions: Some missense ENaC variants identified in the GenSalt study alter ENaC function and may influence salt-sensitivity of blood pressure.

Funding: NIDDK Support, Other NIH Support - NHLBI

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Underline represents presenting author.

SA-OR067

Nephron Specific Deletion of the Prorenin Receptor Modulates Blood Pressure and Urinary Na Excretion
Nirupama Ramakumar, 1 Deborah Stuart, 1 Elena V. Mironova, 2 Vladislav V. Bugay, 2 Mykola Mamenko, 1 Shaping No Wang, 1 Oleh Pochynuk, 1 James D. Stockand, 2 Donald E. Kohan. 1 Medicine, Univ of Utah; 2 Medicine, Univ of Texas Health Sciences Center - San Antonio; 3 Medicine, Univ of Texas Health Sciences Center - Houston.

Background: The nephron prorenin receptor (PRR) may modulate blood pressure (BP) and Na balance.

Methods: Since previous models of PRR knockout (KO) mice had early lethality and/or structural defects, we developed an inducible nephron-wide PRR KO using the Pax8/Luc1 transgenes.

Results: Disruption of PRR at 1 month of age caused no renal histological abnormalities. On a normal Na diet, wild-type (WT) and PRR KO mice had similar BP and Na excretion. However, PRR KO mice had elevated PRC (KO-377 ± 77 vs WT- 127 ± 19 ng/1mL/hr) and a 50% decrease in renal ENaC protein. Proteins levels of NHE3, NKCC2, NCC and ENaC β/γ were similar between the two groups. Treatment with mouse prorenin (10 mM for 30 min) increased ENaC channel number by 2-fold, but not open probability, in isolated split-open cortical collecting ducts (CCD) from WT mice, this was prevented by PRR inhibition (PR020) and Akt inhibition (A6736) but unaffected by blockade of AT1 (losartan), ERK1/2 (U0126) or p38 MAPK (SB203580). Addition of prorenin (10 mM) did not change isolated CCD (Ca2+), as assessed by Fura-2 loading (10 min exposure). On a low Na diet, PRR KO mice had increased Na excretion (Day 2: KO - 66 ± 11 vs WT- 42 ± 6 mmol/day; Day 6: KO - 39 ± 4 vs ET- 23 ± 4 mmol/day) however, no differences in BP were observed. PRC remained elevated in PRR KO mice on a low Na diet. PRR KO mice had an enhanced hypertensive response to Angiotensin-II (Ang-II) infusion at 600 ng/kg/min for 2 weeks (MAP: KO - 117 ± 4 vs WT - 133 ± 4 mm Hg over 2 weeks). Urinary Na excretion was elevated in Ang-II treated PRR KO mice as compared to WT mice (KO-344 ± 14 vs WT-268 ±30 mmol/day).

Conclusions: Taken together, these data indicate that nephron PRR, likely via direct prorenin/reiin stimulation of an Akt-dependent pathway, stimulates CCD ENaC activity. Absence of nephron PRR Na wasting and reduces the hypertensive response to Ang-II.

SA-OR068

Pendrin Localizes to the Adrenal Medulla and Modulates Catecholamine Release
Annie Y. Park, 1 Truyen D Pham, 1 William H. Beierwaltes, 2 Roy L. Sutliff, 2 Jill W. Verlander, 2 Carla L. Ellis, 3 Brandi M. Wynne, 2 Robert S. Hoover, 3 Susan L. Pham, 1 Vesna L. Mironova, 1 Medicine and Pathology, Emory Univ, Atlanta, GA; 2 Medicine, Univ of Florida, Gainesville, FL; 3 Hypertension and Vascular Research, Henry Ford Hospital, Detroit, MI.

Background: Pendrin (Slc26a4) is a Cl-/HCO3- exchanger expressed in renal intercalated cells that mediates renal Cl- absorption. Pendrin gene ablation reduces blood pressure and vascular volume. While pendrin gene ablation increases plasma aldosterone concentration, serum aldosterone is not increased, suggesting that pendrin regulates aldosterone production in the adrenal cortex. The purpose of this study was to determine if pendrin is expressed in the rodent adrenal gland and if it modulates adrenal function.

Methods: Pendrin mRNA and protein abundance were explored by PCR, immunoblotts and immunohistochemistry. Mean arterial pressure (MAP) was measured by telemetry. Catecholamines were measured by HPLC in plasma samples from mice bearing chronic indwelling jugular catheters.

Results: Pendrin localizes to the rodent adrenal gland in epinephrine- and norepinephrine-producing chromaffin cells of the adrenal medulla rather than in adrenal cortical cells. We examined the effect the pendrin gene ablation on adrenal medullary function by measuring stress-induced catecholamine release. While basal levels of epinephrine (E) and norepinephrine (NE) were similar, E and NE levels were ~25–50% higher pendrin null than in wild type mice after 20 min of immobilization stress. 30 min following relief of stress, NE levels were 50% higher in pendrin null than in wild type mice. MAP rose in both wild type and pendrin null mice following immobilization stress, but MAP in pendrin null mice was 16 mm Hg lower than in wild type mice under basal conditions and 12 mm Hg lower following 20 min of immobilization stress (P<0.05). However, 30 min after relief of stress, MAP was the same in both groups (Wild type 121± 33 vs pendrin null mice 117 ± 3.5 mm Hg, pendrin null mice).

Conclusions: Pendrin is expressed in mouse adrenal medulla where it plays a role in restraining catecholamine release during stress, which probably modulates pendrin-dependent changes in blood pressure.

Funding: NIDDK Support, Other NIH Support - DK46493, DK08597, T32 DK07656

SA-OR069

Renal-Selective Silencing of Adrenomedullin Gene Causes Hypertension in Mice
Xiaoyan Wang, Donghai Zhou, Laurenano D. Asico, Hai Lin, John Edward Jones, Pedro A. Jose. Medicine, Univ of Maryland Medical School, Baltimore, MD.

Background: Adrenomedullin (ADM) is a potent hypotensive and natriuretic peptide whose gene variants are associated with human essential hypertension. Although the kidney is one of the ADM producing organs, the mechanism by which ADM induces a natriuresis is not clear.

Funding: Pharmaceutical Company Support - Bristol-Myers Squibb
SA-OR070

Vascular AT1 Angiotensin Receptors Regulate Sodium Transporter Abundance in Kidney Epithelium
Matthew J. Spark1, Susan B. Gurley1, Alicia A. McDonough1, Thomas M. Coffman1. Duke, US.

Background: Vasoconstriction is a physiological action of angiotensin II (AngII) via receptor AT1A (AT1).

Methods: In order to define the contribution of AT1R in vascular smooth muscle cells (VSMCs) to BP control, we generated mice with cell-specific deletion of AT1AR from (AngII) acting via AT1 receptors (AT1R).

Results: Baseline BP was reduced by ~7 mmHg and responses to AngII-induced hypertension were blunted by in SMKO mice compared to controls (16 vs. 30 mm Hg; P<0.02). Baseline renal blood flow (RBF) was higher, and renal vasoconstriction to AngII was impaired in SMKOs. Moreover, SMKO mice displayed Na+ sensitivity and exaggerated natriuresis during chronic AngII. To investigate the mechanism of the lower baseline BP and the enhanced natriuresis during AngII infusion (VSMCs) to BP control, we generated mice with cell-specific deletion of AT1AR from mice was shifted to the right of Mock mice. Immunofluorescence confocal microscopy in normal mice revealed that ADM was mainly located in the cortex, especially in the apical membrane of renal proximal convoluted tubules (RPTC). ADM colocalized with NHE3 but not with NaKCC from RPTC. ADM also coimmunoprecipitated with NHE3 in kidney homogenates. In mouse RPTC cells, ADM silencing decreased ADM protein to 48 ±4 % of Mock (n=4/group) and doubled the protein abundance of NHE3 (192±21) but did not alter aNKA. In polarized human PCT cells, human ADM (1 hr, n=5/group) inhibited apical sodium transport at 10 nM (84±1% of vehicle) and 100 nM (81±3%), similar to results in VSMCs. Introduction of novel transcription factor binding sites introduced by identified SNPs and gene electrophoretic mobility shift assays to assess the binding of a transcription factor to the sequences.

Conclusions: We found an intronic SNP in CLDN14 that occurred with greater frequency in children with hypercalciuria and kidney stones relative to ethnically matched controls (from the 1000 genome project). Dual luciferase assays found the mutant sequence doubled expression while the wild type had no effect (relative to empty vector). Despite similar numbers of the engineered constructs being incorporated into genomic DNA of the stable cell lines, the mutant sequence doubled mRNA and protein expression. In silico studies predicted the SNP introduced a novel INSM1 transcription factor binding site. To assess the function of this SNP, we expressed the WT and mutant luciferase constructs in the presence and absence of INSM1 and found a further increase in expression. Finally, gel electrophoretic mobility shift assays confirmed preferential binding of INSM1 to the mutant sequence. Children with hypercalciuria and kidney stones have a intrinsic mutation in CLDN14 that introduces a novel INSM1 binding site.

Funding: Government Support - Non-U.S.

SA-OR073

Oxalobacter-Driven Bioactive Factors Reduce Urinary Oxalate Excretion in a Mouse Model of Primary Hyperoxaluria
Hatim A. Hassan1, Donna L. Arvans1, Yong-chul Jung1, Dionysios A. Antonopoulos2, John R. Asplin3, Ignacio Granja1, Jason C. Koval4, Mark W. Musch4, Eugene B. Chang5. 1Univ of Chicago; 2Litholink Corporation; 3Argonne National Laboratory.

Background: Hyperoxaluria is a major risk factor for calcium oxalate kidney stones (COKS) and has no therapy. The probiotic bacterium Oxalobacter formigenes (Of) plays a critical role in metabolizing host dietary oxalate, leading to reduced intestinal absorption and urinary excretion. Of also interacts with colonic epithelium by inducing colonic oxalate secretion, leading to reduced urinary excretion, via an unknown secretagogue. Sustaining Of colonization in animals and humans in the absence of high dietary oxalate remains problematic, underscoring the need for identifying Of-driven factors exerting effects similar to live Of.

Methods: We previously found that small molecular weight protein(s) and/or peptide(s) in Of culture conditioned medium (CM) significantly stimulate oxalate transport (~2-fold) by human intestinal Caco2-BBE cells. We hypothesized that CM contains secreted factors that stimulate oxalate secretion in PH1 mice, a ~10-fold higher net oxalate secretory flux (~1.54) is observed in distal colonic tissues from CM-treated mice (absorptive flux) = 39.95±5.29, secretory flux (secretory flux) = 41.53±4.59: CM => 42.62±3.67; Oxalobacter formigenes, Pharmacal, NY.

Conclusions: We conclude that Of-derived bioactive factor(s) retains its bioactivity in vivo and significantly reduces urinary oxalate excretion in PH1 mice by stimulating distal colonic oxalate secretion.

Funding: NIDDK Support, Other Government Support - Digestive Disease Research Center of the University of Chicago/NIBIB P30 DK42088, Private Foundation Support.
Hyperoxaluria Requires TNF Receptors to Initiate Crystal Adhesion and Kidney Stone Disease

Background: Nephro- or urolithiasis involves intratubular mineral hypersaturation as well as lack of crystalization inhibitors to form crystal plugs obstructing renal tubules. Recently, NLRP3 inflammasome-related renal inflammation was added as a pathomechanism of acute oxalosis (Mulay et al, JCI 2013) as well as nephro-urolithiasis (Knauf et al, KI 2013). As TNF receptor (TNF-R) signaling is a major mediator of inflammation in several chronic kidney diseases (CKD), we speculated that TNF-Rs would also drive the progression of nephrolithiasis-related CkD.

Methods: We prospectively examined the association between estimated net endogenous acid production (NEAP), protein intake (vegetarian [VP] and animal non-dairy [AP]) and risk of incident KS in three large ongoing cohorts, the Health Professionals Follow-up Study (n=42,919 men), Nurses’ Health Study I (n=60,128 older women), and Nurses’ Health Study II (n=90,629 younger women). We used Cox hazards regression models to generate hazard ratios (HRs) adjusted for age, BMI, dietary, lifestyle, and medical factors. We also analyzed multivariabler associations between NEAP and 24-h urine composition in >6,000 study participants.

Results: During 3,133,014 person-years of follow-up, there were 6,347 incident KS cases. There was a significant association between NEAP and KS risk in all cohorts (pooled HR 1.98; p <0.001). ESWL was associated with an increased risk of HTN with a HR of 1.34 (95% CI 1.16, 1.72; p-value for trend < 0.001). There was no association between VP intake and risk of KS. There was a significant association between AP intake and risk of KS in HPFS (HR 1.14, 95% CI 0.97, 1.35; p-value for trend =0.04) and NHS I (HR 1.23, 95% CI 1.01, 1.49; p-value trend = 0.05) but not in NHS II. There was no association between DP and risk except in NHS II, where the HR was 0.83, 95% CI 0.72, 0.95; p-value trend =0.003. After multivariable adjustment, participants in the highest compared with lowest quintile of NEAP had 85 mg/d less urine citrate, 0.18 lower pH urine, 177 mL/s less urine volume, and higher urine supersaturations with respect to calcium oxalate and uric acid (all p-values ≤ 0.001).

Conclusions: In 3 large cohorts, higher NEAP is associated with higher risk of KS, as well as lower urine citrate and pH. In contrast with AP, VP and DP are not associated with risk of KS.

Funding: Other NIH Support - NIH grants DK094910, DK94171, CA16107, CA176726 and CA167552

SA-OR076
ALLN-177 Oral Enzyme Therapy Reduces Urinary Oxalate in Patients with Secondary Hyperoxaluria (2° HO) and Recurrent Kidney Stones: Results of a Phase 2 Study

Background: We sought to determine if individuals with urolithiasis, extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) are associated with a higher risk of incident hypertension (HTN) and/or chronic kidney disease (CKD).

Methods: A population-based retrospective cohort study using The Health Improvement Network comprised 11,570 participants (pts) with incident urolithiasis and 127,464 pts without urolithiasis; pre-existing HTN and CKD were excluded. 1319 and 96 pts respectively had 1 ESWL or URS procedure, respectively. Median year for the start of follow-up was 2006. Cox regression, adjusted for age, gender, diabetes, gout, and calendar time, was used to estimate the hazard ratio (HR) for incident HTN and CKD stage 3-5 in separate analyses.

Results: Over a median of 3.7 and 4.1 years, 1423 (12.3%) and 595 (5.1%) of urolithiasis pts developed HTN and CKD, respectively. Urolithiasis was associated with a HR for HTN of 1.42 (95% CI: 1.35, 1.51; p<0.001) and for CKD of 1.82 (95% CI: 1.67, 1.98; p <0.001). ESWL was associated with an increased risk of HTN with a HR of 1.34
Myofibroblasts Activation by Blocking the Auto-Regulatory Loop of miR-21/PDCD4/AP-1 During Renal Fibrosis

Methods: To that end, we induced kidney fibrosis in FoxD1-GC:Z/Red-mice by unilateral ureteral obstruction followed by FACS sorting of dsRed-positive FoxD1-derived cells and profiled for differentially expressed miRNAs.

Results: MiR-132 expression selectively increased 21-fold during pericyte-to-myofibroblast transformation whereas miR-132 was only 2.5-fold upregulated in total kidney lysates (both in UUO and ischemia-reperfusion injury). Antagoni-induced miR-132 silencing in the UUO model resulted in 35% decreased collagen deposition and decreased tubular apoptosis. Immunohistochemistry, Western blot and qRT-PCR analyses confirmed a similar decrease in α-SMA positive cells. Pathway analysis of differential gene expression in myofibroblasts identified a rate-limiting role for miR-132 in myofibroblasts that was confirmed in in vitro studies with cultured fibroblasts. Indeed, UUO kidneys of antagonist-132 treated mice displayed a significant reduction in proliferating, ki67+ myofibroblasts. Interestingly, this reduction in proliferation was selective for the interstitial compartment and did not impair the reparative proliferation of tubular epithelial cells, as evidenced by increased numbers of ki67+ epithelial cells, as well as increased p-RB1 and Cyclin-A and decreased RASA1 and p21 levels in total kidney lysates.

Conclusions: Taken together, silencing miR-132 counteracts the progression of renal fibrosis by selectively decreasing myofibroblast proliferation and could potentially serve as a novel antifibrotic therapy.

SA-OR081

Characterizing the Molecular Identity of Pathogenic Fibroblasts Using Single Cell RNAseq

Background: Fibroblasts are the main effectors of organ fibrosis but their molecular identity is poorly understood. Using Colla1-GFP mice, we isolated pathogenic fibroblasts from 3 fibrin organs and performed single cell RNAseq analysis.

Methods: We induced fibrosis in the kidney (unilateral ureteral obstruction), lung (intratracheal bleomycin) and liver (carbon tetrachloride injections). With fluorescence-activated cell sorting, we isolated collagen-expressing GFP positive cells from each organ. Single cell RNAseq was performed via a fluidic system and libraries generated and sequenced.

We performed hierarchical clustering (HC) analysis, principal component analysis (PCA) and targeted correlation assays on RNAseq data.

Results: We analyzed 130 kidney cells, 160 lung cells and 177 liver cells. HC and PCA analysis revealed 3 distinct groups of fibroblasts in fibrotic kidney and lung. Group 1 express high levels of collagen 1 and 3, express intermediate levels of collagen 1 and 3, express intermediate levels of collagen 3 and express fibrocyte markers. Group 2 express substantially lower levels of collagen 3 and express fibrocyte markers. Group 3 express mostly homogenous population that differs substantially in gene expression from those of the lung and liver fibroblasts. By correlation analysis, we found 63 genes that highly correlate with colla1 in renal, lung and liver fibroblasts. Some of these are known fibroblast-related genes but many are novel.

Conclusions: We characterized the molecular diversity of fibroblasts in 3 fibrin organs. While pathogenic fibroblasts from the kidney, lung and liver are a core fibroblast-related panel of genes. This study may yield new biomarkers and therapeutic targets for treating fibrosis.

Funding: Pharmaceutical Company Support - Abbvie Inc., Private Foundation Support

SA-OR082

Persistent Activation of Autophagy in Kidney Tubular Cells Promotes Renal Interstitial Fibrosis During Unilateral Ureteral Obstruction

Background: Renal fibrosis is the final, common pathway of end stage renal disease. Whether and how autophagy contributes to renal fibrosis remains largely unknown.

Methods: Using pharmaceutical and genetic inhibitory approaches, our study has determined the regulation of renal interstitial fibrosis by autophagy in a mouse model of unilateral ureteral obstruction (UUO) and in TGF-b1-treated proximal tubular cells.

Results: UUO led to renal interstitial fibrosis, which was associated with persistent autophagy in kidney proximal tubules, as indicated by punctate LC3 staining, LC3-II accumulation, P62 degradation as well as autophagosome formation and maturation. Pharmacological inhibitors of autophagy (chloroquine and 3-methyladenine) partially suppressed interstitial fibrosis during UUO. The inhibitors also suppressed apoptosis in renal tubules. Moreover, knock-out of Atg7 specifically from kidney proximal tubules (PT-Ag7 KO) not only blocked autophagy but also attenuated renal fibrosis. Proliferation and activation of fibroblasts, as indicated by the expression of α-SMA and vimentin, was inhibited in these mice, so was the accumulation of extracellular matrix components including fibronectin and collagen fibrils. UUO induced 8.4% interstitial fibrosis in wild-type kidneys after 4 days of obstruction, which was further increased to 13.5% by 1 week and 25% after 2 weeks. The fibrotic lesions were significantly reduced in PT-Ag7 KO kidneys at all three time points, with 4.5% for 4-day, 7.9% for 1-week and 15.2% for 2-week respectively. UUO led to FGF2 expression in wild-type kidneys, which was markedly reduced in PT-Ag7 KO mice. PT-Ag7 KO mice also showed significantly less interstitial macrophage infiltration and tubular apoptosis. In cultured proximal tubular cells, TGF-b1 induced autophagy and the accumulation of fibronectin and, inhibition of autophagy suppressed fibronectin accumulation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral Abstract PO - Poster; PUB - Publication Only
Conclusions: Together, the results suggest that persistent activation of autophagy in kidney proximal tubules promotes renal interstitial fibrosis by regulating tubular cell death, interstitial inflammation, and the production of profibrotic cytokines.

Funding: NIDDK Support, Veterans Administration Support

SA-OR083
Macrophase Migration Inhibitory Factor Promotes Kidney Fibrosis in ADPKD Xia Zhou,1,2 Li Chen,1,2 Dorien J.M. Peters,3 Mihaela Gadjeva,4 Xiaogang Li,1,2 ’Internal Medicine; ’Kidney Inst, Univ of Kansas Medical Center; Kansas City, KS; ’Leiden Univ Medical Center, Leiden, Netherlands; ’Harvard Medical School, Boston, MA.

Background: Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that functions to induce cell proliferation, inhibit apoptosis, and regulate the inflammation. We found that MIF promoted renal cyst growth in different ADPKD mouse models (Chen et al., JCI 2015). Renal cyst progression is accompanied by tubulointerstitial fibrosis which is associated with the renal function decline. However, whether MIF regulates fibrosis in ADPKD remains unknown.

Methods: To understand the role of MIF in regulating renal fibrosis in vivo, we generated Pkd1+/MIF-/- mice. To explore the pathways mediated by MIF in regulating process, we treated renal epithelial cells and fibroblasts with MIF or MIF inhibitor, ISO-1.

Results: We found that knockout of MIF or inhibition of MIF with ISO-1 not only delayed cyst growth but also decreased renal interstitial fibrosis as examined by Trichrome staining.

Conclusions: MIF activates the renal fibroblasts and promotes renal interstitial fibrosis in ADPKD, which may be mediated by TGFβ, ERK, mTOR and Rb signaling pathways. Targeting MIF may be a viable new therapy for ADPKD.

Funding: NIDDK Support

SA-OR084
HGF/c-met Signaling in Macrophages Attenuates Kidney Fibrosis by Regulating Matrix Remodeling and Turnover Haivan Fu,1 Dong Zhou,1 Liangxiao Xiao,1 Roderick J. Tan,2 Youhua Liu.1 ’Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA; ’Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.

Background: Kidney fibrosis results from an excessive accumulation and degradation of extracellular matrix (ECM). This is mainly due to an imbalance between matrix synthesis and degradation. While significant progress has been made recently on identifying the matrix-producing cells and elucidating how they are regulated, relatively little is known about the mechanism controlling matrix degradation and turnover.

Methods: We generated hepatocyte growth factor (HGF) receptor c-met conditional knockout mice in which c-met was deleted specifically in myeloid cells including macrophages (Mac-c-met/-/-). Mice were then subjected to renal unilateral ischemia-reperfusion injury (UIRI) or unilateral ureteral obstruction (UUO), respectively. Cultured bone-marrow-derived macrophages were also used.

Results: Mice with macrophage-specific ablation of c-met were phenotypically normal. We found that at different time points (3, 7, and 14 days after UUO), there was no difference in the mRNA levels of major fibrosis-related genes such as α-SMA, collagen I, collagen III and fibronectin in the kidneys between Mac-c-met/-/- and control mice, suggesting that HGF signaling in macrophages does not affect matrix synthesis. However, kidney fibrotic lesions as assessed by Masson’s-Trichrome staining were more profound in Mac-c-met/-/- mice than controls. Comparable results were obtained after analysis of matrix proteins by Western blot. Similarly, in UIRI model, loss of c-met in macrophage significantly aggravated renal lesions at 10 days, with elevated serum creatinine and increased deposition of matrix proteins, whereas renal mRNA expression of major matrix genes was not changed. In vivo increased deposition of ECM was closely associated with the down-regulation of tissue-type plasminogen activator (tPA) in Mac-c-met/-/- kidneys. In vitro, HGF induced tPA, uPA and MMP-12 expression in cultured bone marrow-derived macrophages.

Conclusions: These results suggested that HGF/c-met signaling in macrophages plays a critical role in reducing kidney fibrosis by promoting matrix degradation and turnover.

Funding: NIDDK Support

SA-OR085
The Hippo-Salvador Signaling Pathway Regulates Renal Tubulointerstitial Fibrosis Yong kyun Kim,1 Sun-ah Nam,2 Wanyong Kim,3 Arum Choi,2 Yumi Kim,2 Jin Kim.3 ’Dept of Internal Medicine, Medical College, The Catholic Univ of Korea, Seoul, Korea; ’Dept of Anatomy and Cell Death Disease Research Center, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Renal tubulointerstitial fibrosis (TIF) is the final common pathway of various renal injuries. The mammalian Hippo-Salvador signaling pathway is a highly conserved system that cascade through contact inhibition, cell proliferation and TGF-β signaling plays a role in TIF development.

Methods: The expression of Hippo-Salvador pathway including WW45, Mst1/2, Lats1/2, YAP/TAZ were examined. TEC-specific WW45 knockout mice (WW45fx/fx;Ksp-Cre) were generated for in vivo experiments and Hippo-Salvador pathway were knocked out or overexpressed in HK2 cells. Unilateral ureteral obstruction (UUO) was used for in vivo model and TGF-β treatment was used for in vitro model of renal fibrosis.

Results: Expression of WW45 (a homolog of Drosophila Salvador and adaptor for the Hippo kinase) and TAZ (transcriptional coactivator with PDZ binding motif, a WW-domain transcriptional regulator) were increased after UUO in mice and in TEC in patients with CKD. In vivo, TEC-specific WW45 deletion enhanced renal TIF after UUO. TEC-specific WW45 deletion enhanced apoptosis and proliferation of TECs after UUO. The expression of TAZ was increased in the kidneys of WW45-deficient mice after UUO. In vitro, WW45 deletion induced EMT by TGF-β treatment. WW45 deficiency enhances TGF-β signaling by the interaction of TAZ with Smads. WW45 deficiency also increases activated β-catenin dependent on TAZ.

Conclusions: Our data showed that Hippo-Salvador pathway regulates renal fibrosis and endothelial TGF-β/Smad and β-catenin signaling. Our experiments suggest that Hippo-Salvador pathway is a new mechanism in the pathogenesis of TIF development and indicate that regulation of Hippo signaling pathway may be a therapeutic target to reduce TIF.

SA-OR086
Cytosine Methylation Levels Determine Regeneration versus Fibrosis After Injury Kritti Gaur, Ae Seo Deok Park, Frank S. Chinga, Katalin Susztak. Renal Electrolyte and Hypertension Div, Univ of Pennsylvania.

Background: Cytosine methylation is an epigenetic mark that regulates gene expression, whereby increased methylation of promoter regions inhibits gene transcription by interfering with transcription factor binding. We previously showed that humans with CKD and DKD samples have differences in cytosine methylation levels. We hypothesized that these gene methylation differences are functionally important in the pathogenesis of CKD.

Methods: We generated a ten-enzyme transfection (TE) family of proteins, regulate DNA methylation status by oxidizing 5-methylcytosine (mC) to 5-hydroxymethylcytosine (5hmC). In the absence of TET2, there is increased cytosine methylation and decreased hydroxylation. Here we examined the functional role of tubular epithelial cell (TEC) methylation levels in vivo by deleting TET2 in TECs.

Results: TET2fx/fx and Cadenherin 16 Cre mice were crossed to generate animals with renal tubular epithelial cell deletion of TET2. Kidney injury was induced by administeringforced acipimox peripherally at a dose of 2.5mg/kg of body weight and sacrificed 1 or 12 weeks later. Mouse kidneys and primary epithelial cells were analyzed by quantitative RT-PCR, and immunohistochemistry to examine fibrotic changes.

Results: Mice with TEC specific deletion of TET2 appeared histologically normal. We hypothesized that this may be due to a low turnover rate of tubule cells in the kidney. Acute kidney injury and regeneration was induced through administration of folic-acid. Twelve weeks after folate administration control animals almost recovered, while fibrosis appeared more severe in mice with TEC specific deletion of TET2. These TET2 null mice also had increased expression of collagen, activated myofibroblast and inflammatory markers. We believe that fibrosis developed as a secondary consequence of impaired epithelial cell differentiation, as TET2-deficient TECs remained undifferentiated and yet continued to proliferate.

Conclusions: TET2 is an epigenetic director of renal epithelial repair following injury. Increased TEC cytosine methylation levels interfere with epithelial cell differentiation and directs cells into a profibrotic phenotype.

Funding: NIDDK Support

SA-OR087
Roles of CCN2 and Caspase Activities in Tubular Epithelial Cells Involved in AKI Transition to CKD Takeru Kusano, Tsutomu Inoue, Hirokazu Okada. Saitama Medical Univ, Iruma-gun, Saitama, Japan.

Background: In AKI, severely injured tubular epithelial cells (TEC) are destined to be removed by apoptosis while a small part of them survive and transform, which then facilitate interstitial fibrosis (IF). (Nat Med 16:535, 2010) We previously reported that CCN2 and caspase activities in TEC are important for IF in CKD models (JASN 16:133, 2005; Clin Exp Nephrol (in press)). In this study, we investigate possible linkages between AKI and CKD, focusing especially on roles of CCN2 and caspase activities in TEC.

Methods: CCN2-haploinsufficiency mice (CCN2fx/fx) and pan-caspase inhibitor p35 gene in a nonexpression state (p35), and mice carrying Cre recombinase under the control of proximal tubule-specific g-glutamyltransferase promoter (g-TCr) were used for generation of following mice; g-TCr fx/p35, p35 is expressed in tubular epithelial cells in vivo.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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TEC; g-GT.Cre:CCN2-/-, CCN2 expression is detected in TEC; g-GT.Cre:p53:CCN2-/-, detected in tubular cells with p53 expression in TEC; and CCN2-/- as the control. We performed a 24 hour ischemia and reperfusion injury (IRI) on these 4 groups of mice and evaluated renal fibrosis on day 14.

Results: The mRNA levels of collagen I (Coll), fibronectin (FN) and TGFB-1 were significantly lower in g-GT.Cre:CCN2-/- mice than the control mice (Coll: 7.26±0.62 vs. 63.5±1.67; FN: 1.29±0.8 vs. 9.66±2.83; TGFB-1: 0.83±0.12 vs. 4.35±0.98; p<0.05). The fibrosis area% in Masson trichrome staining was significantly narrower in g-GT.Cre:CCN2-/- mice than the control mice (74.61±3.6% vs. 34.8±3.1%; p<0.05). The expression of fibrotic markers increased (2.2 folds) in the kidney comparing (-/+) mice than wild type mice. Klotho expression quickly diminished after each ischemic hour ischemia and reperfusion injury (IRI) on these 4 groups of mice and evaluated renal fibrosis. Thus, caspase activities after IRI exacerbate IF irrespectively of CCN2. The expression of Klotho was modified by gene delivery.

Conclusions: It has been recognized that AKI and CKD are not independent disease but a part of the same disease in which there is bidirectional nature of the relationship between them. Especially, frequent occurrence of minor AKI induces acceleration to advancing on the CKD. On the other hand, Klotho protein is one of the key modulator in the preceding the CKD, during which expression of Klotho is markedly suppressed in CKD. Acceleration of renal fibrosis is a basic pathophysiology for progression of CKD, and previously, we showed that recurrent AKI exacerbate IF was severer in the (-/+ ) mice than those in the wild-type mice by ureteral obstruction procedure. So, we hypothesized that kidney with reduced Klotho expression was more vulnerable to minor or repeated stress during the progression of CKD pathophysiology.

We explored the effects of repeated minor AKI on the kidney in the rodent model of reduce Klotho expression. Minor AKI was induced by short time clamping of renal artery, once a week for 3 weeks in kl (+/-) and wild type mice. Serum creatinine level was measured and the expression levels of fibrosis related marker, such alpha SMA, MCP-1 etc., by immunostinig and RT-PCR was assessed. Internal expression of Klotho was modified by gene delivery.

Conclusions: Repeated cerclage of animals can reduce the function of various organs. Klotho induction was suggested in mice. Therefore, this study found that Klotho induction can protect against kidney disease.

Funding: Government Support - Non-U.S.

SA-OR089
Global Prevalence of Protein-Energy Wasting (PEW) in Kidney Disease: Systematic Review and Meta-Analysis of Contemporary Cohort Studies by the International Society of Renal Nutrition and Metabolism (ISRNM)

Juan Jesus Carrero,1 Csaba P. Kovay,2 Miklos Zsolt Molnar,3 Karolina Inst, Stockholm, Sweden; 4Univ of Tennessee Health Science Center, Memphis, TN.

Background: PEW is a common complication in kidney disease, but its prevalence is poorly defined. To increase awareness on the commonness of PEW, we performed a meta-analysis of its global prevalence throughout the kidney disease spectrum.

Methods: We performed a systematic review and meta-analysis of contemporary cohort studies including >50 patients with kidney disease and reporting on PEW prevalence by either subjective global assessment (SGA) or malnutrition-inflammation score (MIS). Searches were restricted to Jan 2000-Nov 2014. Data was reviewed throughout different kidney disease stratas (acute kidney injury [AKI], pediatric chronic kidney disease [CKD], non-dialyzed CKD 3-5, dialysis and renal transplant [Tx]). Because PEW may reflect underlying country-specific malnutrition, studies including dialysis patients were analyzed non-dialyzed CKD 3-5, dialysis and renal transplant (Tx). We also explored the effects of repeated minor AKI on the kidney in the rodent model of reduce Klotho expression. Minor AKI was induced by short time clamping of renal artery, once a week for 3 weeks in kl (+/-) and wild type mice. Serum creatinine level was measured and the expression levels of fibrosis related marker, such alpha SMA, MCP-1 etc., by immunostinig and RT-PCR was assessed. Internal expression of Klotho was modified by gene delivery.

Conclusions: It is likely that reduction of Klotho levels in the kidney, such as in aging or CKD, is a risk factor for accelerating the progression of CKD, resulting in sensitive people. Here, we aim to determine whether dietary salt can play a deleterious role in the pathogenesis of other features of metabolic syndrome besides hypertension and if it is related to sugar metabolism.

Funding: NIDDK Support

SA-OR090
A Novel Deleterious Role for Dietary Salt-Sugar Interplay in Metabolic Syndrome and Elevated Blood Pressure in Mice

Miguel A. Lanapa,1 Christina Cicerchi, Ana Andres-hernando, Carlos Alberto Roncal-jimenez, Takuji Ishimoto, Richard J. Johnson. Univ of Colorado Denver, Aurora, CO.

Background: High amounts and chronic salt intake are important risk factors for the development and progression of hypertension. Our group has described that also sugars, and in particular fructose, contribute to the pathogenesis of elevated blood pressure thus suggesting a potential interplay between both dietary components in hypertension and metabolic syndrome. Consistently, increased sodium excretion is observed in obese people. Here, we aim to determine whether dietary salt can play a deleterious role in the pathogenesis of other features of metabolic syndrome besides hypertension and if it is related to sugar metabolism.

Methods: Wild type and fructokinase deficient mice – that cannot metabolize sugar and fructose- were exposed to 1% salt in drinking water for 30 weeks and features of metabolic syndrome including elevated blood pressure, fatty liver, insulin resistance, leptin resistance and weight gain were determined.

Results: Exposure of mice to salt induced the hypertonic activation of aldose reductase and the endogenous production of fructose in liver, pancreas and fat. Consistent with increased fructose production and metabolism in these tissues, wild type but not fructokinase deficient mice demonstrated significantly higher fat deposition, fatty liver and blood pressure compared to controls. Furthermore, salt intake in wild type mice induced a significant increase in insulin resistance as determined by oral glucose and insulin tolerance test, hyperleptinemia, hypobalimic hepatic lipid resistance, increased food intake and body weight gain compared to fructokinase deficient mice.

Conclusions: Our study indicates that dietary salt can induce multiple features of metabolic syndrome besides high blood pressure. It also suggests interplay between salt and sugar in which salt will induce the endogenous production of fructose. The metabolism of endogenous fructose by fructokinase would be the underlying factor for the induced metabolic syndrome in mice. Thus, blockade of fructokinase could be a novel therapeutic approach for the prevention and treatment of hypertension and metabolic syndrome.

Funding: NIDDK Support

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Underline represents presenting author.

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Conclusions: PEW is common across the entire spectrum of kidney diseases, but it exhibits the highest prevalence among dialysis and AKI patients. Its commonness, together with its well-documented impact on patient outcomes, deserves increased medical attention.

SA-OR091
Sodium Chloride Promotes Tissue Inflammation via Osmotic Stimuli in Subtotal Nephrectomized Mice

Fumiko Sakata,1 Yasuhiko Ito,1 Masashi Mizuno,1 Yasuhiro Suzuki,2 Takeshi Terabayashi,1 Takako Tomita,1 Mitsuhiro Tawada,1 Shoichi Maruyama,1 Euyu Imai,1 Yasuyoshi Takei,1 Seiichi Matsuo,1 Nephrology and Biochemistry, Nagoya Univ, Nagoya, Japan; Nephrology, Nakayamadera Imai Clinic, Takarazuka, Japan.

Background: Chronic inflammation is prevalent in patients with end-stage renal disease, but the precise mechanisms remain unclear. Sodium that is reportedly stored in tissues after high salt intake induces lymphanphoigenesis and autoimmune diseases via osmotic stimuli. We studied the effects and mechanisms of high salt loading on tissues and systemic inflammation (with a focus on macrophage infiltration) in sub-total nephrectomized (5/6Nx) mice and in cultured cells.

Methods: Mice underwent 5/6Nx or sham surgery (Sham), and were provided with either tap water (Water) or 1% NaCl (NaCl) for four weeks. Inflammatory changes in peritoneal wall, heart and paraaortic tissues were evaluated by immunohistochemistry, Western blot, ELISA and quantitative PCR. Inhibition studies were performed in vivo and in vitro.

Results: Significantly more macrophages infiltrated the peritoneal wall (p<0.001), heart (p<0.05) and paraaortic tissues (p<0.001) of sub-total nephrectomized mice with salt loading (5/6Nx/NaCl) compared with 5/6Nx/Water. Tissue levels of IL-6, monocyte chemotactic protein-1 (MCP-1) and toxicity-responsive enhancer binding protein (TonEBP) were significantly increased in the peritoneal wall and heart of 5/6Nx/NaCl compared with 5/6Nx/Water. The administration of furosemide or tap water after NaCl for four weeks, indicating reverse NaCl loading, reduced local macrophage infiltration and the suppression of MCP-1 (p<0.05) and TonEBP mRNA (p<0.01). A high NaCl concentration

Results:

<table>
<thead>
<tr>
<th>Stratum</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>PEW Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>4</td>
<td>387</td>
<td>63% (58-67)</td>
</tr>
<tr>
<td>non-diayed CKD 3-5</td>
<td>12</td>
<td>2682</td>
<td>21% (19-22)</td>
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<tr>
<td>Tx patients</td>
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<tr>
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<td>5920</td>
<td>55% (54-46)</td>
</tr>
<tr>
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<td>53</td>
<td>8923</td>
<td>42% (41-44)</td>
</tr>
<tr>
<td>Dialysis, low-income countries</td>
<td>8</td>
<td>887</td>
<td>62% (58-66)</td>
</tr>
</tbody>
</table>

Dialysis, low-income countries: 8

Funding: Government Support - Non-U.S.
in the culture media of mesothelial cells and cardiomyocytes induced MCP-1 protein, MCP-1 mRNA, sTNF-R1 and -2, and TNF-α, all of which were suppressed by TonEBP siRNA and upregulated in 5/6 NxNxNaCl. The induction of MCP-1 by high salt did not involve Rac1.

**Conclusions:** High salt intake enhances macrophage infiltration via the TonEBP-MCP-1 pathway in association with inflammation, oxidative stress and Sgf1 activation during renal failure.

**Funding:** Government Support - Non-U.S.

SA-OR092

**The Relationship of Chronic Kidney Disease Severity with Urine Sodium Excretion** Cheryl A. Anderson,1 Amanda K. Leong-Bergy,2 Joohae J. Ihx,3 Mark J. Sarnak,4 Lawrence J. Appel.5 1Univ of California San Diego; 2Tufts Medical Center; 3Johns Hopkins Medical Insts.

**Background:** In healthy individuals, the gold standard measurement for sodium intake is 24-hour urine excretion. It is unknown whether chronic kidney disease (CKD) severity affects this measurement. We aimed to evaluate whether sodium excretion differs by level of glomerular filtration rate (GFR). We hypothesized that with increased CKD severity, 24-hr urine excretion is reduced, possibly as a result of a greater fraction of sodium being excreted by non-renal pathways (e.g. sweat or lower intestinal absorption) as kidney function declines.

**Methods:** Baseline data from the African American Study of Kidney Disease and Hypertension (AASK) and the Modification of Diet in Renal Disease (MDRD) Study were used to separately examine the relationship between GFR measured by isohydramic clearance and 24-hour urine sodium excretion. Both studies recruited individuals with reduced GFR. Urine sodium excretion was measured using a single 24-hour urine collection. Linear regression models were used to adjust for age, race, sex, and BMI.

**Results:** In AASK (n=1093) and MDRD (n=814), baseline mean(SD) age was 54.5(10.7) and 51.4(12.4) years; mean(SD) for GFR (mL/min/1.73m2) was 46.8(14.1) and 33.5(12); and mean(SD) for sodium (g/day) was 3.7(2.0) and 3.5(1.5), respectively. After adjustment, each SD reduction in GFR was associated with a 0.24 g/day (p=0.002) lower sodium excretion in AASK; and a 0.15 g/day (p=0.001) lower sodium excretion in MDRD.

**Conclusions:** Our findings challenge the existing paradigm that the amount of sodium excreted in a 24-hour urine collection is roughly equivalent to intake in all persons. Further, the association of baseline level of DASH diet adherence with ESRD after adjusting for other U.S. Government Support - Non-U.S.

SA-OR093

**Lower Risk of ESRD Associated with DASH Diet in Adults with Moderate CKD and Hypertension** Tamanshree Banerjee,1 Deidra C. Crews,2 Meda E. Pavkov,3 Nilka Riros Burrows,4 Jennifer L. Bragg-Gresham,5 Rajiv Saran,6 Neil R. Powe.7 1UCSF; 2JHU; 3CDC; 4U Michigan, Ann Arbor.

**Background:** Although the Dietary Approaches to Stop Hypertension (DASH) diet, rich in fruits, vegetables, and plant derived protein, has been shown to reduce blood pressure in individuals with normal and mildly impaired kidney function, it is not known whether the DASH diet impacts CKD progression among patients with moderate CKD.

**Methods:** We determined a baseline diet adherence score (higher score—greater adherence), consistent with DASH diet recommendations, using a 24-hour dietary recall adjusted for age, sex, race, and BMI.

**Results:** In AASK (n=1093) and MDRD (n=814), baseline mean(SD) age was 54.5(10.7) and 51.4(12.4) years; mean(SD) for GFR (mL/min/1.73m2) was 46.8(14.1) and 33.5(12); and mean(SD) for sodium (g/day) was 3.7(2.0) and 3.5(1.5), respectively. After adjustment, each SD reduction in GFR was associated with a 0.24 g/day (p=0.002) lower sodium excretion in AASK; and a 0.15 g/day (p=0.001) lower sodium excretion in MDRD.

**Conclusions:** Our findings challenge the existing paradigm that the amount of sodium excreted in a 24-hour urine collection is roughly equivalent to intake in all persons. Further, the association of baseline level of DASH diet adherence with ESRD after adjusting for other U.S. Government Support - Non-U.S.

SA-OR094

**Normal Weight with Central Obesity Is Associated with the Highest Risk of Coronary Artery Calcification in Chronic Kidney Disease Patients** Mi Jung Lee,1 Shin-Wook Kang,1 Curie Ahn,2 Tac-Hyun Yoo.2 1Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 2Dept of Internal Medicine, Seoul National Univ, Seoul, Korea.

**Background:** In chronic kidney disease (CKD), body mass index (BMI) showed a U-shaped association with cardiovascular (CV) risk. In contrast, central obesity was directly associated with increased CV risk. This bi-directional relationship prompted us to evaluate the CV risk assessed by coronary artery calcification (CAC) based on a combination of BMI and waist-to-hip ratio (WHR) in CKD patients.

**Methods:** We included 1,217 CKD stage 1 to 5 patients who enrolled in the KoreanN cohort study for Outcome in patients With Chronic Kidney Disease. Patients were divided into 3 groups by BMI (normal, 18.5 to <23.0; overweight, ≥23.0 to <27.5; obese, ≥27.5 kg/m²) and were dichotomized by sex-specific median of WHR (0.92 in male; 0.88 in female). CAC was calculated as >10 Agaston using a multi-slice computed tomography. Logistic regression analysis was used to assess the independent association of CAC with BMI, WHR, and cross-catégorization of BMI and WHR, respectively.

**Results:** CAC was observed in 501 patients (41.4%). Multivariate logistic regression analysis indicated that BMI was not independently associated with CAC (per 1kg/m² increase, odds ratio[OR]=1.03, 95% confidence interval[C1]=0.98-1.08, P>0.24). However, WHR showed an independent linear association with CAC (per 0.01 increase, OR=1.04, 95% CI=1.02-1.07, P<0.001). Furthermore, when patients were categorized into 6 groups according to combination of BMI and WHR, normal BMI but increased WHR (OR=1.91, 95% CI=1.05-3.48, P=0.03) and the highest level of CAC compared to others (normal BMI with lower WHR, as reference; overweight with lower WHR, OR=1.46, 95% CI=0.93-2.30, P=0.10; obese with lower WHR, OR=1.51, 95% CI=0.68-3.40, P=0.31; overweight with increased WHR, OR=1.45, 95% CI=0.95-2.22, P=0.06; obese with increased WHR, OR=1.49, 95% CI=0.88-2.53, P=0.14)

**Conclusions:** In CKD patients, normal weight with central obesity was associated with the highest risk of CAC, suggesting that combining BMI and WHR could be more helpful to stratify CV risk than BMI alone.

**Funding:** Government Support - Non-U.S.

SA-OR095

**MiRona-27a Is Decreased in Skeletal Muscle During Atrophy and Is Regulated by Calcineurin/NFAT Signaling: A Regulatory Mechanism for Myostatin Expression** Xiaoman H. Wang,1 Russ Price,1 Jill A. Rahnert,1 Matthew B. Hudson.1 1Medicine/Nephrology, Emory Univ, Atlanta, GA; 2Atlanta VA Medical Center, Atlanta, GA.

**Background:** Muscle atrophy occurs in chronic conditions like chronic kidney disease and diabetes. Production of myostatin by muscle plays a central role in the pathogenesis of atrophy during these conditions and research has recently focused on understanding how myostatin (MSTN) is controlled in muscle. MicroRNA-27a (miR-27a) can target MSTN mRNA and decrease MSTN protein in muscle; however, the mechanism(s) that control the level of miR-27a under atrophy-inducing conditions are unknown. The objective of our study was to investigate how miR-27a is regulated during muscle atrophy.

**Methods:** Diabetes was induced in rats by a single IV injection of 125 mg streptozotocin (STZ). STZ was incubated for 3 days. Glucocorticoids mediate many atrophy-inducing conditions of diabetes and CKD, some studies were conducted with C2C12 myotubes incubated with dexamethasone (DEX; 100 nM, 48 h). miR-27a was measured by quantitative RT-PCR using U6 as a control miR.

**Results:** In hindlimb muscles of STZ rats, miR-27a was decreased 40-50% (p<0.05), a finding consistent with the reported elevation in MSTN during diabetes. Similarly, treatment of C2C12 myotubes with DEX reduced miR-27a 68 ± 3% within 0.5 h and this suppression was sustained at >51% for at least 48 h. miR-27a/miR24-2/miR-27a cluster has been reported to be regulated by Calcineurin(Cn)/NFAT signaling and earlier, we found that CnA activity is reduced in skeletal muscle during CKD and STZ and in muscle cells following DEX treatment. Therefore, we investigated the relationship between CnA and miR-27a by measuring miR-27a following alteration in CnA activity. Infection of muscle cells with an adenovirus to overexpress constitutively active CnA increased miR-27a by 35-90%.

**Conclusions:** These results are consistent with a model in which atrophy-inducing conditions regulate MSTN production in skeletal muscle in part by reducing the level of miR-27a via a mechanism that involves decreased CnA/NFAT signaling. The resulting increase in MSTN will exacerbate muscle loss by accelerating proteolysis.

**Funding:** NIDDK Support, Veterans Administration Support

SA-SA096

**Systemic Inflammation Affects Skeletal Muscle Protein Homeostasis in Maintenance Hemodialysis (MHD) Patients** Serpl Muje Degi,1 Adriana Hung,1,2 Edward D. Siew,1 Cindy Bookler,1 Talat Alp Ikizer,1,2 1Hundertklap Univ, TN; 2VA, Nashville, TN.

**Background:** Systemic inflammation is closely associated with protein energy wasting (PEW) in MHD. In order to understand its metabolic effects on skeletal muscle metabolism, we examined whole body and skeletal muscle protein turnover in MHD patients with varying degrees of inflammation.
SA-OR097

IL-1 Blockade Improves Adiponectin (ADPN) Levels in Patients with CKD Stages 3 and 4
Adriana Hung,1 Kristen L. Nowak,2 Talat Alp Bizzler,2 Natallie Salas,3 Heather Farmer,4 Rafia I. Chaudhry,5 Michel Chonchol,6 '1Vanderbilt Univ, TN; 2Univ of Colorado Denver, CO.

Background: Adiponectin (ADPN), an adipose tissue-derived hormone, is known to have insulin sensitizing, anti-inflammatory, and anti-atherogenic properties in the general population. ADPN secretion is suppressed by systemic inflammation, a highly prevalent condition in chronic kidney disease (CKD), and may have cardiovascular health implications in this population. In this study, we evaluated whether short-term administration of a interleukin-1 (IL-1) blocker, improves ADPN levels and insulin sensitivity in patients with CKD stages 3&4.

Methods: This study was a pilot randomized placebo-controlled double-blind trial of administration of IL-1 blockade in patients with CKD stages 3&4. Forty-two patients were randomly assigned (1:1) to receive 160 mg of an IL-1 blocker (rilonacept) or placebo for 12 weeks; 37 completed the trial. The primary outcomes for this analysis were the effect of the intervention on the serum levels of ADPN, leptin, leptin to adiponectin ratio (LAR) and HOMA IR. Mixed effect models were used for all analyses.

Results: Mean age was 63±11 years, the median eGFR 37.9 (IQR 29.1, 46.7) ml/min, 76% were males and 24% were African Americans. The values for ADPN, leptin, LAR and HOMA IR at baseline were 17.8±1.72 μg/mL, 27.7±2.88 ng/mL, 2.63±2.76 and 5.6±5.35, respectively. IL-1 blockade resulted in an increase in serum ADPN in the intervention group compared to placebo (p<0.001). Leptin, LAR or HOMA IR levels did not change significantly [table 1].

Table 1. Metabolic indices at baseline and week 12

<table>
<thead>
<tr>
<th></th>
<th>IL-1 blockade</th>
<th>Placebo</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPN (μg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.1±21.7</td>
<td>21.9±8.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Week 12</td>
<td>28.4±24.5</td>
<td>21.7±7.7</td>
<td></td>
</tr>
<tr>
<td>Lepin (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.4±23.7</td>
<td>28.3±23.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Week 12</td>
<td>27.2±19.2</td>
<td>26.7±12.6</td>
<td></td>
</tr>
<tr>
<td>LAR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.86±3.2</td>
<td>2.6±2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.0±2.4</td>
<td>3.0±1.3</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.73±4.7</td>
<td>6.1±6.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>4.38±3.5</td>
<td>6.9±6.1</td>
<td></td>
</tr>
</tbody>
</table>

* P-value for test of the difference in change at week 12 between groups

Conclusions: Short-term administration of an IL-1 blocker significantly increased ADPN levels among patients with CKD stages 3&4. The intervention did not impact other insulin sensitivity parameters, including HOMA-IR, leptin and LAR. Results are consistent with those observed in dialysis patients.

Funding: Veterans Administration Support, Private Foundation Support

SA-OR098

Effects of Chronic Intradialytic Physical Exercises in NrF2 and NF-kB Expression and Antioxidant Enzymes in Hemodialysis Patients
Denise Mafra, Cinthia Da costa Abreu, Milena Barca Stockler-Pinto, Ludmila FmfCardozo.

Post-Graduate Program in Cardiovascular Sciences, Fluminense Federal Univ (UFF), Niterói, Rio de Janeiro, Brazil.

Background: Oxidative stress and inflammation are cardiovascular risk factors in patients with chronic kidney disease (CKD) on hemodialysis (HD). Nuclear factor kappa B (NF-κB) and in the coordinated expression of inflammatory genes, NF-κB. Transduction of a nuclear factor erythroid 2-related factor 2 (Nrf2) increases the transcription of genes encoding enzymes of phase II detoxifying and antioxidant enzymes. Several studies have shown that Nrf2 expression can be modulated by some factors, such physical exercise. The aim of this study was to evaluate the effects of resistance exercise program on the NrF2 and NF-kB expression and antioxidant enzymes HD in patients.

Methods: This study included 44 patients on regular HD program, 25 patients (14 men, 46.1±16.3 years and 71.2±42.2 months HD) composed the exercise group and 19 patients (11 men, 46.8±12.5 years and 67.4±51.7 months HD) the control group. Strength exercise program was performed during HD sessions, 3 times a week (36 exercise sessions). The NrF2 and NF-kB expression were analysed by quantitative real time PCR. Superoxide dismutase (SOD) activity and glutathione peroxidase (GTX) levels were measured using ELISA commercial kits.

Results: The NrF2 mRNA expression increased significantly after intervention in exercises group (0.8 ± 0.4 to 1.7 ± 0.8, p<0.01). In both group there were no changes in NF-kB mRNA expression after intervention. The SOD levels reduced in exercise group (from 51.5±16.1U/ml to 31.9±6.4U/ml, p<0.05) and in control group (from 45.1±6.1U/ml to 31.9±6.4U/ml, p<0.05). However, GTX levels increased in exercise group (from 24.7±12.4nmol/ml/min to 53.4±20.04nmol/ml/min, p<0.001) and in the control group there was tendency to decrease (from 26.0±5.13nmol/ml to 20.6±7.74nmol/ml/min, p=0.06). A negative correlation was found between the differences of NF-κB and GTX plasma levels (before and after 3 months) (r=0.76, p=0.007).

Conclusions: Chronic intradialytic resistance exercises during 3 months seem to be able to modulate theNrF2 activation and increase the antioxidant protection in HD patients.

SA-OR099

Evaluation of Novel Urine Biomarkers for Diagnosis of Subclinical Acute Tubular Necrosis
Dennis C. Moleding, Isaac E. Hall, Mona D. Doshi, Peter P. Reese, Francis L. Weng, Bernd Schroppel, Heather Thiessen Philbrook, Joseph Ficke, Chirag R. Parikh.

TRIBE-AKI.

Background: Rise in serum creatinine (SCr) is currently accepted as the "gold-standard" for clinical diagnosis of acute kidney injury (AKI). However, acute tubular necrosis (ATN) may occur without evidence of AKI, a condition known as “sub-clinical AKI”. We evaluated the performance of SCr and urinary biomarkers of kidney injury for diagnosis of ATN on kidney biopsy.

Methods: This is a substudy of a multicenter prospective cohort of deceased donors and associated kidney transplant. A diagnosis of ATN was assigned if the kidney biopsy report (read at organ procurement) indicated acute injury in >25% of tubules. AKI was defined by AKIN criteria based on admission and terminal SCr. Urinary biomarkers were measured from stored samples collected at procurement.

Results: Of 581 donors with isolated kidney biopsy assessed, 229(38%)had AKI (Stage I or higher). Of the 57 donors with ATN on biopsy, 28 (49%) did not have AKI. SCr had an area under the ROC curve (AUC) for diagnosing ATN of 0.589(95% CI=0.49, 0.67). Sensitivity and specificity for ATN were 51% and 64% using the AKIN stage 1 SCr cut-off; 26% and 83%, respectively, using the AKIN stage 2 cut-off. In the 361(62%) donors without AKI, ATN was noted in 79[95%CI: 72.2-99.5%] of those with SCr, P=0.03. Median L-FABP and YKL-40 were higher (though not significantly) in ATN compared to no ATN [L-FABP 25.6(6.4, 64.0) vs. 10.4(3.4, 41.0) ng/mL, P<0.008; YKL-40:43.0(13.6, 13.6) vs 6.0(5.5, 5.2)ng/mL, P<0.01]. In 18-3, KIM-1 and MCP-1 concentrations were similar regardless of ATN. Adding NGAL to SCr correctly reclassified 26% of donors for ATN events. We noted a trend for lower 6-month recipient estimated glomerular filtration rate (eGFR) [-2.69(5CtI 5.4, 0.2) ml/min] for worsening degrees of ATN, but 6-month eGFR was paradoxically better [-3.69(CI 5.7, 5.4) ml/min] for each higher stage of SCr-defined donor AKI.

Conclusions: SCr lacks sensitivity and specificity for diagnosing ATN. Urinary biomarkers like NGAL, L-FABP and YKL-40 may help distinguish “subclinical AKI,” if not improve clinical prediction of biopsy-proven ATN over that of SCr alone.

Funding: NIDDK Support, Private Foundation Support

SA-OR100

The Epidemiology and Outcome of Worldwide Acute Kidney Injury in Critically Ill Children: A Prospective Multinational Study
Ahmad Kaddour,1 Bui Diem Thuy Trinh,2 Snart Gruber,3 Pierre-Antoine Thibault,2 Marissa E. Gomes,2 Ahmad Kaddour,1 Bui Diem Thuy Trinh,2 Snart Gruber,3 Pierre-Antoine Thibault,2 Marissa E. Gomes,2 "Evaluation of Novel Urine Biomarkers for Diagnosis of Subclinical Acute Kidney Injury, Renal Angina and Epidemiology in Critically ill Children (AWARE)" investigators; "Cincinnati Children’s Hospital Medical Center."

Background: Epidemiological data for pediatric acute kidney injury (AKI) is limited to retrospective single-center studies. We conducted a prospective observational study of critically ill children to provide an international epidemiological description of pediatric AKI and associated outcomes.

Methods: 12 centers from 5 continents collected data for 3 consecutive months in 2014 from children (aged 3 months to 25 years) admitted to a pediatric intensive care unit.

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

Underline represents presenting author.

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unit: AKI was defined and classified by serum creatinine and urine output KDIGO criteria within the first 7 days of admission (Stage 2–3). Outcomes were assessed at 28 days. Children with end-stage kidney disease (ESKD) or kidney transplant in the last 90 days were excluded.

**Results:** Five thousand two hundred thirty-seven children (55% males) were studied. Median age was 64.6 months (IQR 10.5–120.9). On multivariate analysis, shock on admission (OR 2.4, p=0.007), history of prior rhabdomyolysis (OR 2.2, p=0.007), and history of AKI (OR 1.7, p=0.001) were independent predictors of Day 3 severe AKI. Table 1 depicts the univariate outcome associations with AKI.

<table>
<thead>
<tr>
<th>No/ stage 1 AKI</th>
<th>Severe AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=4142</td>
<td>n=541</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>2.6</td>
</tr>
<tr>
<td>Length of stay, mean (SD)</td>
<td>3.9 (6.1)</td>
</tr>
<tr>
<td>ECMO use (%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Dialysis (%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, mean (SD)</td>
<td>5.2 (6.3)</td>
</tr>
</tbody>
</table>

Severe AKI independently predicted mortality after adjustment for illness severity (OR 5.1, p<0.001). In a multivariate regression model, a 1-unit change in stage of AKI was associated with 1.28 days increase in illness-severity-adjusted length of stay (p<0.001).

**Conclusions:** These prediction models represent the largest epidemiologic assessment of AKI in critically ill children. We demonstrate AKI is independently associated with multiple deleterious outcomes. Our data will help guide future research to develop accurate and early diagnostic models of AKI.

**SA-OR101**

**Derivation and Validation of Risk Models for Chronic Kidney Disease Following Hospitalization with Acute Kidney Injury**

**Method:** We studied patients with baseline eGFR<30 mL/min/1.73m² who survived>3 months following a hospitalization with AKI. We identified those with a sustained reduction in eGFR<30 mL/min/1.73m² for >3 months.

**Results:** Seven variables were associated with a higher risk of progression to CKD: older age, female sex, higher baseline serum creatinine, higher urine albumin, greater AKI severity (KDIGO Stage), lesser recovery of kidney function by the time of discharge, and heart failure. The full model showed good discrimination in the derivation and validation cohorts (c-statistics of 0.85 and 0.82, respectively). A reduced model that included age, sex, baseline serum creatinine, AKI severity, and recovery of kidney function at discharge performed similarly to the full model, but better than a base model that included age, sex, and AKI severity alone (c-statistic of 0.73 vs. 0.65). For the final model, improvement in c-statistic was 0.17.

**Conclusions:** These prediction models can stratify patients for risk of CKD following hospitalization with AKI. The impact of these models for guiding CKD follow-up in the community should be prospectively evaluated.

**Funding:** Government Support - Non-U.S.

**SA-OR104**

**Micronutrient Loss in Renal Replacement Therapy for Acute Kidney Injury**

**Method:** We examined urine pellet podocin and nephrin mRNA in 39 ADHF patients during hospitalization and post-discharge as well as 172 adult healthy controls by reverse transcription-polymerase chain reaction. Urine pellets were created by patient urination (U) and urine nephrin mRNA:creatinine ratio (uNephCr) were considered as indices of podocyte stress and podocyte injury, respectively.

**Results:** Mean age of the patients was 58.9±10.9 years and 29 were male, uPODCr and uNephCr were measured (P<0.001) and 19 (P<0.001 times) greater in ADHF compared to healthy controls respectively. Post-hospital discharge uPODCr was not different from that of ADHF phase, whether it was measured within a month of discharge or after 3 months of hospital discharge. However, post-hospital discharge uNephCr was not different from ADHF phase when it was measured within a month of discharge; but it was 14 times smaller when it was measured after 3 months of hospital discharge (P<0.03).

**Conclusions:** In ADHF, podocytes might be under greater stress compared to healthy individuals and may become injured. Podocyte stress level remains markedly elevated several weeks after clinical stabilization of ADHF, but then drops remarkably. Podocyte injury, however, continues to progress even after 3 months of clinical stabilization. Measurement of uPODCr and uNephCr during ADHF may help with risk stratification for permanent kidney damage. Potential interventions to prevent advancement of podocyte stress to podocyte injury in the setting of ADHF, may help prevent permanent kidney injury.

**Funding:** Other U.S. Government Support

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

Underline represents presenting author.
Renal Replacement Therapy Intensity for Acute Kidney Injury and Recovery to Dialysis Independence

Ying Wang,1 Serigne N. Lo,2 Martin P. Gallagher,1 Qiang Li,1 Alan Cass,3 Alan J. Myburgh,2 Robert Faulhaber-Walter,2 John A. Kellum,1 Paul M. Palevsky,2 Claudio Ronco,3 Patrick Saudan,4 Ashita J. Tolwani,3 Rinaldo Bellomo,1 George Inst for Global Health; Hanover Medical School; University of Pittsburgh School; Bortolo Hospital; Univ Hospital; The Univ of Alabama.

Background: In acute kidney injury, randomized controlled trials (RCTs) have not found differences in survival with higher intensities of renal replacement therapy (RRT), but trials have not been powered for renal outcomes such as recovery of renal function.

Methods: Through an individual patient data meta-analysis we merged individual patient data from RCTs comparing high with standard intensity RRT. We assessed mortality at 28, 60 days and recovery to dialysis at 7, 14, 28, 60 & 90 days post randomisation. Renal recovery was assessed two ways; by the proportion of patients RRT dependent and by time to RRT independence at these time points.

Results: Of the eight prospective RCTs assessing different RRT intensities, seven contributed individual patient data (n=5688) to the analysis. Mortality was not different between the high and standard intensity groups across these 7 studies at 28 days (775/1890 and 744/1798 respectively, 41% vs 41.4%, p = 0.24) after randomization, nor at any of the other time points. The proportion of patients RRT dependent at the 14 day point was greater in patients receiving high compared to standard intensity RRT (RR 1.36, 95%CI 1.12-1.65, p = 0.0016), but not at any other time point. Analysis by time to RRT independence suggested that patients receiving higher intensity therapy had less time independent of RRT (Day 28: HR 0.87, 95% CI 0.78 to 0.97, p=0.014, Day 60: HR 0.87, 95%CI 0.78 to 0.97, p=0.012, Day 90: HR 0.94, 95% CI 0.94 to 0.94, p=0.0022). This effect was more pronounced in trials that allowed the use of intermittent hemodialysis (IHD) to deliver higher intensity RRT. The robustness of these effects was confirmed in multiple sensitivity analyses.

Conclusions: Higher intensity RRT does not affect mortality but does appear to delay recovery to RRT independence. This effect appears to relate to the use of IHD to deliver higher intensity RRT.

Funding: Government Support - Non-U.S.

Outcomes of In-Hospital Cardiopulmonary Resuscitation (CPR) in Patients with Acute Kidney Injury

Fahad Saeed,1 Jean L. Holzmann,2 Devag Demirjian,1 Cleveland Clinic; Univ of Illinois at Urbana-Champaign.

Background: There is paucity of data on the CPR-related outcomes in patients with AKI. Herein, we have analyzed the impact of AKI on the outcomes of in-hospital CPR.

Methods: We extracted data from the Nationwide Inpatient Sample (NIS, 2005-2011) including patients with and without AKI who had undergone in-hospital CPR. Baseline characteristics, in-hospital complications and discharge outcomes were compared between the two groups. We determined the effect of AKI on length of hospital stay, discharge destination, and hospital mortality in patients who underwent in-hospital CPR.

Results: 180,970 patients with primary or secondary diagnosis of AKI underwent in-hospital CPR compared to 323,620 patients without AKI. Unadjusted in-hospital mortality rates were higher in the AKI group (78.2 % vs. 71.8%, p<0.001). After adjusting for age, sex, and potential confounders, patients in the AKI group had higher odds of mortality with odds ratio 1.3, 95% confidence interval 1.2-1.4, p<0.001. Survivors in the AKI group were more likely to be discharged to nursing homes; odds ratio 1.4, 95% confidence interval 1.2-1.5, p<0.0001. Mean length of stay was significantly higher in patients with AKI, 11.3±44 days versus 7.2±6 days, p<0.0001.

Conclusions: AKI independently increases the odds of in-hospital mortality and nursing home placement after in-hospital CPR. These data may facilitate CPR decisions and decision-making.

SA-OR106

Outcomes of In-Hospital Cardiopulmonary Resuscitation (CPR) in Patients with Acute Kidney Injury

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Results: 180,970 patients with primary or secondary diagnosis of AKI underwent in-hospital CPR compared to 323,620 patients without AKI. Unadjusted in-hospital mortality rates were higher in the AKI group (78.2 % vs. 71.8%, p<0.001). After adjusting for age, sex, and potential confounders, patients in the AKI group had higher odds of mortality with odds ratio 1.3, 95% confidence interval 1.2-1.4, p<0.001. Survivors in the AKI group were more likely to be discharged to nursing homes; odds ratio 1.4, 95% confidence interval 1.2-1.5, p<0.0001. Mean length of stay was significantly higher in patients with AKI, 11.3±44 days versus 7.2±6 days, p<0.0001.

Conclusions: AKI independently increases the odds of in-hospital mortality and nursing home placement after in-hospital CPR. These data may facilitate CPR decisions and decision-making.

SA-OR107

Acute Kidney Injury After Surgical Aortic Valve Replacement and Long-term Risk of Death and End-Stage Renal Disease

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Background: Acute kidney injury (AKI) is a common complication after cardiac surgery that is associated with adverse outcomes. The incidence of AKI after surgical aortic valve replacement (SAVR) and its association with long-term mortality and end-stage renal disease (ESRD) is not known. The aim of this study was to determine the incidence of AKI and its relationship to mortality and long-term renal outcomes in a large cohort of patients who underwent a first isolated SAVR from 1999 to 2013 in AKI.

Methods: We included all 9,047 patients from the SWEDHEART register who underwent primary isolated SAVR between 1999 and 2013 in Sweden. AKI was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria: stage 1: serum Creatinine (sCr) concentration ≥ 0.3 mg/dL (26.5 mmol/L) or 1.5- to 1.9-fold increase in sCr; stage 2: 2.0- to 2.9-fold increase in sCr; Stage 3: 3.0-fold increase in post-op sCr compared to baseline value; initiation of renal replacement therapy.

Results: In total, 17% of patients developed AKI postoperatively, of whom 13% were AKI stage 1 and 3.7% AKI stages 2-3. During a mean follow-up of 5.6 (standard deviation [SD] 3.7) years, 2109 patients (23%) died and 29 (0.3%) developed ESRD. After multivariable adjustment, the hazard ratio (HR) with 95% confidence interval (CI) for death in AKI stage 1 was 1.27 (1.12 -1.44) and in AKI stages 2-3 was 2.47 (2.03-3.00). The subdistribution HR for ESRD in AKI stage 1 was 4.4 (1.7-12), and in stage 2 to 3 was 5.3 (1.6-18).

Conclusions: AKI is common after a first isolated SAVR and is associated with an increased long-term risk of both death and ESRD, independent of preoperative renal function.

SA-OR108

Incidence and Predictors of Acute Kidney Injury After Total Hip Replacement

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Background: Total hip replacement (THR) is a common procedure that has increased in number with the improvement in life expectancy. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used pre and post THR but their risk in causing acute kidney injury (AKI) in this setting is not well quantified.

Methods: Between 2004 and 2014, 10,327 patients underwent THR. We retrospectively collected demographic and co-morbidities data on those who developed AKI (defined by AKIN criteria) after THR. A control group without AKI was matched by age, gender and year of surgery. Variables associated with AKI were determined by univariate and multivariate logistic regressions.

Results: Mean age was 64.6 ± 13.8 years, 48.6% were male and 114 patients (1.1%) developed AKI (79% stage 1, 18.4% stage 2, 2.6% stage 3). Older age (RR 1.8, per decade, p<0.001) and male gender (RR 1.8, p=0.0016) were associated with AKI. Characteristics of those with and without AKI are shown in table-1. Several variables were associated with AKI (table-1) on univariate analysis but on multivariate analysis only CHF (OR 27.7, p<0.001); HTN (OR 2.9, p<0.001); CKD (OR 2.9, p<0.001) and transfusion (OR 3.5, p<0.001) remained significant. Diabetes (OR 2, p = 0.064); NSAID (OR 0.9, p=0.9); ACEI/ARB (OR 1.5, p<0.23) and diuretics exposure (OR 0.8, p=0.6) were not associated with AKI.

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

Underline represents presenting author.
inhibitor. Several classes of compounds gave good PK in rats with predicted therapeutic concentrations in blood and urine. Salt-sparing diuretic action was demonstrated in control, hydrated rats and rats administered dDAVP acutely. Up to a 2.5-fold increase in hourly urine volume and 2-fold reduction in urine osmolality was found. Compounds also prevented hypertonia in rats chronically treated with dDAVP.

**Methods:** Preincubation of TAL segments with 5,6-EET (10 µM) increased protein levels in CNT, CCD, and OMCD with close proximity to TAL profiles. dDA VP treatment resulted in renal cortical collecting duct (CCD) outer (OMCD) and inner (IMCD) medullary collecting duct. dDA VP increased Nedd4-2 expression, Nedd4-2 relieved Nedd4-2 inhibition of Nedd4-2 that interacted with ENaC. The V2R-dependent increase in Nedd4-2 expression was blocked with inhibition of protein synthesis that eliminated phosphorylation of Ser-444 of Nedd4-2. When V2R increased Nedd4-2 expression, V2R still relieved Nedd4-2 inhibition of Nedd4-2 cell surface expression if Ser-338, Thr-363, and Ser-444 remained intact. If all three residues were disrupted, V2R-mediated stimulation of Nedd4-2 was attenuated but not fully prevented, suggesting that V2R signals through additional residues on Nedd4-2 or independent of Nedd4-2.

**Conclusions:** Our findings provide a molecular basis for how AVP signals through Nedd4-2 to increase ENaC activity and demonstrate how the level of Nedd4-2 expression or interaction with Nedd4-2 is not necessarily an accurate surrogate for Nedd4-2 function.

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**SA-OR112**

**Role of Nedd4-2 Underlying V2R Activation of ENaC**

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**Background:** Arginine vasopressin (AVP) can increase renal sodium (Na+) reabsorption in the cortical collecting duct (CCD) by stimulating the epithelial Na+ channel (ENaC). One presumed mechanism by which AVP stimulates ENaC is through activation of the vasopressin V2 receptor (V2R) and inhibition of the E3 ubiquitin ligase Nedd4-2. Snyder and colleagues first demonstrated that CAMP/PKA signaling reverses Nedd4-2 inhibition of ENaC. However, how V2R signals through Nedd4-2 to regulate ENaC is not fully understood.

**Methods:** We therefore tested mechanisms by which V2R inhibits Nedd4-2 and increases ENaC cell surface expression in transfected HEK293T kidney cells, an established model for the study of Nedd4-2 function.

**Results:** We found that V2R, similar to CAMP, relieved Nedd4-2 inhibition of ENaC cell surface expression, but surprisingly V2R did not decrease the interaction between Nedd4-2 and ENaC. Instead, V2R increased expression of Nedd4-2, which in turn increased the pool of Nedd4-2 that interacted with ENaC. The V2R-dependent increase in Nedd4-2 expression was blocked with inhibition of protein synthesis that eliminated phosphorylation of Ser-444 of Nedd4-2. When V2R increased Nedd4-2 expression, V2R still relieved Nedd4-2 inhibition of ENaC cell surface expression if Ser-338, Thr-363, and Ser-444 remained intact. If all three residues were disrupted, V2R-mediated stimulation of ENaC was attenuated but not fully prevented, suggesting that V2R signals through additional residues on Nedd4-2 or independent of Nedd4-2.

**Conclusions:** Our findings provide a molecular basis for how AVP signals through Nedd4-2 to increase ENaC activity and demonstrate how the level of Nedd4-2 expression or interaction with Nedd4-2 is not necessarily an accurate surrogate for Nedd4-2 function.

**Funding:** NIDDK Support

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**SA-OR113**

**Vasopressin Lowers Renal Epoxyeicosatrienoic Acid Levels by Activating Soluble Epoxy Hydrolase**

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**Background:** Activation of the thick ascending limb (TAL) Na+(1,K+)-2Cl-(1) cotransporter (NKCC2) by vasopressin (AVP) is an essential mechanism of volume homeostasis and may also contribute to the development of arterial hypertension and chronic kidney disease. AVP effects in the kidney are counteracted by locally produced eicosanoids including epoxyeicosatrienoic acids (EETs). The effects of AVP on the renal expression of EET-metabolizing enzymes have not been determined.

**Methods:** Adult AVP-deficient Brattleboro rats were treated with the AVP receptor agonist desmopressin (dDAVP, 5ng/h, 3d) via osmotic minipump. RENAL EET-levels were measured by mass spectrometry. Regulation of EET-metabolizing enzymes was determined by Affymetrix microarray analysis. Microarray results were confirmed by real-time PCR, immunohistochemistry and Western blot. EET effects on TAL transport activity were studied using the isolated perfused tubule setup.

**Results:** dDAVP treatment significantly lowered renal EET levels (-56±3% for 5,6-EET, -50±3% for 11,12-EET and -60±3.7% for 14,15-EET relative to controls, p<.05). Microarray analysis revealed elevated mRNA levels for the principal EET-degrading enzyme soluble epoxy hydrolase (sEH) and unchanged mRNA-levels for the EET-synthesizing epoxygenases. Regulation of sEH was confirmed by real time PCR (+160±37%, p<.05) and Western blot (20±26%, p<.05). Immunohistochemistry in control animals demonstrated abundant expression in the macula densa, connecting tubule (CNT), and in the cortical (CCD), outer (OMCD) and inner (IMCD) medullary collecting duct. dDAVP treatment increased protein levels in CNT, CCD, and OMCD with close proximity to TAL profiles. Preincubation of TAL segments with 5,6-EET (1µM; 30 min) significantly reduced furosemide inhibitable short circuit current (-45±5%; p<.05) thus confirming inhibitory effects of EETs on NKCC2 transport activity.

**Conclusions:** We have shown that activation of AVP signaling causes upregulation of renal sEH biosynthesis and enzyme activity. The resulting reduction of EET tissue levels may be instrumental for increased NKCC2 transport activity during AVP-induced antidiuresis.

**Funding:** Government Support - Non-U.S.

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**SA-OR114**

**MicroRNA-132 Regulates Diuresis by Mediating Vasopressin Production**

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**Background:** The collecting duct (CD) principal cells of our kidneys are critical in the maintenance of blood water levels, as binding of vasopressin (AVP) to its V2-receptor and the subsequent translocation of aquaporin-2 (AQP2) water channels to the apical membrane fine-tunes water balance. AVP dependent regulation of water homeostasis can be modulated
by renal prostaglandin E$_2$ (PGE$_2$), a metabolite of the cyclooxygenase (COX) pathway, by inducing a transcript and lysosomal degradation of AQP2. A trafficking defect in the early endosome (miRNAs) in the regulation of water and electrolyte balance remains virtually unexplored.

**Methods:** We generated antagonists to silence miR-132 function. Synthetic AVP (dAVP) was administered with osmotic minipumps. Mice were housed in metabolic cages and sacrificed after i.v. or i.c.v. injection of the antagonists or scrambled controls.

**Results:** Silencing of miR-132 caused severe weight loss as a result of acute diuresis characterized by increased plasma osmolality and decreased urine osmolality. In addition, urinary PGE2 levels were elevated and hypothalamic AVP mRNA expression and blood AVP levels were decreased; there was less translocation of AQP2 in CD cells. We also altered ILK Cox2 as a direct target of miR-132, but administration of Cox2-inhibitor Colecid did not affect antagonist-induced diuresis, suggesting a PGE2 independent pathway. In contrast, infusion of synthetic AVP (dAVP) reversed antagonist-induced diuresis, suggesting an effect on hypothalamic AVP production. Confirming this hypothesis, i.v. injection of antagoniR-132 similarly resulted in acute diuresis and decreased AVP production and we found miR-132 to target and increase hypothalamic MeCP2, which is known to block AVP transcription.

**Conclusions:** Taken together, silencing of miR-132 causes acute diuresis. Our data indicate that this is the result of a MeCP2 mediated decrease in hypothalamic AVP synthesis.

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**SA-OR115**

**Dephosphorylation at Ser-261 Is a Determinant for the Regulated AQP2 Apical Accumulation**

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**Background:** AQP2 apical plasma membrane accumulation is crucial for vasopressin (VP)-regulated urine concentration. It is well known that VP induces post-translational modification on AQP2 phosphorylation at several serine (S) sites in its C-terminus, however, how these complicated phosphorylation and dephosphorylation regulate AQP2 apical accumulation is unknown. Recently, we identified that 1) pS261-AQP2 is continuously targeted to the apical plasma membrane, then internalized into the cytoplasm without any stimulations, 2) pS269-AQP2 is observed intracellularly at 1 min in the initial phase of forskolin (FK) stimulation, 3) S269 phosphorylated preceded S261 dephosphorylation in polarized MDCK cells. Therefore, we hypothesized that dephosphorylation at S261 at 261 is crucial for regulated AQP2 apical accumulation at the downstream step during the stimulation.

**Methods:** To test this hypothesis, we expressed mutated AQP2 and analyzed them in MDCK cells focusing on phosphorylation status at S261 and S269.

**Results:** In P262L-AQP2, a recessive NDI causing mutant, pS269 was greatly increased with continuous S265 phosphorylation after forskolin (FK) stimulation (20 µM, 10 min) as well as wild-type AQP2 (WT-AQP2), whereas, pS261 was increased after FK treatment contrary to WT-AQP2 (20 µM, 10 min). Surprisingly, pS269-AQP2 was accumulated in the basolateral membrane after FK treatment (20 µM, 5 min). S269/A-AQP2, a S269-dephosphorylation mimic, accumulates in the apical membrane after FK treatment (20 µM, 30 min) with a striking reduction of phosphorylation at S261. Interestingly, it took longer time (20 min) to dephosphorylate S261 in S269/A-AQP2 compared to WT-AQP2 (within 5 min).

**Conclusions:** These results demonstrated that FK-mediated subcellular translocation of pS269/A-QQP2 is greatly affected by phosphorylation status at S261 and that FK-mediated AQP2 apical accumulation might be determined by S261 dephosphorylation, which is likely to be facilitated by precedent phosphorylation at S269. Further investigation how VP-mediated S269 phosphorylation catalyzes dephosphorylation at Ser-261 would be important to draw a complete picture of AQP2 translocation mechanism.

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**SA-OR116**

ILK Is Important for Recycling of AQP2 and Its Subsequent Entry into the Exocytic Pathway

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**Background:** Within the past decade tremendous efforts have been made to understand the mechanism behind aquaporin-2 (AQP2) water channel trafficking and recycling, in order to open a path towards effective diabetes insipidus therapeutics. A recent study has shown that Integrin Linked Kinase (ILK), a downstream polycystic kidney disease (pKD-ILK) is a downstream polycystic polyuria along with decreased expression of AQP2.

**Methods:** To better understand the role of ILK in this process, we performed in vitro analysis using LLC-PK1 cells stably expressing rat AQP2 (W2 cells).

**Results:** Upon treatment of W2 cells with ILK-SiRNA and the ILK inhibitor, Calbiochem-cpd22, we observed a accumulation of AQP2 in the perinuclear region, without accumulation of AQP2 in the plasma membrane. We next examined the effect of ILK inhibition on endocytosis using a fluid phase marker, FITC-dextran (10 KDa). There was a significant decrease in endocytosis of FITC-dextran in W2 cells after ILK inhibition. When we examined the clathrin mediated endocytotic pathway using rhodamine conjugated transferrin, a perinuclear accumulation of rhodamine transferrin was detected in the presence of ILK inhibition, which colocalized with AQP2. To further test whether we could see AQP2 accumulation in the perinuclear patch, lysine vasopressin (LVP) was added in conjunction with ILK-SiRNA or ILK inhibitor. Interestingly, the canonical LVP induced AQP2 membrane accumulation was prevented. To examine whether these effects were due to an alteration of AQP2 phosphorylation, we performed western blotting of AQP2 phosphorylated forms, targeting the S256, 269 and 264 sites. The data did not reveal any significant effects on AQP2 phosphorylation patterns after ILK inhibition.

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**Underline represents presenting author.**

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Water, Urea, and Vasopressin

and NCC (coefficients of variance 5.6 and 3.3%). To verify whether expected effects of vasopressin on AQP2 and NCC were captured by our uEV-ELISA, we performed overnight thirsting followed by water loading in 4 volunteers. After water loading, similar 2-3 fold decreases in AQP2 and NCC were observed using either uEV-ELISA or immunoblotting after isolating uEVs with ultracentrifugation. The results by uEV-ELISA showed good correlations with immunoblot (r=0.8 for AQP2, r=0.6 for NCC, both P<0.001).

Conclusions: We successfully developed an ELISA to capture and quantify uEV-proteins and validated this technique for AQP2 and NCC. Our uEV-ELISA set-up does not require ultracentrifugation or measurement of urinary creatinine and may be used as a platform to examine other uEV proteins of interest in nephrology.
The Long Non-Coding RNA Landscape in Hypoxic and Inflammatory Renal Epithelial Injury

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Background: Long non-coding RNAs (lncRNAs) are emerging as key regulators of disease processes. To identify lncRNAs involved in acute renal epithelial injury, we performed whole transcriptome profiling of human proximal tubular epithelial cells (PTECs) in hypoxic and inflammatory conditions.

Methods: Strand-specific RNA-seq (50 million paired-end reads per library) was performed on poly-adenylated RNA fraction of control PTECs and PTECs subjected to 12 hours of hypoxia or cytokine (IL-6, TNF-α, and IFN-γ) cocktail stimulation. A transcript was considered differentially expressed (DE) between control and stimulation at >1.5 fold change with FDR-adjusted p < 0.05.

Results: 3,728 mRNAs and 69 lncRNAs were DE between cytokine-stimulated and control PTECs, while 2730 mRNAs and 70 lncRNAs were DE between hypoxic and control cells. Three lncRNAs were prioritized for further study based on abundance. Linc-ATP13A4-8 was specifically upregulated (8.1-fold at 12 hours, FDR p < 0.001) in control cells. Three lncRNAs were prioritized for further study based on abundance. Linc-KIAA1737-2 was specifically upregulated after cytokine treatment (4.6-fold at 12 hours, FDR p < 0.001), was over 50-fold upregulated at 48 hours, is located in hypoxia, peaked its expression 15-fold at 24 hours, is located in the nucleus and cytoplasm, and has both synergy and 80.6% conservation of a 206 bp sequence with the mouse genome. Lnc-KIAA1737-2 was specifically upregulated after cytokine treatment (4.6-fold at 12 hours, FDR p < 0.001), was over 50-fold upregulated at 48 hours, is located primarily in the nucleus with an enhancer region (high H3K4me1/1H3K4me3 overlying H3K27ac mark for adult kidney on NH Epigenomics Roadmap), and is syntenic with mouse with no sequence conservation. Lnc-POUSF1-1 increased in expression (2 to 4 fold, FDR p < 0.001) in both stimulations, declined in expression after 12 hours, is located in the nucleus with a canonical promoter region shared with protein-coding POUSF1, and is human-specific. All three lncRNAs are expressed in human PTECs from healthy donor nephrectomy kidneys previously micro-dissected and sequenced.

Conclusions: Transcriptome profiling of stimulated renal epithelial cells reveals different lncRNAs that may regulate the cellular response to distinct stressors relevant to acute kidney injury.

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TH-PO002

Cortical Consequences of Ischemia-Reperfusion Injury: Computational Studies of the Renal Microvasculature

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Background: The acute injury of the ischemia-reperfusion (I/R) kidney model affects mainly the outer stripe (OS) of the outer medulla, but its long-term consequence is extensive cortical involvement. We were therefore interested in the long-term effects of such ischemic injury on the cortical capillary network.

Methods: Male C57BL/6 mice (n=11) were subjected to bilateral renal I/R for 25 min and sacrificed 2 weeks later. Untreated mice (n=5) served as controls. Kidney sections were stained for MECA-32 to visualize the renal microvasculature. Vessel geometry was selectively quantified in damaged tissue regions by computer-assisted morphometric analysis.

Results: In normal subcapsular cortex peritubular capillaries appeared elongated and formed an organized network. Although I/R initially affects the OS, 2 weeks after I/R, marked chronic tubular atrophy occurred in the cortex. Adjacent microvessels’ shape remarkably changed: capillaries were significantly smaller (perimeter, diameter decreased) and rounder (circularity and roundness increased, see Figure, aspect ratio decreased) compared to control vessels.

Conclusions: If translatable from mice to human, these data have important therapeutic implications.

Funding: Pharmaceutical Company Support - ISIS Pharmaceuticals, Private Foundation Support

TH-PO003

Glomerular Injury Induces a Calcium Signal in Proximal Tubular Cells – A Multiphoton In Vivo Study

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Background: Recently it has been demonstrated that renal tubular cells undergo synchronized necrosis after ischemic injury, implying that the death of a single cell can induce a disastrous chain reaction. An early event in damage signaling is a massive increase in intracellular calcium levels. Therefore we investigated if a localized damage to glomerular cells can influence tubular calcium levels downstream of the damage site.

Methods: 4 weeks old mice expressing the calcium indicator GCaMP3 in proximal tubular cells (Pax8cre) were anaesthetized, an arterial catheter was placed into the right carotid artery and the left kidney was exteriorized for in vivo multiphoton microscopy. Blood vessels were labelled by injection of 70 KDa Texas Red dextran. Acute glomerular injury was induced by focusing the laser beam on a podocyte to cause a localized injury. The resulting calcium response in tubular cells was recorded with a time series of the glomerulus and the originating proximal tubulus.

Results: Upon laser induced injury of a podocyte, a strong calcium signal can be observed within seconds in the continuous stretch of proximal tubular cells downstream of the glomerulus. The signal lasts for a few seconds and then the calcium signal returns to baseline. The calcium response in proximal tubular cells is faster than the known calcium wave in podocytes after injury.

Conclusions: Glomerular injury induces a calcium signal in proximal tubular cells in vivo, linking glomerular injury to tubular damage signaling. The almost instantaneous calcium increase in tubular cells suggest that the release of podocyte cell content and most probably damage-associated molecular pattern molecules (DAMPs) affects tubular cells, unjured by the initial damage.

TH-PO004

Inhibition of Oxygen-Sensing Prolylhydroxylases 1 (PHD1) Protects from Acute Kidney Injury

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Background: Acute kidney injury (AKI) due to ischemia is associated with dramatic increases of morbidity and mortality. Conditions of ischemia with limited oxygen availability inhibit oxygen-sensing prolyl hydroxylases (PHD1-3) with subsequent stabilization of hypoxia-inducible factors (HIFs) resulting in a transcriptionally regulated response towards hypoxia adaptation. Thus, we hypothesize that a new pharmacological approach to inhibit PHDs on a transcript level via specific antisense treatment before the onset of ischemic injury mediates protection.

Methods: Mice were studied in two ischemic models of AKI. With a hanging weight system we only compress the renal artery whereby we clamp the whole pedicle by using micro vessel clamps. Renal function was determined by inulin clearance, serum creatinine, BUN, renal NGAL and KIM-1.

Results: Our previous studies in gene-target mice (PHD1-3 KO mice) has shown that renal protection from ischemia was associated with PHD1. To pursue our hypothesis, we first treated wild type mice with PHD1 specific antisense inhibitors (ASO1 and ASO2). We tested the compounds over 2 to 6 week treatment periods in different doses. The optimal treatment length was 2 weeks before renal ischemia (30min ischemia and 24 hours reperfusion by utilizing the hanging weight system) in a dose of 100mg/kg per week. Treatment reduces renal PHD1 RNA by 90% and 60%, respectively and improved the glomerular filtration rate (GFR) by almost 300% in both treatment groups compared to untreated mice following 30min of renal ischemia. In a next step we used the clamp model to induce kidney ischemia. PHD1 specific antisense inhibitor treatment showed comparable kidney protection as in the hanging weight model demonstrated in GFR improvement, serum creatinine and renal tubular injury markers (NGAL, KIM1).

Conclusions: In conclusion, PHD1 oligo treatment before renal ischemia in two different ischemia models shows a tremendous attenuation from renal injury due to ischemia. If translatable from mice to human, these data have important therapeutic implications.

Funding: Pharmaceutical Company Support - ISI Pharmaceuticals, Private Foundation Support
Role of Thioredoxin-Interacting Protein (TXNIP) in Mitochondrial Function of Renal Tubular Cells in Ischemia Reperfusion Injury AKI Model 
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Background: Thioredoxin-interacting protein (TXNIP) has been found to regulate the cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin in a redox-dependent fashion. However, little is known about the role of TXNIP in acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of TXNIP in renal function in bilateral ischemia/reperfusion injury (IRI) model using TXNIP knock-out (KO) and wild type (WT) mice. cultured renal tubular cells (NRK-52E cells) as an in vitro model. To elucidate the functional roles of TXNIP, we evaluated mitochondrial enzymes, morphology, and apoptotic change by transfection of siRNA for TXNIP in cultured renal tubular cells.

Results: TXNIP KO mice had significantly higher SCr (0.78 ± 0.28 versus 0.45 ± 0.20 mg/dL) and significantly decreased blood urea nitrogen (BUN) (152.5 ± 32.5 versus 75.3 ± 18.2 mg/dL) at 24 h post ischemia compared to WT mice. Immunohistological examination showed severe tubular injury in cortex and outer medulla in TXNIP KO mice compared to WT mice. The number of TUNEL positive tubular cells was increased in TXNIP KO mice compared to WT mice. The protein expressions of mitochondrial enzymes (ATP5a, UCP2 and complex IV) were decreased in TXNIP KO mice at 24 h post ischemia. In vitro experiments, protein and mRNA levels of ATP5a, complex IV, UCP2, PGC-1α were significantly decreased by H2O2, and siRNA for TXNIP amplify the reduction of these enzymes in NRK-52E cells.

Conclusions: TXNIP changes mitochondrial function in oxidative conditions. These results indicate that TXNIP plays a key role in the pathophysiology of AKI.

TWEAK Decreases PGC-1α Expression in Renal Injury and Promotes Mitochondrial Dysfunction in Tubular Cells 
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Background: There is currently no satisfactory therapy for acute kidney injury (AKI). Successful testing of mitochrondria-targeted nephroprotective agents suggests a key role of mitochondrial injury in AKI. We hypothesized that an improved understanding of the regulation of factors responsible for mitochondrial biogenesis may provide clues to novel therapeutic approaches to AKI. Thus, we explored the interaction between inflammation and mitochondrial biogenesis regulators.

Methods: Transcriptomics databases from cultured murine tubular epithelial cells and folic acid-induced AKI in mice identified downregulation of PGC-1α and target genes regulated by the inflammatory cytokine TWEAK. Functional studies in vitro and in vivo cultures characterized the TWEAK-PGC-1α relationship.

Results: Transcriptomics identified decreased expression of PGC-1α mRNA and mRNA of PGC-1α-dependent genes encoding mitochondrial proteins (Ndufs1, Sdhb and Tfam) as a shared feature between AKI and TWEAK-stimulated cultured tubular cells. Neutralizing anti-TWEAK antibodies prevented the decrease in kidney PGC-1α and its targets during AKI. TWEAK stimulation decreased kidney PGC-1α expression in healthy mice. TWEAK also decreased the expression of PGC-1α and its targets as well as mitochondrial membrane potential in cultured tubular cells. Adenoviruses-mediated PGC-1α overexpression prevented TWEAK-induced downregulation of PGC-1α-dependent genes and the decrease in mitochondrial membrane potential. TWEAK promoted histone H3 deacetylation at the murine PGC-1α promoter. TWEAK-induced downregulation of PGC-1α was prevented by histone deacetylation (HDAC) or sirtuin inhibitors.

Conclusions: TWEAK decreases PGC-1α and target gene expression in tubular cells through sirtuin activation and histone deacetylation. This information may be used to design therapeutic approaches that preserve mitochondrial function during kidney injury. 

Funding: Private Foundation Support, Government Support - Non-U.S.:

miR-21 Targets Prolyl Hydroxylase Domain Protein 2 in Renal Ischemia/ reperfusion 
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Background: MicroRNAs are important regulators in various pathological conditions including ischemic acute kidney injury (AKI). We identified miR-668 that was significantly up-regulated in ischemic AKI. miR-668 induction was attenuated in kidney proximal tubule-HIF-1α knockout mice, suggesting a role of HIF-1α in the inductive response. In vitro, miR-668 up-regulation was a consequence of the potential promoter region of miR-668 predicted two HIF-1 binding sites. The binding of HIF-1 to one of the sites was verified by Chromatin immunoprecipitation (CHIP) assay, suggesting that HIF-1 may directly regulate miR-668 transcription.

Methods: Functionally, inhibition of miR-668 exacerbated kidney injury, supporting a protective role of this microRNA. Consistently, inhibition of miR-668 led to apoptosis in cultured rat proximal tubular cells (RPTC) and overexpress miR-668 reduced ATP-depletion mediated RPTC apoptosis. Interestingly, miR-668 inhibition also induced significant mitochondrial fragmentation, a pathogenic event in renal tubular cell death in ischemic AKI. To further examine the regulation mechanism of mitochondrial morphology by miR-668, we identified a list of potential miR-668 targets by Ago2 immunoprecipitation and RNA deep sequencing.

Conclusions: In summary, miR-668 is up-regulated via HIF-1 during ischemic AKI. Following the induction, miR-668 may play a role in the preservation of mitochondrial dynamics and morphology for the protection of kidney cells and tissues. n also induced significant mitochondrial fragmentation, a pathogenic event in renal tubular cell death in ischemic AKI. To further examine the regulation mechanism of mitochondrial morphology by miR-668, we identified a list of potential miR-668 targets by Ago2 immunoprecipitation and RNA deep sequencing.

Funding: NIDDK Support, Veterans Administration Support, Private Foundation Support

Impact of AMPK Activation in Experimental Aristolochic Acid Nephropathy: Use of a Targeted Metabolomic Analysis 
Anne-Emilie Declercq, Ines Jadot, Vanessa Colombo, Kefeng Li, Nathalie Caron, Joelle L. Nortier, Robert K. Naviaux.
Free Univ of Brussels; 2 Univ of California, San Diego; 3 Univ of Namur.

Background: Experimental aristolochic acid nephropathy (AAN) is a progressive tubulointerstitial injury, characterized by early and transient acute tubular necrosis. In order to better explore the pathogenesis of AAN, a targeted metabolomic analysis was performed in plasma of AA-intoxicated mice. In addition, the effect of AMP-activated Protein Kinase (AMPK) activation with AICAR was also investigated.

Methods: C57BL/6 mice were subjected to i.p. injection of either sterile saline solution, AA, AA+AICAR, the specific AMPK activator for 4 days. Mice were euthanized at day 5. Targeted metabolites were detected in plasma using an AB SCIEX QTRAP 5500 triple quadrupole mass spectrometer equipped with a Turbo V electrospray ionization (ESI) source, and Shimadzu LC-20A UHPLC system.

Results: Thirty metabolites were dysregulated in this acute phase of the experimental AAN model. Among them, 23 metabolites were significantly increased in AA-treated mice and 7 were significantly decreased. AICAR treatment ameliorated the change of 15 of these metabolites. Among the observed changes, several metabolic pathways were affected, in particular gut microbiome metabolism, liver and bile acid metabolism, tryptophan metabolism, purine and pyrimidine metabolism and mitochondrial metabolism. Tryptophan-derived metabolites considered as uremic toxin such as xanthurenic acid, kynurenine acid were increased in AA-treated mice and reduced with AICAR.

Conclusions: These metabolomic approach provided novel findings regarding early perturbations occurring in metabolic pathways in AAN. Moreover, our results suggest 1)
a crosstalk between gut microbiome and kidney, especially in relation with tryptophan metabolism and accumulation of uric acid toxins, 2) a beneficial role of AMPK, in reducing the level of uric acid toxins.

Funding: Private Foundation Support

TH-PO010

Suppressed Renal Mitochondrial Biogenesis After Liver Transplantation in Rats

Zhong Zhong, 1 Qinlong Liu, 1 Yasodha Krishnasamy, 1 Habibur Rehman, Peifeng Deng, 1 John J. Lemasters, 1 Rick G. Schnellman, 1, 3 1 Medical Univ of South Carolina, Charleston, SC, 2 Darlai Medical Univ, 2nd Affiliated Hospital, Darlai, China; 3 Ralph H. Johnson VA Medical Center, Charleston, SC.

Background: Suppressed mitochondrial biogenesis (MB) contributes to acute kidney injury (AKI) after renal ischemia-reperfusion and sepsis. AKI occurs frequently after liver transplantation (LT), which substantially increases mortality. This study investigated whether MB is suppressed in AKI after LT.

Methods: Livers were explanted from Lewis rats and implanted after 18 h cold storage. Liver, kidney and blood were collected 18 h after reperfusion. Liver, kidney and blood were collected 18 h after LT or survival was determined at 7 days.

Results: Seven-day survival after LT decreased to 25%. Focal necrosis, apoptosis and leukocyte infiltration occurred in liver grafts, and serum ALT and total bilirubin increased markedly after LT. In the kidney, nuclear DNA-encoded oxidative phosphorylation (OXPHOS) protein ATP synthase-β and mitochondrial DNA (mtDNA)-encoded OXPHOS protein NADH oxidase-3 decreased 34% and 81%, respectively, and their associated mRNAs decreased 72% and 46%, respectively, indicating suppressed OXPHOS protein synthesis. Renal PGC-1α, the master regulator of MB, decreased 57% after LT and mitochondrial transcription factor-A (TFAM), which controls mtDNA replication and transcription, decreased 66%. PGC-1α and TFAM mRNA also decreased. mtDNA was reduced by 60%.

Conclusions: MB is disrupted in the kidneys of recipients of liver grafts after cold storage, which may contribute to the occurrence of AKI and increased mortality after LT.

Funding: NIDDK Support

TH-PO011

TXNIP Is Involved in the Mitochondrial ROS Mediated NLRP3 Inflammasome Activation in Ischemia/Reperfusion Induced AKI Lii Yiran, Wen Yi, Tang Taotao, Bi-Cheng Liu. Inst of Nephrology, Southeast Univ, Nanjing, Jiangsu Province, China.

Background: Renal ischemia reperfusion is a leading cause of acute kidney injury (AKI). Previous studies suggest that mitochondrial dysfunction and NLRP3 inflammasome activation are important events of AKI. TXNIP, an endogenous inhibitor of the antioxidant thioredoxin and ROS sensor, may have a role in NLRP3 inflammasome activation. In this study, we explored the relationship between TXNIP on NLRP3 inflammasome activation in ischemia/reperfusion induced AKI.

Methods: Ischemic mice models were built as previously reported. MitoTEMPO, a mitochondria-targeted antioxidant, was used to attenuate ROS production. Also, H2 cells were cultured for 8h with hypoxia-hypoglycemic plus 2 h normoxia/normoglycemia incubation. SiRNA of NLRP3 and TXNIP were applied to interrupt the signaling.

Results: In this study, we established an ischemia reperfusion-induced AKI model characterized by tubular necrosis and excessive ROS production. The renal expression of NLRP3 inflammasome, IL-1β and IL-18 were significantly increased in this animal model. However, kidney dysfunction and mitochondrial damage were attenuated obviously in NLRP3-/- mice compared with WT mice with ischemia AKI. In vitro study, oxygen-glucose deprivation injury time dependently increased the expression levels of NLRP3 inflammasome axis and TXNIP. The mitochondrial injury in damaged HK2 cells was suppressed by TXNIP silencing. Methylprednisolone and L-1 also increased in the kidney after LT, indicating inflammation. Serum creatinine increased >2 fold.

Conclusions: MB is disrupted in the kidneys of recipients of liver grafts after cold storage, which may contribute to the occurrence of AKI and increased mortality after LT.

Funding: NIDDK Support

TH-PO012

PPAR Activation in Regulatory T Cells Enhances Protection from Kidney Ischemia Reperfusion Injury Gilbert R. Kinsey, Didier Portilla, Liping Huang, Mana Yang, Michael N. Pham, Brian K. Stevens. Medicine, Univ of Virginia, Charlottesville, VA.

Background: Regulatory T cells (Tregs) are anti-inflammatory lymphocytes that protect the kidney from multiple types of injury. Our recent studies suggest that Tregs must express the surface receptor programmed death 1 (PD-1) to mediate protection. A metabolic program favoring mitochondrial oxidative phosphorylation (OXphos) over glycolysis in Tregs is critical for Treg development and function in other models. PD-1 and peroxisome proliferator-activated receptors (PPARs) promote OXphos in several cell types, but their role in Treg-mediated renal protection is not known.

Methods: Mitochondrial membrane potential (TMRE) and mass (MitoTracker) were assessed in vitro in primary Treg cultures. Tregs isolated from WT or PD-1 KO mice were adoptively transferred into naïve WT recipients 1 hr prior to ischemia reperfusion injury (IRI). WT and PD-1 KO Tregs were exposed to the pan PPAR activator bezafibrate (BEZA) or vehicle (DMSO) overnight, then washed, prior to adoptive transfer in the IRI model.

Results: Treatment of WT Tregs with bezafibrate overnight significantly enhanced the ability of a sub-optimal number of Tregs to protect the kidney from IRI (24 h plasma creatinine (mg/dl): Sham 0.4±0.1; IR1 + saline 1.8±0.1; IR1 + WT Tregs (DMSO) 1±0.3; IR1 + WT Tregs (BEZA) 0.6±0.1*, N=7 per group, *P<0.01 vs. DMSO). Bezafibrate treatment also improved PD-1 KO Tregs with modest, but statistically significant, protective ability in the kidney IRI model.

Conclusions: These results demonstrate that PD-1 must be expressed on Tregs in order for them to suppress kidney IRI and that PPAR activation ex vivo enhances subsequent Treg activity in this model. Our findings suggest that enhanced OXphos in Tregs promotes their ability to protect the kidney.

Funding: NIDDK Support

TH-PO013

Effects of Short Chain Fatty Acids on Inflammatory Process in Acute Kidney Injury Sang Yoon Lim, 1 Young Ju Na, 1 Myung-gyu Kim, 2 So-young Lee, 2 Sang-Kyung Jo, 1 Won-Yong Cho, 1 1 Dept of Nephrology, Korea Univ Hospital, Seoul, Korea; 2 Dept of Nephrology, Eulji Univ Hospital, Seoul, Korea.

Background: Short chain fatty acids (SCFAs) are the metabolic end products of normal bacterial fermentation of fibers in the large intestine. Emerging evidence suggest the role of gut-kidney crosstalk in regulating inflammatory processes. The purpose of the present study was to elucidate the role of SCFAs in an acute kidney injury (AKI) in which the inflammatory process plays a major role.

Methods: Bilateral ischemia reperfusion injury (IRI) was induced in C57BL/6 mice. Sodium acetate were given to mice 30 minutes before ischemia and at the moment of reperfusion. Biochemical values, histological kidney damage and tissue inflammation were assessed. In in vitro analysis, immune cells harvested from mice spleen were stimulated with LPS and the effect of sodium acetate on cytokine production was measured. Effects of SCFAs on T cell proliferation was also determined.

Results: Treatment with SCFAs attenuated IRI and reduced inflammation. Tubular cell apoptosis, determined by TUNEL stain also decreased by SCFAs. The anti-inflammatory effects of SCFAs persisted until IRI day 14, thereby attenuating renal fibrosis after injury. Significantly lower level of pro-inflammatory cytokines was observed in the supernatant of cells from spleen co-treated with LPS and SCFAs, compared with those treated with LPS alone. Especially, IL-12p70, major inflammatory cytokine of dendritic cells was also reduced, suggesting that SCFAs might modulate the function of dendritic subset. In addition, administration of SCFAs can dose dependently inhibit normal T cell proliferation induced by anti-CD3 Ab stimulation.

Conclusions: Thus, our findings provide evidence that the SCFAs have renoprotective effect in AKI and also that this might be partially mediated by its immune modulatory effect.

TH-PO014

The Renoprotective Effect of Abatacept in Ischemia/Reperfusion Injury in Mice Masaki Saito, Shinya Kaname, Hideki Shimizu, Yoshihiro Komagata, Yoshihiro Arimura. Kyorin Univ School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo, Japan.

Background: Although AKI is still an important complication in hospitalized patients, its prognosis remains poor, thus elucidation of the pathogenic mechanism and its effective treatment is urgently needed. Recently, a role for T cells in the renal ischemia/reperfusion injury (IRI) and also the renoprotective effect of abatacept, an inhibitor for CD28-Cd80 T cell costimulatory signals, in the IRI have been reported, while its precise mechanisms are not fully understood. The purpose of this study is to determine the effect and mechanism of abatacept in the IRI model in mice.

Methods: Hemiparenchymized mice were divided into three groups; the mice treated with ischemia reperfusion injury (IRI) and also the renoprotective effect of abatacept, an inhibitor for CD28-Cd80 T cell costimulatory signals, in the IRI have been reported, while its precise mechanisms are not fully understood. The purpose of this study is to determine the effect and mechanism of abatacept in the IRI model in mice.

Results: Compared with normal saline-treated mice, renal injury in the abatacept-treated mice were markedly attenuated both functionally and pathologically, with serum parameters improved to almost control levels. In addition, in abatacept-treated mice, apoptosis and expression of MCP-1 and PD-1 were significantly decreased, compared with normal saline-treated mice. Although the number of inflammatory cells and expression of MCP-1 were reduced by abatacept, the number of CD3-positive T cells, which was increased after ischemia/reperfusion, was not altered by abatacept.

Conclusions: We here showed that abatacept dramatically ameliorate IRI in mice, suggesting that it might be a new therapeutic option. It may be that abatacept, by blocking CD80-mediated signal in some cells responsible for the pathogenesis, exhibit anti-inflammatory effects, resulting in improvement of IRI, independently of T-cell-mediated acquired immune mechanisms.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO0015
Autophagy Is Activated to Protect against Kidney Injury following in Lipopolysaccharide Treatment
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Background: Sepsis, characterized by systemic inflammation, is a major cause of acute kidney injury (AKI) in hospitalized patients, especially in intensive care unit. The pathogenesis of septic AKI is poorly understood. Autophagy is a conserved, cellular catabolic pathway that plays crucial roles in cellular homeostasis including the maintenance of cellular function and viability. The regulation and role of autophagy in septic AKI remains unclear.

Methods: Lipopolysaccharide (LPS), an endotoxin, was injected in C57BL/6 mice to induce endotoxic/septic AKI. Autophagy reporter (CAG-RFP-EGFP-LC3) mice were used to monitor the dynamic changes of autophagy following LPS treatment. To determine the pathological role of autophagy, autophagy was inhibited pharmacologically with chloroquine or genetically by using proximal tubule-specific Atg7 (Autophagy gene-7) ablated mice. Blood area nitrogen (BUN) and serum creatinine were measured to evaluate renal function. HE staining and TUNEL staining were used to detect kidney injury. For in vitro study, cultured proximal tubular cells were treated with LPS in the absence or presence of chloroquine.

Results: LPS induced AKI in mice as indicate by increased in BUN and serum creatinine, and tubular injury, which was accompanied by an increase in LCH expression. In CAG-RFP-EGFP-LC3 mice, LPS induced mRFP and EGFP-labeled autophagic puncta in renal tubular cells, further verifying the activation of autophagy. Chloroquine enhanced the pathological role of autophagy, autophagy was inhibited pharmacologically with chloroquine or genetically by using proximal tubule-specific Atg7 (Autophagy gene-7) ablated mice. Blood area nitrogen (BUN) and serum creatinine were measured to evaluate renal function. HE staining and TUNEL staining were used to detect kidney injury. For in vitro study, cultured proximal tubular cells were treated with LPS in the absence or presence of chloroquine.

Conclusions: Autophagy is activated in LPS-induced AKI and plays a renoprotective role.

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

TH-PO0016
Vascular Endothelial Growth Factor (VEGF) Contributes to Sepsis-Induced Acute Kidney Injury
Arnaldo F. Lopez-Ruiz, Andrea P. Solajinc, Kiran B. Chandrashekar, Luis A. Juncos. Nephrology, Univ of Mississippi Medical Center, Jackson, MS.

Background: Sepsis is the most common cause of acute kidney injury (AKI) in the ICU. However, we still have an incomplete understanding of the mechanisms that cause it, and consequently our therapies provide only suboptimal protection at best. Previous studies have shown that VEGF is upregulated in sepsis and plays a role in its associated morbidity and mortality. We recently found that sFlt-1, an endogenous VEGF inhibitor is upregulated in both sepsis and AKI; however not sufficiently to normalize VEGF levels or neutralize its deleterious effects. We tested whether administering additional sFlt-1 protects against AKI and improves the balance between deleterious and protective cytokines and factors.

Methods: We used the cecal ligation and puncture technique (CLP) to induce sepsis. Male Sprague-Dawley rats were randomized into 4 groups: 1) Sham. 2) Sham + sFlt-1, 3) CLP. 4) CLP + sFlt-1. We administered sFlt-1 (12 μg/kg SQ) 6 hs after the CLP or sham procedure. At 24hs the rats were euthanized after collecting blood and kidneys for determination renal function and injury.

Results:

<table>
<thead>
<tr>
<th>VEGF (mg/ml)</th>
<th>Sflt-1 (pg/ml)</th>
<th>Creat (mg/dl)</th>
<th>sKIM-1 (pg/ml)</th>
<th>TNF (pg/ml)</th>
<th>iNOS (pg/ml)</th>
<th>HO-1 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAM</td>
<td>370± 10</td>
<td>30± 5</td>
<td>0.5± 0.07</td>
<td>135± 5</td>
<td>20± 0.8</td>
<td>1.8± 0.3</td>
</tr>
<tr>
<td>CLP</td>
<td>790± 15</td>
<td>330± 10</td>
<td>2.2± 0.09</td>
<td>1900± 50</td>
<td>265± 13</td>
<td>13± 0.5</td>
</tr>
<tr>
<td>CLP+Sflt-1</td>
<td>550± 10</td>
<td>500± 15</td>
<td>1.4± 0.1</td>
<td>1100± 45</td>
<td>130± 6</td>
<td>6± 0.4</td>
</tr>
</tbody>
</table>

Data: Mean ± SEM * p<0.05 vs Sham #p<0.05 vs CLP

Conclusions: CLP causes AKI within 24hs and is associated with increased intra-renal expression of VEGF, iNOS, TNF and only a modest increase in renal HO-1. Administering Sflt-1 during sepsis attenuated the severity of AKI and blunted the increase in sNOS, VEGF and TNFα, while paradoxically causing a large increase in HO-1. Our data demonstrate a protective effect of sFlt-1 in sepsis-induced AKI, suggesting that excessive VEGF is deleterious in this condition, and that sFlt-1-associated induction of HO-1 may play a role in its beneficial actions.

Funding: NIDDK Support, Private Foundation Support

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

TH-PO0017
Up-Regulation of miR-98 in the Kidney with Ischemia Reperfusion Injury Protects Endothelial Cells against Apoptosis by Targeting Caspase-3
Gang Yu, Xueli Lai. Dept of Nephrology, Changhai Hospital, the Second Military Medical Univ, Shanghai, China.

Background: Endothelial dysfunction is one of the main pathophysiological processes involved in renal ischemia reperfusion injury. In our previous study, we screened the aberrantly expressed miRNAs in the kidney with ischemia reperfusion injury (IRI) by microarray assay, among which miR-98 was predicted to target caspase-3. The present study was performed to whether miR-98 was involved in the regulation of endothelial apoptosis under hypoxia and re-oxygenation (HR) conditions.

Methods: The level of miR-98 in IRI kidney and HR HUVECs was determined by real-time PCR. HUVECs were treated with HIF-1α siRNA to investigate the role of HIF-1α on miR-98 regulation. HUVECs were transfected with miR-98 mimics or antisense oligonucleotides against miR-98 to identify the effect of miR-98 on the expression of caspase-3, as well as the hypoxia-induced apoptosis. Finally, the relationship between miR-98 and caspase-3 was confirmed by dual-luciferase reporter assay.

Results: Both of IRI and HR induced significantly up-regulation of miR-98 in the ischemic kidney and hypoxic HUVECs, respectively (Figure 1A). HIF-1α siRNA remarkably down-regulated the expression of miR-98 in both normal and hypoxic HUVECs (Figure 1B). MiR-98 mimics significantly inhibited caspase-3 expression in HUVECs, while anti-miR-98 significantly up-regulated it (Figure 1C). Furthermore, miR-98 protected HUVECs against apoptosis induced by hypoxia, while anti-miR-98 had the reverse effect (Figure 1D). The dual-luciferase reporter assay showed that miR-98 decreased the luciferase activity when transfected with wild-type caspase-3 sequence, but not mutant sequence at the predicted binding site (Figure 1E).

Conclusions: Renal IRI induces up-regulation of miR-98 potentially dependent on HIF-1α, which protects endothelial cells against apoptosis by targeting caspase-3.

Funding: Government Support - Non-U.S.

TH-PO0018
Endothelial Caspase-8 Is a Key Mediator of Sepsis-induced Acute Kidney Injury
Bradley K. Hack, Lilhua Bao, Chang Xu, Patrick Cunningham. Section of Nephrology, Univ of Chicago, Chicago, IL.

Background: Acute kidney injury (AKI) is a frequent complication of gram negative sepsis. Prior work has demonstrated the importance of tumor necrosis factor (TNF) in endothelial (LPS)-induced AKI. Caspase-8 is a key downstream effector of TNF, leading to apoptosis, and possibly facilitating inflammation. Mice genetically deficient in caspase-8 die in utero due to abnormal cardiovascular development.

Methods: To define the importance of caspase-8 activation in the endothelium in sepsis, we generated mice deficient in endothelial cell caspase-8 (EC-Casp8−/−), using Cre expressed in the endothelium under inducible control of the VE-cadherin promoter, activated after tamoxifen administration. After one week of tamoxifen followed by a washout period, mice were injected with 0.25 mg/kg E. coli LPS i.p. At baseline, EC-Casp8−/− mice showed an absence of caspase-8 staining in endothelium after tamoxifen. Mice were sacrificed at 24 h and blood collected for cytokines, BUN, and creatinine. Kidney tissue was analyzed for light microscopic and immunohistochemistry. A subset of mice underwent renal cortical blood flow measurement by laser Doppler.

Results: As expected, wildtype mice developed significant AKI with elevation of BUN and subtle pathologic injury. In contrast, EC-Casp8−/− mice had significantly less AKI (24 h BUN of 45.3 ± 11.2 vs. 114.9 ± 9.9 mg/dl, p < 0.01). LPS induced a decrease in renal cortical blood flow that was restored in EC-Casp8−/− mice (24 h renal blood flow of 1472 ± 61 perfusion units (BPU) in saline injected controls, 614 ± 89 BPU in LPS injected wildtype mice, and 1320 ± 159 BPU in LPS injected EC-Casp8−/− mice, p < 0.01). EC-Casp8−/− mice...
also had reduced evidence of pathologic injury on light microscopy (cortical injury score 0.9 ± 0.20 in LPS injected EC-Casp8 mice v. 1.7 ± 0.15 in wildtype; p < 0.05), and evidence of less vascular and tubular apoptosis on TUNEL staining.

**Conclusions:** These findings point to a key role of endothelial caspase-8 in sepsis-induced AKI. Further work will determine the relative role of caspase-8 in affecting renal microvascular perfusion, inflammation, and apoptosis in sepsis-induced AKI.

*Funding:* NIDDK Support

### TH-PO019

**Sepsis Reduces Kidney Function in Mice Before Hemodynamic Alterations or Clinical Symptoms Become Apparent**

**Jonathan Street, Yuning George Huang, Peter S.T. Yuen, Robert A. Star. NIDDK, Bethesda, MD.**

**Background:** Acute kidney injury (AKI) increases the mortality and morbidity of sepsis. A rise in serum creatinine is used to detect AKI clinically and experimentally, but the slow kinetics prevents early detection of injury. To expand our understanding of the onset of AKI following sepsis we used a novel transcutaneous measurement of the plasma clearance of a fluorescent marker to directly measure GFR in near real-time.

**Methods:** Sepsis was induced in male CD-1 mice by cecal ligation and puncture (CLP). Blood pressure, heart rate, and activity/locomotion were simultaneously monitored by an implanted telemetry device. FITC-Sinisinrin was injected at 0 and 90 min after surgery enabling GFR to be monitored for 5 hours via transcutaneous fluorescence, measured by a miniaturized fluorimeter attached to the mouse back.

**Results:** Log transformation of FITC-Sinisinrin fluorescence decay allowed easy identification of when single pool kinetics applied, permitting calculation of GFR. GFR following CLP was similar to baseline during the first hour. During the second hour GFR fell by 30%, and dropped to 20% of baseline by 5 hours (p<0.01). In contrast, mean arterial pressure, and heart rate were stable immediately following CLP but then began to decrease, and were statistically significantly different from sham 3, and 4 hours later, respectively (p<0.01). Activity/locomotion began to decline in the second hour, and was significantly different from sham 4 hours after CLP (p<0.01).

**Conclusions:** Transcutaneous fluorescence measurement of plasma clearance longitudinally enables greater temporal resolution in measured GFR than prior approaches, revealing novel pathophysiology during early AKI. GFR was initially stable after sepsis surgery, then fell rapidly 2 hours later. The fall in GFR preceded hemodynamic alterations and the appearance of clinical symptoms such as reduced activity.

*Funding:* NIDDK Support

### TH-PO020

**Urinary AIM/CDS Interacts with Kidney Injury Molecule-1 (KIM-1) and Promotes Recovery from Acute Kidney Injury via Enhancing Intraluminal Urinary AIM/CD5 Interacts with Kidney Injury Molecule-1 (KIM-1) and TH-PO020**

**Toru Miyazaki, Katsuo Kitada, Satoko Arai. Molecular Biomedicine for Pathogenesis, Faculty of Medicine, The Univ of Tokyo, Tokyo, Japan.**

**Background:** Acute kidney injury (AKI) is associated with prolonged hospitalization and high mortality, and may predispose patients to chronic kidney disease. To date, no effective treatments have been established for AKI. The apoptosis inhibitor of macrophage (AIM; also called CD5L) protein is a circulating protein that associates with IgM pentamers in blood, which protects AIM from renal excretion and maintains high levels of AIM (approximately 5 mg/mL in humans and mice) in blood.

**Methods:** By in vitro studies using AKI mouse models on a wild-type and AIM-deficient background, as well as in vitro experiments including phagocytosis assay focusing on the functional relationship between AIM and kidney injury molecule-1 (KIM-1), we here present that AIM is a ligand of KIM-1 and promotes prominent clearance of pathogenic dead cell debris by tubular epithelial cells, which is crucial for overall recovery from AKI.

**Results:** The blood AIM dissociates from IgM upon AKI attack and excreted in urine in AKI patients and mice. The urinary AIM accumulates on intratubular dead cell debris by tubular epithelial cells, which is crucial for overall recovery from AKI. The apoptosis inhibitor of macrophage (AIM; also called CD5L) protein is a circulating protein that associates with IgM pentamers in blood, which protects AIM from renal excretion and maintains high levels of AIM (approximately 5 mg/mL in humans and mice) in blood.

**Methods:** By in vitro studies using AKI mouse models on a wild-type and AIM-deficient background, as well as in vitro experiments including phagocytosis assay focusing on the functional relationship between AIM and kidney injury molecule-1 (KIM-1), we here present that AIM is a ligand of KIM-1 and promotes prominent clearance of pathogenic dead cell debris by tubular epithelial cells, which is crucial for overall recovery from AKI. The blood AIM dissociates from IgM upon AKI attack and excreted in urine in AKI patients and mice. The urinary AIM accumulates on intratubular dead cell debris by tubular epithelial cells, which is crucial for overall recovery from AKI.

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**Conclusions:** Our study demonstrates that the AIM/KIM-1 cooperation efficiently promotes recovery from acute kidney injury through rapid clearance of intraluminal debris. These findings could be the basis for novel AKI therapies.

*Funding:* Government Support - Non-U.S.

### TH-PO021

**Renal Handling of Circulating and Renal Synthesized Hepcidin and Its Protective Effects against Hemoglobin-Mediated Kidney Injury**


**Background:** In multiple clinical observational studies it has been demonstrated that increased urinary hepcidin levels are associated with reduced risk of developing acute kidney injury (AKI) due to hemolysis in cardiac surgery patients. This study aimed to get more insight in renal hepcidin handling and its potential protective effects against heme-mediated AKI.

**Methods:** C57Bl/6 mice were treated with i) a single i.p. dose of 10 μg human hepcidin-25 (hhep25) to study renal handling of systemic hepcidin, ii) a single i.v. dose of 5 mg hemoglobin (Hb) to induce AKI, and iii) Hb combined with hhep25 to evaluate the protective effects of hhep25 on Hb-mediated kidney injury.

**Results:** Systemic hhep25 was rapidly cleared from plasma and excreted to urine. In addition to hhep25, we also detected the smaller isoforms hhep22 and hhep20 in urine, but not in plasma, showing that hhep25 is degraded in the tubular lumen. Urine hhep25 was 20-fold increased in megalin deficient mice compared to control (p<0.05) and immunofluorescence staining showed that hepcidin was present in tubules expressing megalin, but not in megalin-deficient tubules, demonstrating that megalin is responsible for hhep25 uptake in the proximal tubules. Administration of hhep25 simultaneously or 4h after Hb injection in wildtype mice significantly attenuated the Hb-induced rise in urinary NGAL and KIM1 levels, and renal IL6 and NGAL mRNA expression. Interestingly, simultaneous administration of Hb and hhep25, but not Hb or hhep25 alone, resulted in an increase in renal Hamp1 mRNA expression (15 fold, p<0.05). Administration of hhep25 to Hb-treated mice reduced renal mRNA expression of HO-1, DMT1, H-ferritin and L-ferritin (all p<0.05), possibly reflecting the mechanisms by which hepcidin exerts its protective effects.

**Conclusions:** Systemic hepcidin is filtered to the urine, partly reabsorbed via megalin in the proximal tubules and degraded in the tubular lumen. Moreover, our data suggest that both systemically delivered hepcidin and locally produced hepcidin are involved in renal protection against heme-induced AKI.

### TH-PO022

**The Lungs in Mice with Acute Kidney Injury Have an Exuberant Inflammatory Response to Endotoxin**

**Hyo-Wook Gil, Chris Altmann, Ana Andres-hermando, Danielle Soranno, Sarah Faubel. Internal Medicine Renal, Univ of Colorado, Denver, CO.**

**Background:** Sepsis occurs in 40% of patients after the diagnosis of acute kidney injury (AKI) that may be related to impaired immune function. We sought to determine immune function specifically in the lungs in mice with AKI.

**Methods:** AKI was induced by bilateral renal pedical clamping. Lung immune function was assessed by intratracheal instillation of either endotoxin (LPS) or Pseudomonas bacteria to induce pneumonia.

**Results:** Intratracheal LPS was administered 4 hours or 7 days after Sham or AKI. 4 hours after intratracheal LPS, lung inflammation as judged by bronchoalveolar fluid TNF, lung myeloperoxidase (MPO) activity (a marker of lung neutrophils), and lung CXC1L (a neutrophil chemokine) was greater after AKI+IT LPS versus Sham+IT LPS in both the 4 hour and 7 day group (p<0.05 for all endpoints n=4). To determine the role of alveolar macrophages, alveolar macrophages were recovered by bronchoalveolar lavage 4 hours after Sham or AKI, placed in culture, and exposed to endotoxin. Media TNFα was significantly higher in alveolar macrophages from AKI mice. Since the response to endotoxin was excessive, we tested the response to pneumonia. AKI or Sham was performed and pneumonia was induced at 2 different time points post procedure: 1) 5 minutes and 2) 7 days. 24 hours after induction of pneumonia, blood cultures were colony forming units (CFU) in Sham and 61 CFU in AKI (n=10); notably, 0% of Sham were bacteremic (n=0 of 10) and 60% of AKI mice were bacteremic (n=6 of 10 mice in bacteremic group; in the 7 day group, blood cultures were higher in AKI and were 31% positive in sham (4 out of 13), and 70% positive in AKI (7 out of 10). Inflammation, as judged by lung MPO activity, was greater in AKI + pneumonia versus Sham + pneumonia in both 5 min and 7 d groups. Lung cultures were similar in Sham and AKI in both time groups indicating similar infection fighting ability between Sham and AKI.

**Conclusions:** In mice with AKI, the lung immune response to bacteria or gram negative bacteria is characterized by an exuberant inflammatory response which leads to bacteremia during pneumonia.

*Funding:* Other NHII Support - NHLBI

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

**Underline represents presenting author.**

94A
Inhibition of MEK/ERK by Trametinib Attenuates Sepsis-Induced Systemic Inflammation and Multi-Organ Injury in Mice

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Background: MEK/ERK signaling is an essential component of the innate immune response in sepsis. We previously demonstrated that a potent and specific inhibitor of MEK1/2, trametinib, prevents endotoxin-induced renal injury in mice. Our goal was to further assess the efficacy of trametinib in a more clinically relevant model of sepsis induced by cecal ligation and puncture (CLP) in mice.

Methods: Male C57BL/6 mice (40 weeks of age) were subjected to CLP, and trametinib (1 mg/kg, i.p.) was administered at 6 h post-CLP. Serum cytokine levels were determined by using a Luminex-based multiplex assay. Standard assays were used to measure clinical markers of organ/cellular injury including serum creatinine (SCr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), creatinine kinase (CK), and lactate dehydrogenase (LDH) in the serum. Renal microvascular perfusion was evaluated by intravital microscopy. Transcript levels of tubular injury markers and pro-inflammatory cytokines in the renal cortex were determined by qPCR.

Results: Delayed trametinib administration partially attenuated increases in circulating pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, GM-CSF) and development of hypothermia at 18 h post-CLP. In addition, MEK/ERK inhibition restored Scr to baseline levels and reduced other markers of organ/cellular injury (serum ALT, CK, LDH) in CLP animals. In the kidney, trametinib completely reversed the early deficits in peritubular capillary perfusion and decreased mRNA expression of tubular injury markers including KIM-1, NGAL, and HO-1. MEK/ERK blockade also attenuated CLP-mediated up-regulation of cytokines (TNF-α, IL-1β, IL-6) in the renal cortex.

Conclusions: These data reveal that the MEK/ERK inhibitor trametinib attenuates systemic and renal inflammation and may protect against other organ injury in a clinically relevant model of sepsis, even with delayed administration. Since trametinib is FDA approved, this drug may represent a readily translatable approach to limit organ injury in sepsis.

Funding: Other NIH Support - NIGMS Support, Veterans Administration Support

TH-PO024

Chemokine Receptor 5 Blockade Modulates Inflammation and Immunity in Renal Ischemic Reperfusion Injury

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Background: The CC chemokine receptor (CCR5) is an important regulator of macrophage trafficking in the kidney in response to inflammation and immunity. Therefore, we investigated a role of CCR5 in the pathogenesis of experimental ischemic reperfusion injury (IRI).

Methods: Bilateral renal artery pedicles clamping for 30 min followed by reperfusion was performed on B6 wild type and CCR5 KO mice. We performed adoptive transfer of LPS treated RAW cells following depletion of macrophage by liposome clodronate (LC) in mice.

Results: CCR5 KO mice showed less aggravated IRI compared to the apoptosis of epithelial cells. Significant up-regulation of RORalpha was found after renal I/R injury. These results suggest that RORalpha protects kidney from I/R damage through transcriptional activation of HIF-1alpha (HIF-1α) and represents a potential therapeutic target for AKI.

Conclusions: These findings show that CCR5 deficiency favors M2 macrophage activation and provide a potential strategy for treating acute kidney injury through blocking CCR5.

TH-PO025

Early Activation of Inflammasome in Acute Kidney Injury After Renal Sympathetic Denervation in Pig

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Background: Renal sympathoexcitation (RDN) is available and implemented as a strategy for the treatment of resistant hypertension. In the aspect of chronic safety, renal function, as assessed by serum creatinine, eGFR(MDRD), and cystatin C was reported to remain unchanged from baseline at 6 months. We investigated whether RDN might cause subtle inflammation and subclinical damage in the early phase of acute kidney injury (AKI).

Methods: Female pigs were divided into 6 groups; normal control (group A), Sham-operated control (group B), contrast media control (group C), and renal sympathetic denervation groups subdivided into 3 groups according to the time of sacrifice; immediately (group D), 1 week later (group E), and 2 weeks later (group F) after RDN. We checked IL-1α, IL-1β, IL-6, 18, 6, 10, TNF-α, cystatin C, caspase-1, ASC, and NLRP3 as early biomarkers of inflammation and AKI.

Results: There were no significant changes in group B and C compared to group A. BUN, serum Na, K, Cl, CRP, urine protein/creatinine ratio, and urine albumin/creatinine ratio showed no significant changes between groups. Serum creatinine and cystatin C were increased from 1st week after RDN. Serum LDH was increased immediately after RDN, and then decreased at 2nd week. IL-1α, IL-1β, IL-6 and IL-8 were increased immediately after RDN, and showed a tendency to be decreased at 2nd week after RDN. TNF-α was increased immediately after RDN, and also increased in contrast media control group. Caspase-1 and ASC expression were increased from 1st week, and decreased at 2nd week after RDN. However NLRP3 expression showed no significant changes between groups.

Conclusions: RDN did not cause clinically significant damages on kidneys. However, RDN can induce the activation of pro-inflammatory cytokines, caspase-1 and then cause transient and self-limited acute kidney injury.

TH-PO026

The Orphan Nuclear Receptor ROR Alpha Exerts a Protective Potential in Acute Kidney Injury via Transcriptional Activation of HIF-1

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Background: Emerging evidence indicates that retinoid-related orphan receptor alpha (RORalpha), a member of the ROR subfamily of nuclear receptors, mediates key cellular adaptions to hypoxia and contribute to pathophysiology of many disease states. However, the potential renal functions of RORalpha in response to ischemia/reperfusion (IR) injury remain unclear. Here, we investigated the renal expression and biological function of RORalpha in acute kidney injury (AKI).

Methods: IR injury was induced by 35min bilateral clamping of the renal pedicle and 24h reperfusion in wild-type and staggerer (RORalpha(gl/g)) mice, a natural mutant strain lacking RORalpha expression. Renal injury and RORalpha abundance were analyzed. In addition, human proximal tubular cell line (HK-2) was used to investigate the expression of RORalpha under hypoxia.

Results: RORalpha was detected in both mouse renal endothelial and tubular epithelial cells. Significant up-regulation of RORalpha was found after renal IRI. Compared with wild-type, RORalpha(gl/g) mice displayed significantly increased levels of serum creatinine (2.3±0.02 vs. 1.18±0.35mg/dl, P<0.01), renal tissue damage, and pro-inflammatory cytokine production after ischemic kidney injury.

Further mechanistic studies indicated that RORalpha agonists enhanced transcriptional activity of hypoxia-inducible factor alpha (HIF-1alpha) in HK-2 cells, which was abolished by siRNA-mediated silencing of endogenous RORalpha.

Conclusions: These results suggest that RORalpha protects kidneys from I/R damage through transcriptional activation of HIF-1 and represents a potential therapeutic target for AKI.

Funding: Government Support - Non-U.S.

TH-PO027

Immunosuppressive Double Negative αβ T Cells Protect Mice from Ischemic Acute Kidney Injury

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Background: TCRαβ+CD4-CD8- double negative (DN) T cells are one of the least understood T cells, partly due to their rarity. We recently found them at high frequency in both murine and human kidney and demonstrated that they secrete large amounts of the anti-inflammatory cytokine IL-10. We tested the hypothesis that DN T cells are immunosuppressive in a mouse model of ischemic AKI and in vitro.

Methods: Immunosuppressive functions of kidney DNT cells were assessed by their ability to inhibit CD4 T cell proliferation using a standard T cell suppression assay. DNT cells isolated from the periphery of Fls-deficient gld mice (which accumulate large numbers of DN T cells in lymph nodes) were adaptively transferred in to wild type (WT) mice in the presence or absence of anti-IL-10 antibody and assessed their ability to
modulated ischemic AKI. Serum creatinine (Scr) was measured to assess kidney function and histology was studied. DNT cells from human peripheral blood was studied to lay the foundation for translational studies.

Results: Murine kidney DNT cell significantly (p<0.001) inhibited proliferation of CD4 T cells in vitro, using CD4-CD25- T cells as controls. Transfer of DNT cells significantly (p<0.01) improved kidney function (Scr) in WT mice. DNT cell injection into WT mice did not affect Scr compared to WT mice that either received no cells (Scr=1.3±0.4) or conventional T cells (Scr=1.4±0.4). Histological evaluation showed significantly reduced tubular necrosis (p<0.03) in mice that received DNT cells. This protection was lost in mice that received DNT cells from IL-10 KO DNT cells (Scr=2.0±0.01). DNT cells were found in human peripheral blood and increase with kidney cancer. Future studies are warranted to better understand immunosuppressive properties of DNT cells and their clinical significance in AKI and other kidney diseases.

Funding: NIDDK Support

TH-PO028

Interleukin-37 Diminishes the Inflammatory Response of Ischemia/Reperfusion-Susceptible Renal Tubular Epithelial Cells

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Background: Renal ischemia and subsequent reperfusion (IR) induces excessive local inflammatory responses and renal injury and dysfunction. Therapeutic strategies aiming to dampen inflammation might therefore provide new opportunities to diminish renal IR injury. The human cytokine Interleukin (IL)-37 inhibits inflammation via nucleolar as well as cell-surface receptors. IL37 is expressed by different cell types, including renal epithelium and circulating monocytes. Cell type-specific effects of IL37 in renal IR remain however unknown.

Methods: Primary tubular epithelial cells (PTECs) and bone marrow-derived macrophages (BMDMs) were isolated from WT and transgenic mice expressing human IL37 (hIL37tg) and cultured. In vitro, cells were pretreated with different concentrations of recombinant human IL37 protein (rhIL37) or vehicle and subsequently stimulated with LPS for 4 or 24hrs. Cytokine release (ELISA) and mRNA expression (quantitative RT-PCR) were determined.

Results: After 24hrs of LPS stimulation, the release of both CXCL1 and IL6 was reduced in hIL37tg PTECs as compared to WT PTECs. This was preceded by diminished CXCL1 and IL6 mRNA levels after 4hrs of LPS stimulation. rhIL37 pretreatment of WT PTECs reduced CXCL1 mRNA, but not IL6 mRNA expression after 4hrs. In hIL37tg BMDMs CXCL1 mRNA levels and protein release were both reduced after 4 and 24hrs of LPS stimulation, as compared to WT BMDMs. IL6 release was only diminished after 24hrs, whereas IL6 mRNA levels did not significantly differ. In contrast, rhIL37 pretreatment of WT BMDMs reduced IL6 mRNA expression after 24hrs of LPS stimulation, but neither affected CXCL1 nor IL6 release.

Conclusions: Our data indicate that both endogenous and exogenous IL37 diminishes inflammatory responses of renal epithelial cells and macrophages, both central players in the pathophysiology of renal IR injury.

TH-PO029

Compensatory Induction of IL17 in Proliferating NKT Cells in Post Ischemic T Cell Deficient Rats Fed High Salt Diet

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Background: Surviving AKI patients have a higher risk for developing chronic kidney disease (CKD) but the mechanism of AKI to CKD transition is unclear. Previous studies have shown inhibition of T-cell activity by mycoprotein blocked the proteinuria, fibrosis and hypertension in post-injury rats fed a high dietary salt and that Th17 helper cells are dramatically increased in post ischemic rats on high salt diet. Therefore, we hypothesized that T-cell deficient athymic rats would manifest an attenuated salt sensitive progression of CKD following AKI.

Methods: Athymic rats (Foxn1-/-) or heterozygote control euthymic rats (Foxn1+/-) were subjected to a model of AKI-to-CKD in which rats are allowed to recover from unilateral I/R (40 min ischemia) for 5 weeks on standard salt diet (0.4% NaCl) and then subjected to contralateral UNX and 4% NaCl diet for 4 additional weeks.

Results: As expected we observed that MMF treatment in control euthymic rats (day 35-63) lead to significant reduction in renal CD4+ inflammation (35%±4.8, p<0.05), Th-17 cells (78%±5.2, p<0.05%) and reduced fibrosis by 50% vs vehicle. T cell deficient athymic rats showed an unexpected and similar level of renal fibrosis as compared to euthymic rats and MMF treatment did not affect this effect. The increased fibrosis could not be explained by enhanced initial injury in athymic vs euthymic rats, which was similar 24 hours following bilateral I/R, indicating that athymic rats may operate an alternative pro-inflammatory pathway in the absence of T cells. Interestingly, athymic rats showed an increased population of IL17+ Natural Killer T cells (NKT) (126018±6707) as compared to euthymic rats (63892±12656), which was not sensitive to MMF treatment.

Conclusions: Taken together these data suggest that in the absence of T cells, compensatory NKT cell activity may mediate cytokine production and participate in salt diet induced fibrosis post AKI.

Funding: NIDDK Support

TH-PO030

Chronic Kidney Disease and the Chronomgranin A Pathway: From Pathogenic Molecular to Disease

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Background: The human chromogranin A gene (CHGA) variants are associated with autonomic blood pressure regulation and hypertension in the majority population, as well as hypertensive renal disease in African Americans. CHGA proprotein is the master switch for nucleation of catecholamine granules in neuroendocrine tissue. In this study we address the effect of CHGA in acute kidney injury.

Methods: Experimental chronic kidney disease (5/6 nephrectomized) mouse models were used to study susceptibility of mouse strains (wild type and Chga-/-) to kidney injury. Kidney tissues of sham and nephrectomized mice were examined by immunohistochemistry and also profiled for genome-wide expression using NimbleGen microarray. The murine glomerular function was measured by LC-mass spectrometry based assay for creatinine. Array data was analyzed for differentially expressed genes using Bioconductor. The differentially regulated genes were analyzed by GO enrichment analysis using David Bioinformatics Resources. The molecular function and biological process terminologies in the PANTHER database were considered during the GO analysis; the P-value cutoff was set at 0.01. The human study involved twin data set of European ancestry 129 monozygotic and 58 dizygotic twin pairs.

Results: A significantly greater loss of GFR function was observed in nephrectomized mice expressing CHGA as compared to Chga knock out mice. Kidney injury resulted in far greater response of increased plasma CHGA, azotemia, catecholamine and systolic blood pressure in Chga+/+ mice. Kidney biopsy also showed greater pathology and interstitial fibrosis associated with nephrectomized Chga+/+ mice. In nephrectomized mice, the differentially up regulated genes in the Chga+/+ strain include panoply of mitochondrial genes, oxidoreductases and extracellular matrix proteins, wound healing genes and transcription factors. In humans the plasma CHGA concentration has an inverse relationship with plasma creatinine levels which are a measure of kidney function.

Conclusions: CHGA expression is inversely correlated to glomerular function and is detrimental to kidney injury outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO031

Inhibition of avß5 Integrin Protects against Renal Ischemia-Reperfusion Injury

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Background: Ischemia-reperfusion injury is a leading cause of acute kidney injury (AKI), which is a common clinical complication that lacks effective therapies and can lead to chronic kidney injury and progression to chronic kidney disease (CKD). Integrin avß5, a key mediator of kidney injury, is expressed on tubular epithelium and circulating monocytes. Cell type-specific effects of avß5 in renal IR remain however unknown.

Methods: We ingested avß5 in renal IR injury and protection. We sought to determine the effect of different doses of avß5 on renal injury after ischemia in vivo. We administered a single administration 6 hours prior to ischemia. avß5 inhibition led to significantly reduced renal damage by 3 days after ischemia as assessed by histopathological scoring of fixed kidneys. Antibody blockade of avß5 also resulted in significantly fewer apoptotic tubular cells, and significantly reduced transcripts of injury markers. The human study was comprised of healthy controls and AKI patients. The human study included 24 patients with stage 1 kidney injury. The patients were divided into groups of no treatment, low dose treatment, and high dose treatment. The high dose treatment group consisted of patients who received a high dose of avß5 antibody. The low dose treatment group consisted of patients who received a low dose of avß5 antibody. The no treatment group consisted of patients who received no treatment.

Results: In the in vivo model of AKI, treatment of mice with avß5 antibody reduced kidney injury by 50% vs vehicle. In the human study, treatment of patients with avß5 antibody reduced kidney injury by 50% vs vehicle. In the human study, treatment of patients with avß5 antibody reduced kidney injury by 50% vs vehicle. In the human study, treatment of patients with avß5 antibody reduced kidney injury by 50% vs vehicle.

Conclusions: These data indicate a novel role for avß5 integrin biology in the pathogenesis of renal ischemia-reperfusion injury. Inhibition of avß5 integrin with antibody administration may hold therapeutic promise for the treatment of acute kidney injury.

Funding: Pharmaceutical Company Support - Biogen

TH-PO032

Blocking avß6 Integrin Provides Protection in Renal Ischemia-Reperfusion Injury

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Background: The avß6 integrin is a key mediator of TGF-ß activation and plays an important role in promoting tissue injury and fibrosis. avß6 is expressed at low levels in normal tissue and upregulated on epithelial cells in disease, providing a target for localized suppression of TGF-ß. Function-blocking avß6 antibodies are protective in models of kidney, lung and liver fibrosis and a humanized avß6 antibody (BG00011) is in clinical development in patients with idiopathic pulmonary fibrosis. We evaluated the role of avß6 in renal ischamia reperfusion injury (IRI), a model in which avß6 is upregulated in tubular epithelium.

Methods: IRI was induced in rats by removing the right kidney and clamping the renal artery of the left kidney for 30 minutes. A single 3 mg/kg dose of avß6 antibody (3G9)

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or an isotype control was administered 6, 12 or 18 hours pre-ischemia or 4, 8 or 12 hours post-ischemia. Serum creatinine (Scr) was evaluated 24, 48 and 72 hours post-injury and gene expression and histology in kidneys evaluated at 72 hours.

**Results:** 3G9 treatment significantly reduced SCR levels at all time points evaluated whether administered pre- or post-induction of ischemia. Equivalent effects were detected when 3G9 was administered 12 or 18 hours pre- or ischemia and maximal effects observed when administered 4 to 8 hours post-ischemia. 3G9 reduced kidney damage as assessed by histopathological scoring of tubular necrosis, dilation and casts. Gene expression profiling of kidneys identified transcripts impacted by aAV6 inhibition suggesting promotion of repair. This included reduced levels of cell death and necroptosis markers such as GADD45, ATF3, and RIPK3, and an upregulated cell growth signature including cyclins, cyclin-dependent kinases, and epidermal growth factor.

**Conclusions:** The combined role of αvβ6 in regulating IRI and fibrosis highlight the potential for therapeutic intervention with BrG0011 in acute kidney injury, a common clinical complication that lacks effective therapies and can lead to the development and progression of chronic kidney disease.

*Funding: Pharmaceutical Company Support - Biogen Idec*

**TH-PO033**

Suramin Protects from Cisplatin-Induced Acute Kidney Injury  
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**Background:** Acute kidney injury (AKI) resulting from cisplatin administration remains an obstacle in chemotherapeutic treatments. Suramin, an FDA approved drug for the treatment of trypanosomiasis, has been previously shown to speed recovery from multiple models of AKI and chronic kidney disease and is currently in clinical trials for combination therapy with cisplatin for the treatment of lung cancer.

**Methods:** In this study we examined the efficacy of the prophylactic use of suramin in a murine model of cisplatin-induced AKI. Nine-week old C57Bl/6 male mice were pre-treated with 10mg/kg suramin via tail vein injection 72h prior to cisplatin administration (20mg/kg, i.p) and sacrificed 72h after cisplatin treatment.

**Results:** Our data indicate that pre-treatment with suramin protects the kidney from cisplatin injury according to markers of kidney function (BUN, Serum Creatinine), kidney injury (urinary Km-1, and NGAL). Assessment of renal histology also indicated that suramin pre-treatment significantly protects mice from cisplatin-induced injury. The expression of many pro-inflammatory chemokines and cytokines (TNF-α, IL-1β, IL-6, MCP-1, and CXCL-1) involved in the response of cisplatin-induce AKI were examined when administered 4 to 8 hours pre-ischemia. 3G9 reduced kidney damage as assessed by qRT-PCR. Mice pretreated with suramin had significantly reduced expression of all the above inflammatory markers. Western blot analysis indicated that mice pre-treated with suramin were protected from death receptor-mediated apoptosis. We also utilized the same experimental design using 10-month old FVB mice expressing mutant KRAS driven lung tumors. The assessment of both renal and pulmonary histology and markers of kidney function (BUN and Serum Creatinine) indicate that suramin protects mice from cisplatin-induced kidney injury and more importantly does not inhibit cisplatin’s anti-tumor efficacy.

**Conclusions:** Thus, data presented suggest that suramin shows great potential as a renoprotective agent for the treatment and prevention of cisplatin-induced AKI.

*Funding: NIDDK Support*

**TH-PO034**

ATIII Attenuates Acute Kidney Injury following Acute Severe Pancreatitis  
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**Background:** Antithrombin III (ATIII) is the major anti-coagulation molecule in vivo and has anti-inflammatory effects. Acute kidney injury (AKI) is the most common organ failure following acute severe pancreatitis (ASP), which often results in death. Herein, we hypothesized that ATIII could protect against AKI following ASP.

**Methods:** Acute severe pancreatitis was induced in rats by retrograde pancreatic duct infusion of 3.5% sodium taurocholate. Intravenous injection of ATIII (500mg/kg) was carried out 30 minutes before induction of ASP. Animals were sacrificed 24 hours later. Renal tubular injury and renal function were assessed. Serum amylase, glutamic-pyruvic transaminase (ALT), and serum Ca2+ were also measured.

**Results:** Renal tubular injury scores were increased from 0.5±0.2 to control rats to 4.2±0.5 in the ASP group and to 2.7±0.3 in the ASP+ATIII group 24 hours after ASP induction (P<0.05, one-way ANOVA, n=6). Serum creatinine was increased from 23.2±1.6 mmol/L to 92.3±8.6 mmol/L in the ASP group and to 34.8±3.2 mmol/L in the ASP+ATIII group (P<0.05, n=6). Blood urea nitrogen was increased from 5.2±3.3 mmol/L to 47.0±1.3 mmol/L in the ASP group and to 30.0±1.9 mmol/L in the ASP+ATIII group (P<0.05, n=6). There were no significant differences between ASP group and ASP+ATIII group in serum amylase, ALT, serum Ca2+ and pancreatic injury.

**Conclusions:** ATIII ameliorates AKI following ASP.  
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Conclusions: C3siRNA and CHBP ameliorated IR injury, both of which might have certain synergetic effects. CHBP might reduce active caspase-3, subsequently affect apoptosis, and improve renal function and structure.

Funding: Government Support - Non-U.S.

TH-PO037
Resveratrol Ameliorates Contrast-Induced Nephropathy Through Activation of SIRT1-PGC-1α-FoxO1 Signaling in Murine Model
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Background: Contrast-induced nephropathy (CIN) is a common cause of acute kidney injury among patients, but the pathogenesis has not been clearly defined. We aimed to investigate whether upregulation of sunitin (SIRT1)-dependent signaling by resveratrol could attenuate CIN through modulation of renal oxidative stresses and tubular apoptosis.

Methods: CIN were established in vivo and vitro model by administration of iohexol in male C57BL/6J mice and rat tubular cells (NRK-52E). Resveratrol (30mg/kg in vivo/10 and 50μM in vitro) was treated with iohexol or saline as an activator of SIRT1. SIRT1 expression was reduced by siRNA treatment in vitro study. Tubular cell injury caused by iohexol was examined.

Results: Increase of serum creatinine and tubular injury measured by histologic examinations after iohexol administration was significantly attenuated by resveratrol treatment (creatinine 1.79±0.48 vs 0.72±0.59 mg/dL, p<0.001). It resulted in reduction of oxidative stress which were demonstrated by reduced malondialdehyde (MDA) levels and increased Mn superoxide dismutase (SOD). Increased apoptosis in CIN was also reduced by resveratrol treatment examined with caspase 3 expression and TUNEL staining. Attenuation of CIN with resveratrol treatment was accompanied with the increase of SIRT1 expression, activation of PPARY co-activator 1α (PGC-1α) and dephosphorylation of forkhead box O (FoxO1). Resveratrol treatment also reduced inflammatory cell infiltration induced by iohexol into kidney. On the other hand, SIRT1 inhibition by siRNA treatment accentuated cytotoxicity by iohexol.

Conclusions: Our results suggest that resveratrol attenuates CIN by modulation of renal oxidative stress and apoptosis through the activation of SIRT1-PGC-1α-FoxO1 signaling, and SIRT1 provides a potential therapeutic target to minimize CIN.

TH-PO038
Loss of Alpha(E)-Catenin-Fscn2 Signaling Increases Cisplatin-Induced Apoptosis in Aged Kidney
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Background: Aging patients are highly susceptible to acute kidney injury. Previous studies in our laboratory demonstrated a dramatic decrease of α(E)-catenin expression in proximal tubular epithelium in the aged kidney.

Methods: We created stable α(E)-catenin knock-down NRK-52E (C2) cells (NT3 is the non-targeted control) and observed a significant loss of viability in C2 cells as compared with NT3 cells after cisplatin challenge. In this study, we aimed to delineate the pathway by which loss of α(E)-catenin increases cisplatin injury.

Results: Increased caspase-8 and -9 activation, BID cleavage and cytochrome C release were observed in C2 cells after cisplatin treatment. Blocking apoptosis, using caspase-8 or -9 inhibitors, completely abolishes the increased susceptibility of C2 cells. Interestingly, the expression of fascin actin bundling protein 2 (Fscn2) is decreased in α(E)-catenin knock-down cells. Re-expression of Fscn2 in C2 cells attenuates the increased apoptosis following cisplatin challenge. Furthermore, our in vitro study showed a significant increase in serum creatinine, KIM-1 and in situ apoptosis level at 72 hr after a single dose of cisplatin in 24-month-old rats, but not in 4-month-old rats. The expression of Fscn2 was also decreased in aged kidney.

Conclusions: Taken together, these results suggest that loss of α(E)-catenin-Fscn2 signaling increases cisplatin-induced apoptosis in aged kidney.

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TH-PO039
Adenosine A1 Receptors Alleviate Cisplatin-Mediated Acute Kidney Injury
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Background: We have observed the incidence of acute kidney injury (AKI) in 479 lung cancer patients using platinum is 10.39% and AKI is the independent risk factor of in-hospital mortality. The results of previous studies about adenosine A1 receptors (A1ARs) in cisplatin-mediated AKI are controversial. In this study, we aimed to investigate the role of A1ARs in AKI induced by cisplatin and the involvement of mitochondria-mediated cell apoptosis.

Methods: 8- to 10-week-old male C57BL/6J wild type (WT) and A1AR−/− mice were given a single intraperitoneal injection of either vehicle (saline) or cisplatin (25mg/kg, 1mg/ml). Weight, blood pressure and heart rate were monitored. Mice were euthanized 24h/72h after cisplatin. Blood samples were collected to measure serum creatinine and urea. Acute tubular necrosis assessments were done through PAS staining. Western Blot and RT-PCR were used to study the expression change of CD73, A1AR and mitochondria-mediated apoptosis markers.

Results: 1) 72h after cisplatin injection, serum creatinine and urea were substantially elevated (85.9±65.9 vs 8.5±1.16mmol/L, 63.3±33.84 vs 6.7±1.24mmol/L, p<0.05) in WT mice which suggested AKI induced by cisplatin happened. The systolic blood pressure, heart rate and body weight remarkably declined (64±4mmHg vs 105±2±2mmHg, 41±2±616 bpm vs 72±1±48 bpm, p<0.05) compared with control mice. 2) 24h after cisplatin, the expression of A1AR in WT mice was significantly higher than control mice. Cisplatin also induced the expression of A2bAR and Bax, targets of mitochondria-mediated apoptosis. 3) Compared with WT mice, serum creatinine elevation and tubular injury were more obvious in A1AR−/− mice (25±19.28 vs 11.4±0.43mmol/L, p<0.05). But contrast to WT mice, A2bAR and Bax expression were not elevated in A1AR−/− mice. The expression of CD73 was up-regulated significantly.

Conclusions: A1AR may be involved in cisplatin-mediated AKI and could alleviate the cisplatin nephrotoxicity. But it doesn’t work through mitochondria-mediated apoptosis pathway. A1AR agonists are potential to protect the kidney in cisplatin-mediated AKI.

Funding: Government Support - Non-U.S.

TH-PO040
Testosterone Uprgulates Heme-Oxygenase-1 – A Potential Mechanism to Protect against Acute Kidney Injury
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Background: Six hormones modulate renal injury during ischemia-reperfusion-induced acute kidney injury (I/R-AKI). We reported that testosterone is reduced during I/R-AKI and that supplementing this hormone ameliorates the renal injury. This protective effect is dependent on the chronicity of therapy and dose (chronic exposure and high doses may exacerbate injury). In this study, we investigated a possible mechanism by which acute administration of low-dose testosterone propionate (A-LD-TP) can protect against I/R-AKI.

Methods: SD rats were randomized into 4 groups; 1) Sham, 2) I/R-AKI, 3) I/R-AKI+TP, 4) I/R-AKI+A-LD-TP+2-ME. I/R-AKI was induced by 40 min bilateral renal pedicle clamping. A-LD-TP during I/R-AKI is mediated by HIF-1α dependent upregulation of HO-1. We hypothesized that the protective effect of A-LD-TP during I/R-AKI is mediated by HIF-1α dependent upregulation of HO-1. Measurement of A1ARs in AKI induced by cisplatin and the involvement of mitochondria-mediated apoptosis.

Results:

Conclusions: A-LD-TP supplementation ameliorated I/R-AKI-induced renal dysfunction, inflammation and tubular injury. These beneficial changes were associated with further upregulation of HO-1. Blocking HIF-1α attenuates the cytoprotective effects mediated by A-LD-TP. This data supports the hypothesis that A-LD-TP supplementation activates the renal HIF-1α pathway and its downstream cytoprotective factor (HO-1), which protects against I/R-AKI, thus providing a potential therapeutic target.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

98A
Endothelial Preconditioning Induces an Effective Immune Response That Avoids Collateral Tissue Damage

**Background:** Endothelial preconditioning is a powerful model of renoprotection against a variety of insults. Harnessing these protective pathways has important therapeutic potential in sepsis. However, the protective molecular pathways remain unknown. Here we examined the metabolic and immunological changes induced by preconditioning.

**Methods:** Mice were divided into 3 groups: control, endothoxygen (LP5 2 mg/kg ip) and preconditioning (0.25 mg/kg followed by 5 mg/kg LPS). Renal injury was assessed by serum creatinine (Ccr) and tissue KIM1/Cecal ligation and puncture (CLP) was used to evaluate mortality and bacterial load. Tissues and sera were examined using cytokine assays, 2DGE proteomics and metabolomics.

**Results:** Preconditioning improved survival after CLP (75% vs. 25% in non-preconditioned mice). This protection was accompanied by reduced bacterial load in solid organs and kidneys (32%, 1.200 cfu/g kidney). Macrophages harvested from preconditioned mice exhibited robust phagocytic activity. Preconditioning also resulted in renal protection after toxic dose LPS (mean serum creatinine 0.08 mg/dl vs. 0.40 mg/dl in non-preconditioned mice; tissue KIM1 mRNA fold changes 110 vs. 2,960). 2DGE proteomics analyses revealed upregulation of molecules required for the activation and maintenance of phagocytosis in the preconditioned group. These molecules include clusterin, serum amyloid-P component, neutrophil gelatinase-associated lipocalin, and complement factor B. Despite the activation of these efficient clearing pathways, serum and tissue proinflammatory cytokine levels were broadly downregulated in preconditioned animals. Tissue metabolic analysis revealed that preconditioning increased metabolites that are the natural ligand for five G-protein coupled receptors (S1P1-5Rs), and S1PR agonists that is the natural ligand for five G-protein coupled receptors (S1P1-5Rs), and S1PR agonists.

**Conclusions:** Preconditioning confers tissue protection and increases survival through an organized upregulation of a modified innate immune response characterized by enhanced bacterial clearing and yet lacking the proinflammatory tissue damage frequently observed with full-blown sepsis.

**Funding:** NIDDK Support

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**TH-PO044**

Spleen Plays a Critical Role in Hepcidin-Mediated Protection against Renal Ischemia-Reperfusion Injury

**Background:** Endotoxin preconditioning is a powerful model of renoprotection against ischemia-reperfusion (IR) injury. We tested the therapeutic potential of preconditioning in aged mice.

**Methods:** Young (7-8wks) and old (32-48wks) male Lysm keap1 mice underwent 30 minute bilateral kidney ischemia. Serum creatinine (SCr) was measured at 0, 24, 48 and 72h post ischemia. Histological and inflammatory changes in kidney were examined at 72h.

**Results:** We observed significantly reduced SCr levels in young (0.6±0.1 vs 1.3±0.2, p<0.02, 24h) and elderly (0.4±0.2 vs 1.3±0.3, p<0.02, 48h and 0.2±0.03 vs 0.9±0.2, p<0.02, 72h) Lysm keap1 mice as compared to age matched keap1f/f mice. Histological examination of corticomedullary region of kidney tissue revealed a significantly lower necrotic debris (24±8 vs 54±38, p<0.01), regression (22±1.7 vs 41±4.0, p<0.004) and higher percent of normal tissue (53±1.5 vs 5±0.6, p<0.01) in elderly Lysm keap1 mice. Young Lysm keap1 mice did not show any significant difference in kidney histology post AKI compared to young keap1f/f mice. Cytokine analysis showed significantly (p<0.04) higher levels of TGF-β, IL-10, IL-2, IL-6, IL-13, IL-17 and TNF-α in elderly Lysm keap1 mice. These cytokines were comparable in young Lysm keap1 and keap1f/f mice post AKI.

**Conclusions:** These data demonstrate that enhancing Nrf2 activity in myeloid cells can provide protection against IR-induced AKI, which is markedly enhanced in elderly mice. These findings indicate that myeloid cell oxidative stress responses are a mechanism by which elderly are more susceptible to AKI.

**Funding:** NIDDK Support

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**TH-PO043**

Sphingosine-1-Phosphate-3 Deficient Dendritic Cells Modulate Splenic Responses to Ischemia-Reperfusion Injury

**Background:** The plasticity of dendritic cells (DCs) permits phenotypic modulation ex vivo by gene expression or pharmacological agents, and these DCs can exert immunomodulatory effects on T cells through direct interactions with T-cells by either inducing T regulatory (Treg) cells or causing anergy. Sphingosine 1-phosphate (S1P), a sphingolipid that is the natural ligand for five G protein coupled receptor (S1P1-S5Rs), and S1PR agonists

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

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**TH-PO045**

Endothelial Krüppel-Like Factor 4 Mediates the Protective Effect of Statins against Ischemic Acute Kidney Injury

**Background:** Endothelial cells participate in the pathophysiology of ischemic acute kidney injury (AKI) by increasing the expression of cell adhesion molecules and by recruiting inflammatory cells. Results of our previous studies showed that endothelial Krüppel-like factor 4 (KLF4) regulated Vcam1 expression and neonatal formation following carotid injury. The aim of the present study was to determine if endothelial KLF4 is involved in ischemic AKI.

**Methods:** Endothelial Klf4 conditional knockout (Klf4 /cKO) mice were generated by breeding TercCre mice and Klf4 floxed mice, and their phenotype was analyzed after bilateral renal ischemia.

**Results:** Klf4 /cKO mice were phenotypically normal before the surgery. However, endothelial Klf4 deletion exacerbated renal ischemia-reperfusion injury, as indicated by elevated serum levels of urea nitrogen and creatinine and aggravated renal histology. Moreover, Klf4 /cKO mice exhibited the enhanced accumulation of neutrophils and the expression of cell adhesion molecules including Vcam1 in the kidneys of injured kidneys. Interestingly, statins accelerated renal ischemia-reperfusion injury in control mice, but not in Klf4 /cKO mice, suggesting that the protective effect of statins against ischemic AKI is mediated by endothelial KLF4. Mechanistic analyses in cultured endothelial cells revealed that statins increased Vcam1 expression, and that KLF4 mediated the suppressive effect of statins on tumor necrosis factor-a-induced Vcam1 expression through the binding of NF-kB to the Vcam1 promoter.

**Conclusions:** These results provide evidence that endothelial KLF4 is a mediator of statins and plays a protective role in ischemic AKI by regulating the expression of cell adhesion molecules with concurrent recruitment of neutrophils.

**Funding:** Government Support - Non-U.S.
Kidney Endothelial Progenitors Play a Critical Role in Susceptibility to Acute Kidney Injury  

Katherine V. Maringer, Natasha M. Rogers, Jeffrey S. Isenberg, Sunder Sims-Lucas.  

Univ of Pittsburgh, Pittsburgh, PA.

Background: Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function leading to renal failure, and contributing to high percentages of morbidity and mortality. Kidney formation involves the production of nephrons each with a rich vascular network. This complex and highly vascularized structure makes the kidney especially susceptible to ischemic injury. We hypothesize that malformations of the vascular system during kidney development compromise its ability to cope and recover from AKI.

Methods: We generated mice with a conditional deletion of VegfR2 (floxed) in the Follistatin (Fst) promoter (VegfR2<sup>FL/FL</sup>), and evaluated the formation of the vasculature via histology, immunohistochemistry and fluorescent microangiography. Furthermore we performed ischemia reperfusion injury (IRI) on control and mutant mice and determined their ability to recover 1 (injury phase) and 7 days (repair phase) post injury. Lastly, we performed a lineage tracing study where FstFoxd1cre mice were bred with a Tg(ROTA)-reporter (permanently labeling all Foxd1 derived cells) and performed IRI and interrogated the percentage of Foxd1 derived endothelial cells that were present in the IRI and contralateral control kidneys.

Results: We determined that the VegfR2<sup>FL/FL</sup> mice had dilated microvasculature embryonically and post-natally. Furthermore, when we stressed the VegfR2<sup>FL/FL</sup> animals with IRI they had an increased injury compared to controls (both histologically and inflammatory markers). This increased susceptibility in the mutants continued to be observed 7 days following the injury. Lineage tracing experiments showed the Foxd1 derived endothelial cells are highly plastic during the repair phase of IRI and their deletion in the VegfR2<sup>-/-</sup> likely the reason for the increased susceptibility to injury.

Conclusions: From this we determined that Foxd1 derived endothelial cells are highly pertinent to normal function of the renal vasculature and their risk of AKI. Patients that have an underlying perturbation of the renal microvasculature are likely at higher risk of suffering long term renal damage following AKI.

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Conclusions: From this we determined that Foxd1 derived endothelial cells are highly pertinent to normal function of the renal vasculature and their risk of AKI. Patients that have an underlying perturbation of the renal microvasculature are likely at higher risk of suffering long term renal damage following AKI.

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Underline represents presenting author.
TH-PO051
A Comparison of Three Prediction Models for Acute Kidney Injury Requiring Renal Replacement Therapy After Coronary Artery Bypass Graft Surgery
Ailene Ramos Buelva-Martin, Aina Bautista-Duque, Oscar D. Naidas. Dept of Medicine, Section of Nephrology, St. Luke's Medical Center, Quezon City, Metro Manila, Philippines.

Background: Acute kidney injury (AKI) following cardiac surgery is associated with increased post-operative morbidity and mortality. Scoring systems to predict acute kidney injury requiring renal replacement therapy (RRT) among patients undergoing cardiac surgery have been developed to assess risk pre-operatively and give necessary prophylactic agents and also assist clinicians on the management post-operatively.

Methods: Cross sectional analytic study of 427 patients who underwent coronary artery bypass graft (CABG) surgery from January 2009-October 2014. The following were excluded: a) on hemodialysis b) with missing data. Primary outcome: acute kidney injury requiring RRT after CABG. Risks were calculated using the three models: Cleveland scoring by Thakar, Simplified Renal Index by Wijeysundera, and the Bedside Tool for Predicting Risk of Postoperative Dialysis by Mehta. The area under the receiver operating curve (AUROC) was determined for each model.

Results: AKI was documented in 25.5% (n=109), 13.3% (n=57) underwent post-operative RRT. Discrimination for the prediction of RRT was good for the three scoring models using AUROCs: Mehta: 0.94 (95% CI, 0.916 to 0.963); Thakar: 0.92 (95% CI, 0.890 to 0.944), and SRI: 0.90 (95% CI, 0.867 to 0.926). Mehta showed the highest predictive value, with significant difference with SRI (P = 0.0053). However, it was not significantly different with Thakar (p=0.23).

Conclusions: The Bedside Tool for Predicting Risk of Postoperative Dialysis by Mehta showed the highest predictive value but with no significant difference with the predictive value of the Cleveland scoring system. The advantages of the Cleveland scoring over Mehta are the applicability in cardiac surgeries other than CABG and the lesser number of variables.

TH-PO052
Effect of Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery on Acute Kidney Injury
Ailene Ramos Buelva-Martin, Oscar D. Naidas. Dept of Medicine, Section of Nephrology, St. Luke's Medical Center, Quezon City, Metro Manila, Philippines.

Background: Acute Kidney Injury (AKI) is one of the serious complications of cardiac surgery. AKI is associated with increased mortality and morbidity. Coronary artery bypass graft (CABG) surgery can be done with a beating-heart (off-pump) or with a cardiopulmonary bypass machine (on-pump). There are conflicting studies regarding reduction of acute kidney injury with the use of the Off-pump CABG vs. On-Pump CABG.

Methods: Adult patients who underwent CABG using Off-pump and the On-pump technique from January 2005 to October 2014 were included in this retrospective cohort study. The following patients were excluded: a)chronic hemodialysis b)baseline eGFR <15ml/min/1.73m2 c)missing data. The outcomes were: AKI defined as absolute increase in the serum creatinine concentration of >0.3 mg/dl from baseline within 48 hours after CABG and AKI requiring renal replacement therapy. Odds ratio were calculated between the use of Off-pump and On-pump CABG with the respective outcomes.

Results: Postoperative Acute Kidney Injury The incidence of acute kidney injury with off-pump group was lower (4/28 [14.3%]) vs on-pump group (109/427 [25.5%]) with OR 2.05 [95% CI, 0.69 to 6.59]; however, it was not significantly different at p-value 0.19. Postoperative Acute Kidney Injury with Renal Replacement Therapy Out of the 109 patients who had acute kidney injury after On-pump CABG, 53 (48.6%) patients underwent hemodialysis. While in the Off-pump CABG group, no one underwent hemodialysis out of the 4 patients who had acute kidney injury postoperatively (OR 8.8 [95% CI 0.537 to 146.9], P=0.1283). [table1]

Conclusions: There was a lower incidence of AKI and AKI requiring renal replacement therapy in the Off-pump CABG group, however, it was not statistically significant with the On-pump CABG group. There is still insufficient evidence to say that the use of Off-pump CABG technique reduces incidence of AKI. Limitations of this study are: small sample size, confounding variables since this study is a retrospective study, off-pump CABG population may not have been represented accurately. A multi-center study to increase sample size is recommended.

TH-PO053
Renal Dysfunction Detected by an Automatic Alert System: DETECT-H

Background: The aim was to analyze the prevalence of chronic kidney disease (CKD) and acute kidney injury (AKI), length of stay (LOS) and in-hospital mortality. Methods: To evaluate renal dysfunction in admissions we developed a fully automated electronic alert system which identifies all adult patients with reduced glomerular filtration rate according to KDIGO-EPI. Two alert levels were established, <60 and >30 mL/min/1.73m² in patients over 80 years. Patients admitted to nephrology unit and on dialysis were excluded. Detected patients were retrospectively analysed. CKD and AKI was defined according to KDIGO guidelines. Baseline serum creatinine was the lowest between 0.5-6 months before admission. LOS and in-hospital mortality was recorded.

Results: Between January and June 2014, issued alerts were 1,241 from 11,022 adult admissions (11.3%), from 1,079 patients (13.1% multiple admissions). Median age 77 years (interquartile range (IQR) 70-81), and 53.9% were men. Previous renal function was present in 1,842 patients (84%). Stage 1 9.6%, stage 2 23.7%, stage 3a 25%, stage 3b 17.5%, and stages 4-5 10%. Previous CKD was only registered in 31.9%. AKI was present in 88% of admissions (69.9% of alerts and 7.7% of overall admissions). AKI stage 1, 2, and 3 respectively was 421 (49.7%), 207 (24.5%) and 218 (25.8%). AKI episode was specified to be suffered in 33.2% patients at discharge. In patients with CKD not AKI 7.5%, in overall AKI patients 45.3%, in AKI 1 30.4%, in AKI 2 47.8% and in AKI 3 71.6%; p<0.001. LOS in overall admissions in the same period was 5.31 days, for overall detected patients median LOS was 8 days (IQR 4-13 days). Median LOS for CKD not AKI, or AKI stage 1, 2 and 3 was 6 (3–10), 8 (5–13), 8 (6–14) and 10 (5-19) days; p=0.001. Mortality for all detected patients was 14.9% (185 patients). In-hospital mortality for CKD not AKI or AKI stage 1, 2 and 3 was 4.3%, 10.9%, 22.7% and 33.9%. Mortality in patients with AKI stage 3 requiring dialysis was 57.1%, p<0.001.

Conclusions: Electronic alerts could be a useful tool to detect in-hospital renal dysfunction patients to improve CKD and AKI hospital outcomes.

Funding: Private Foundation Support

TH-PO054
Identification of a Pediatric Inpatient Cohort at Risk for Developing Acute Kidney Injury Using Machine Learning Methods
Michael G. Semanik, Sangeeta R. Hingorani. Pediatric Nephrology, Seattle Children's Hospital, Seattle, WA.

Background: Acute kidney injury (AKI) is prevalent amongst pediatric inpatients, and its prevention requires rapid detection of those at risk. A rise in creatinine often comes too late for prevention to be effective. Therefore, this study seeks to apply machine learning methods to routine clinical data in order to identify patients at risk for AKI before creatinine levels rise.

Methods: A cohort of pediatric inpatients with at least one creatinine value was created, then split into AKI and non-AKI groups. AKI was defined using KDIGO creatinine-based criteria. Information on demographics, vital signs, lab values, procedures, and medications was collected for each patient. For the AKI group, only data collected 24 hours before each patient's peak creatinine value were used. Simple logistic regression was used to identify features that predicted the development of AKI, and these features were used to produce two algorithms: a logistic regression-based algorithm and a Bayes Net probability-based algorithm. Both algorithms used 10-fold cross validation to create a training and test set.

Results: 4064 patients were included in the cohort, of whom 370 (9.1%) developed AKI. Sixty features were significantly associated with AKI. The logistic regression algorithm created from these features identified 144/370 AKI patients and 3653/3694 non-AKI patients (giving it a specificity of 39% and specificity of 99%). The Bayes Net algorithm's sensitivity was 48% (identifying 176/370 AKI patients) and its specificity was 91% (identifying 3347/3694 non-AKI patients). The ROC areas for the algorithms were 0.84 and 0.81, respectively.

Conclusions: Machine learning methods can be used to identify a cohort of pediatric inpatients that are at increased risk of developing AKI before serum creatinine rises. Identification of this population allows for both additional testing (such as urinary biomarkers) and preventative treatment (such as removal of nephrotoxic drugs). Acute kidney injury predictive algorithms have the potential to improve patient care, and, if correctly implemented, will become more accurate as more data is collected.

Funding: Other NIH Support - NIH T32 Training Grant
TH-PO055

The Jelliffe Method for GFR Estimation with Non-Steady State Creatinine Performs Better for Subjects with Higher Weight and Baseline Chronic Kidney Disease

Rejees Stephen, Sevag Demirjian, Steve Campbell.
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Background: The Jelliffe method is used to estimate the glomerular filtration rate (GFR) when creatinine is in a non-steady state, such as in patients with acute kidney injury (AKI). We explored the agreement between iothalamate-measured renal function (iGFR) and estimated GFR by the Jelliffe method (eGFR) in subjects after undergoing partial nephrectomy.

Methods: iGFR was measured within a week of partial nephrectomy in subjects who sustained AKI (>0.3 mg/dl rise in serum creatinine from baseline) after partial nephrectomy. iGFR was calculated based on creatinine drawn at the time of iGFR measurement, were compared using Pearson’s correlation (r) in subjects grouped by weight (above and below median weight; 86 Kg) and baseline chronic kidney disease status (CKD; GFR=60ml/min.1.73m²).

Results: 60 of 90 subjects undergoing partial nephrectomy sustained AKI. Mean age was 61±11 years, and 55 were male. iGFR had a high correlation with iGFR (r=0.75, p<0.001). Correlation of GFR with iGFR was shown and was significant except in the group with both CKD and low weight (Table). Subgroup analysis showed that subjects with lower body weight and no CKD had lower correlation (r=0.54) than those with both CKD and the higher weight (r=0.96). The group with no CKD but higher weight had a strength of correlation in between these extremes.

Conclusions: GFR estimated by the Jelliffe equation correlates well with measured GFR in the AKI setting. Higher body weight and CKD at baseline are associated with higher creatinine levels, which may account for the better performance of the Jelliffe method in these states.

TH-PO056

Development of a Multicenter Ward-Based Acute Kidney Injury (AKI) Prediction Model

Jay L. Kovner, Richa Adhikari, Dana P. Edelson, Matthew M. Churpek.
Dept of Medicine, Univ of Chicago.

Background: Early identification of those at risk for the development of AKI on the general wards prior to increases in serum creatinine (SCR) would enable preemptive evaluation and intervention to minimize the risk and severity of AKI. We aimed to develop an AKI risk prediction algorithm using electronic health record (EHR) data in non-ICU patients.

Methods: All hospitalized ward patients who had SCR measured in 5 hospitals were included. Patients with a first measured SCR > 3.0mg/dl or who developed inpatient AKI outside the general ward were excluded. Using a discrete-time survival model, demographics and estimated GFR by the Jelliffe equation correlates well with measured GFR in the AKI setting. Higher body weight and CKD at baseline are associated with higher creatinine levels, which may account for the better performance of the Jelliffe method in these states.

Results:

- Among the 206,192 included patients, 17,522 (8.5%) developed KDIGO AKI.
- Using a discrete-time survival model, demographics, severity of illness (SOI), and iGFR risk model predicted AKI within 12 or 24 hours. Subgroup analyses were conducted across baseline glomerular filtration rate (eGFR) groups and severity of AKI stage.

Conclusions: Survivor curves for multiple admissions (dashed lines) fell above the curve for single admissions, demonstrating survivor bias. Combining random selection and adjustment for Med# resolved the survivor bias, permitting inclusion of patients with multiple admissions in risk models for inpatient mortality.

TH-PO057

Survivor Bias: Utilization of Multiple Admissions for Evaluation Risk of Inpatient Mortality Associated with Hospital-Acquired (HA) Acute Kidney Injury (AKI)

David G. Warnock, T. Clark Powell, John P. Donnelly.
Univ of Alabama at Birmingham, Birmingham, AL.

Background: Inpatient deaths censored the cohort at risk, introducing survivor bias favoring those with >1 admission. Analysis of first admissions avoids this bias, but also loses information about those who survive multiple admissions. We evaluated inpatient mortality associated with AKI for adult admissions to UBAP Hospital for FY2010-FY2013.

Methods: We used ICD9 codes and all inpatient serum creatinine (sCr) values for 109,456 adult patients with 5,452 inpatient deaths. We excluded patients with patients with <2 sCr values, ESRD, post-renal transplant, eGFR (<5 or >500 ml/min.1.73 m²), length of stay <1 and >28 days, and patients with community-acquired AKI. Minimum sCr for each admission was used as baseline, and HA-AKI was defined by peak sCr > (0.3 mg/dl + minimal sCr) and date-time for minimal sCr < date-time peak sCr. No-AKI was defined as (peak Scr - minimal sCr) <0.3 mg/dl. Survival functions included HA-AKI, median age, black race, male gender, Deyo-Chlarnson comorbidity score, and median admissions for each patient (Med#).

Results:

- For 40,471 patients with 1 admission, there were 7,594 cases of HA-AKI (19%) with 1,290 deaths (17%). For 14,860 patients with 23,633 admission, there were 6,633 cases of HA-AKI (22%) with 732 deaths (11%). Figure shows survival curves for 1 versus >1 admissions (A); 1 versus >1 admissions adjusted for Med# (B), 1 versus selected >1 random selected admission (C), and 1 versus >1 random selected admission adjusted for Med# (D).

TH-PO058

Validation of the Acute Renal Failure Trial Network (ATN) Study Risk Model for Predicting Mortality in Critically Ill Adults with Acute Kidney Injury

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Background: Disease specific severity of illness scoring systems have been developed to predict survival of patients with acute kidney injury. Performance of these scoring systems outside of the population in which they have been generated has been poor. We therefore evaluated the performance of the recently developed ATN Study risk model predicting 60 day all-cause mortality in intensive care unit (ICU) patients at initiation of dialysis for acute kidney injury (AKI).

Methods: We evaluated the performance of the ATN Study risk model using the High Density Intensive Care (HiDenIC) Database which contains data on all adult patients admitted to any of the eight ICUs at UPMC between July 2000 and October 2008. Clinical data and physiologic variables were closely matched with the original study model; missing data were imputed by either assuming clinical normality or viewing these data elements following similar rules used to build the original model. Model discrimination was assessed via area under the receiver operating characteristic curve (AUROC). Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Results:

- 1,374 patients were initiated on renal replacement therapy (RRT) for AKI during this interval; full data for model testing were available for 1,300 patients (74%). The AUROC for the model was 0.78 (95% CI: 0.75-0.80) with a Hosmer-Lemeshow goodness-of-fit test p-value of 0.59 (Figure).
Conclusions: The ATN score demonstrated good discrimination and calibration for predicting 60-day all-cause mortality in ICU patients initiating RRT for AKI in a population separate for the population in which it was developed.

TH-PO059
A Multifaceted Quality Improvement Programme for Tackling Acute Kidney Injury in a Large Teaching Hospital

Leonard Ebah, Prasanna Hunumapura subbegowda, Deryn Jennifer Waring, Rachael Challiner, Robert Henney, Alastair J. Hutchison. Manchester Acute Kidney Injury Strategy, Dept of Renal Medicine, Central Manchester Univ Hospitals, Manchester, United Kingdom.

Background: Acute kidney injury (AKI) is now widely recognised as a serious health care issue. Up to 25% of hospital patients have been reported to develop it, often with worse outcomes compared to those without AKI. AKI care in hospitals has been shown to be substandard. This study aimed to use quality improvement methodology to improve AKI care and outcomes in a large teaching hospital.

Methods: Several areas of documented poor AKI care were identified and specific improvement activities implemented through sequential Plan-Do-Study-Act (PDSA) cycles. An electronic alert system for AKI was developed, a ten point Priority Care Checklist (AKI PCC) was tested with the aid of specialist nurses and pharmacists whilst targeted education activities were carried out. Impact on key AKI care processes and patient outcomes was studied.

Results: The electronic alert had a sensitivity of 99% for the detection of new cases of AKI. Nine aspects of the PCC saw significant improvements in their attainment: Baseline creatinine 66% to 84%, identification of a cause for AKI 62% to 77%, fluid balance assessment 77% to 92%, appropriate investigations 61% to 77% catheterisation 92% to 99% ultrasound scans 79% to 95% renal or intensive care referrals 80% to 100%, fluid charts 64% to 71% after, and appropriate drugs review 57% to 87%. The intervention led to a significant reduction in variability of delivered AKI care. AKI incidence showed a trend towards reduction; 9.9% of all hospitalisations before any intervention to 7.8% after intervention. Improvements in this important aspect of care for patients with AKI are urgently needed.

Funding: NIDDK Support, Other NIH Support - National Center for Research Resources, a component of the NIH and the NIH Roadmap for Medical Research

TH-PO061
Prognosis of Contrast Induced Nephropathy After Outpatient Computed Tomography in Chronic Kidney Disease Patients

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Background: Most studies regarding contrast induced nephropathy (CIN) were done in angiography era but computed tomography (CT) is more common cause of contrast exposure in general populaton. There were few prognosis data concerning CIN after outpatient CT.

Methods: Patients with estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m² underwent outpatient CIN prophylaxis program for contrast CT from 2008 to 2014 in Seoul National University Hospital. Patients received intravenous isontric acid and oral N-acetylcysteine. Baseline blood sample was done within 2 weeks before CT. Basic data was collected retrospectively by medical chart review. Prognosis was surveyed from death registry of National Statics Korea and dialysis registry of The Korean Society of Nephrology. CIN was defined by ³0.5mg/dl or ³25% increase of serum creatinine (sCr) from baseline within 48-96 hours after CT. Primary outcome was event of renal replacement therapy (RRT), duration from CT to RRT and survival period after CT. Results: 12179 cases of CT were performed with CIN prophylaxis protocol and 2816 cases of CT had baseline eGFR≤60 without RRT history and follow up sCr 48-96 hours after CT. 84 (3%) cases of CIN were found and 99 (3.5%) cases went RRT, 551 death reported after CT. Prognosis was analyzed after adjustment with age, sex, baseline eGFR, history of diabetes and hypertension. No relationship between death, RRT incidence, doubling of sCr and CIN was shown. However, we found shorter period from CT to RRT in CIN cases. So we performed analysis with RRT within 6 months as outcome with subgroup devided by eGFR. CIN was risk factor for RRT within 6 months in cases with baseline eGFR<30 (aRR 4.70, 95% CI 1.39-15.90, P=0.013). However, in cases with eGFR³30, start of RRT in acute period was not increased by CIN.

Conclusions: CIN due to CT contrast after appropriate prophylaxis was not related to long term renal prognosis. CIN was a risk factor for start of RRT within 6 months after CT in cases with baseline eGFR<30, but even this relationship was not seen in patients with relatively preserved renal function.

TH-PO062
Outcomes following Intra Arterial Contrast in Chronic Kidney Disease

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Background: Contrast Induced Nephropathy (CIN) is a recognised complication of angiography. Risk factors include chronic kidney disease (CKD), advanced age, diabetes and cardiac insufficiency. Although incidence in the general population is 2-5%, reported

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
incidence of CIN in CKD is 15-27%. The risk of CIN may have been over-estimated in CKD 3a stage and hence the pre-procedure optimisation decreases incidence and improves outcome of CIN. The aim of this study is to determine the incidence and outcome of CIN in CKD patients in our centre.

Methods: Consecutive patients with stage III-V CKD, undergoing peripheral (group 1) or cardiac (group 2) angiography, at a regional Australian hospital between 2005-2015 were included. Pre procedure optimisation included oral N-Acetylcysteine, intravenous hydration with Normal Saline and withholding Metformin and Frusemide. Low osmolality contrast diluted to 1/3 strength (group 1) or half strength (group 2) was used. CIN was defined as serum creatinine rise of >25% from baseline within 72 hours. Primary outcome was incidence of CIN. Secondary outcomes were mortality at 6 months, progression to dialysis and disappearance of CKD. Follow up ranged from 2-73 months.

Results: 537 patients with CKD stage III-V underwent angiography. 222 patients concurrently dialysing were excluded. Median ages were similar in both groups (75 years in group 1, 76 years in group 2, P=0.25); diabetes was more prevalent in group 1 (70.5% versus 48.4%, P=0.001) and ischaemic heart disease more prevalent in group 2 (60.0% versus 44.3%, P=0.002). Median volume of contrast used was significantly lower for group 1 (35mls, range 2.5-350mls) than group 2 (75mls, range 20-357mls) (P<0.001). The incidence of CIN was 3.7%. Incidence of CIN did not differ between groups (group 1 4.1%, group 2 3.2%, P=0.74). No patient with CIN died within 6 months or progressed to higher CKD stage or dialysis.

Conclusions: Pre procedure optimisation of CKD patients may reduce incidence of CIN. In our study, incidence of CIN in CKD patients was low and did not lead to death or progression of chronic kidney disease.

TH-PO063

AKI Risk Scores in Acute Admissions: Selecting the High-Risk or Missing the Vulnerable? Amy Jeanne Riddell, Christopher J. Mulgrew. Renal Unit, Royal Devon and Exeter Hospital, Exeter, Devon, United Kingdom.

Background: AKI commonly complicates acute illness. 2014 NICE AKI guidelines stress early identification of those at high risk. In patients with many co-morbidities, while risk scores in select groups have been studied, there remains debate as to the effective use of AKI risk scoring in 1° and 2° care populations (currently being investigated by the UK National AKI Programme). If correctly identified, steps could be taken to minimise risk and manage AKI earlier. Alternatively, should we not treat all acutely ill patients as 'at risk'?

Methods: Review of acute admissions to the AMU on 4 weekdays between Mar’14 & Mar’15. 158 cases were reviewed and risk scored based on NICE/KDIGO published risk factors. Any AKI, demographic data, specialist nephrology input, length of stay and overall outcomes were recorded.

Results: Of 158 patients, 35 (22%) had AKI during their hospital stay. Most had AKI1 (24/35), vs AKI2 (7/35) and AKI3 (4/35). 28 had AKI on admission vs 7 after admission. Patients with AKI (at any time) had higher median scores (4, (0-9)) than non-AKI (2, (0-7)).

Conclusions: The 7 post-admission AKI cases had a median score of 4 (2-5). Length of stay (LoS) was greater in AKI group (9.2d v 5.8d). AKI was due to sepsis/volume depletion in 68%, alongside other risk factors. There was one death in the AKI group (AKI3).

Conclusions: 2° care AKI risk scoring aims to identify those at high risk to prevent deterioration, but a greater challenge seems to be in 1° care than acute settings. Our data would suggest that while patients developing AKI post-admission may have a range of risk scores on arrival, with high scores correlating with AKI and LoS, the majority with AKI arrive from primary care with high scores. A validated risk score for use in 1° care, aiming to prevent admission, may be more more useful than stratifying all acute hospital admissions - are they not all ‘high risk’ anyway?

TH-PO064

Acute Kidney Injury Care Bundle Compliance in a Large District General Hospital in UK Preetham Boddana, Shiva Sreenivasan, Israr Baig, Nerys Conway. Renal Unit, Gloucestershire NHS Foundation Hospitals, Gloucester, Gloucestershire, United Kingdom.

Background: AKI is a common and harmful condition, which is often treatable and avoidable. The incidence of AKI in patients admitted to a hospital is approximately 3 – 7%. Gloucestershire Hospitals NHS Foundation Trust sees about 500 cases of acute kidney injury (AKI) monthly from a catchment population of 612,000.

Methods: An audit of patients with AKI showed deficiencies in care. We created an AKI care bundle (senior review, medication review, fluid balance, and repeat creatinine within 24 hours) for those patients with AKI, prompted by an AKI sticker for the case notes.

Results: For patients receiving an AKI flag, case notes were audited for appropriate use of the care bundle. We reviewed audit results over a 2-year period to see if the AKI bundles were being used appropriately and if patient care had improved. There has been improvement in AKI care bundle compliance. Figures up to August 2014 show that compliance for AKI care bundle use is 87%.

The compliance since its launch has generally exceeded the Commissioning for Quality and Innovation (CQUIN) targets set in place by the project.

Conclusions: We have shown an improved care in patients with acute kidney injury by using an electronic alert system prompting early management. AKI can be easily identified and managed early and appropriate interventions delivered. This approach has the potential to reduce AKI in the elderly population. It is likely to be adopted in most hospital settings. These results should encourage initiatives towards developing AKI prevention protocols.

TH-PO065

Reducing Post-CABG Acute Kidney Injury by Multipronged Preventive Interventions Wisit Cheungpasitporn, Michael A. Mao, Chatur Thongprayoon, Qi Qian. Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Acute kidney injury (AKI) post cardiac surgery is frequently a multifactorial event, associated with an increased morbidity and mortality. As AKI has no specific treatment, prevention is critical. This study aims to apply multipronged preventive measures to reduce AKI after coronary artery bypass grafting (CABG).

Methods: Prospective randomized interventional study. Non-dialysis and non-kidney transplant adults (18 years old) undergoing elective CABG in March 2014-February 2015 were randomized (1:1 ratio) to control and intervention groups. The intervention group was intervened to minimize potential nephrotoxic conditions perioperatively (48 hours prior to the operation to 5 days postoperation). Outcome measures included the incidence and severity of post-CABG AKI using the AKIN criteria, length of hospital stay, discharge disposition and hospital mortality. Data from a similar cohort in March 2013-February 2014 were extracted and compared with the results from the control group to assess the spillover effects.

Results: Post-CABG AKI occurred in 19% (n=33) of the 174 patients in the intervention group; 30% (n=51) of the 172 in the control group, p=0.02, consistent with a 36% AKI risk reduction with the interventions [RR = 0.64 (95% CI: 0.44-0.94)]. Number needed to prevent one AKI was 10. The AKI severity was mostly mild and similar between the two groups; 98% and 94% were in stage 1 AKI in the control and intervention groups, respectively. Compared to non-AKI, AKI patients in both groups had a longer length of hospital stay and higher risk of being discharged to a care facility. No hospital mortality was noted in both groups. The AKI occurrence in the year prior to the study was similar to that in the control group.

Conclusions: Multipronged preventive measures can significantly reduce post-CABG AKI. The implementation of the preventive measures is uncomplicated. This approach can potentially be adopted in most hospital settings. These results should encourage initiatives towards developing AKI prevention protocols.

TH-PO066

Outcomes of Early Initiation of Continuous Renal Replacement Therapy in Elderly Patients with Acute Kidney Injury: A Multicenter Prospective Cohort Study Jae Yoon Park, Dong Ki Kim, Hyung Jung Oh, Kwon Wook Joo, Young Kyu Oh, Chun Soo Lim, Shin-Wook Kang, Yon Su Kim, Jung Tak Park, Jung Pyo Lee. Seoul National Univ College of Medicine, Seoul, Korea; Yonsei Univ College of Medicine, Seoul, Korea.

Background: Continuous renal replacement therapy (CRRT) is essential in the management of critically ill patients with acute kidney injury (AKI). However the optimal timing for initiating CRRT remains controversial, especially in elderly patients. Therefore we investigated outcomes of early initiation of CRRT in elderly patients with AKI.

Methods: A total of 616 patients aged equal or over 65 years who started CRRT due to AKI from August 2009 to December 2013 were enrolled prospectively at three centers. They were divided into 2 groups based on the median 6-hours urine output immediately before CRRT was applied.

Results: The mean age of both group was 74.3 years. The median 6-hours urine output was 80 mL. 186 patients (60.0%) were male in early initiation group and 179 patients (60.3%) in late initiation group. The most common cause of AKI was sepsis (45.9%) versus 60.0%). Mean arterial pressure was higher in early initiation group (79.8 mmHg versus 76.8 mmHg). Prothrombin time-interval normalized ratio, total bilirubin, aspartate aminotransferase and alanine aminotransferase were lower in early initiation group (P<0.05).

Conclusion: Early initiation of CRRT in elderly patients with AKI is potentially beneficial.
Overall cumulative survival and 28-days survival rates were higher in early initiation group (Log-rank P<0.001 for both). Furthermore, early CRRT treatment was associated with lower mortality rate after adjustment for age, sex, mean arterial pressure, Charlson comorbidity index, Sequential Organ Failure Assessment score, hemoglobin, serum C-reactive protein, serum albumin level and prothrombin time (hazard ratio, 0.75; 95% confidence interval 0.595-0.951; P = 0.008).

Conclusions: Early initiation of CRRT was associated with a better prognosis in critically ill elderly patients with AKI.

TH-PO067

Outcomes in Patients with Persistent Dialysis-Dependent AKI

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Background: We sought to describe clinical characteristics & outcomes in patients with persistent dialysis-dependent AKI at the time of hospital discharge.

Methods: We performed a retrospective descriptive study of patients requiring dialysis for AKI at the time of hospital discharge in Lehigh Valley Health Network Subacute Dialysis Program between October 2012 & July 2014.

Results: Of 55 patients enrolled in the program, 26(47.3%) recovered renal function & 29(52.7%) developed ESRD. Clinical characteristics of these patients are shown below. The median duration of dialysis in the renal recovery group was 3.5 weeks. Although 75% of patients who recovered renal function did so by 5.1 weeks, 2(27.7%) recovered >3 months after dialysis initiation.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Renal Recovery (n=26)</th>
<th>No renal recovery (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>74</td>
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<tr>
<td>Comorbidities - n(%)</td>
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<tr>
<td>HTN</td>
<td>18 (69)</td>
<td>23 (86.2)</td>
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<tr>
<td>CHF</td>
<td>9(34.6)</td>
<td>10 (34.5)</td>
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<tr>
<td>CAD</td>
<td>6 (23.1)</td>
<td>10 (34.5)</td>
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<tr>
<td>DM</td>
<td>16 (61)</td>
<td>10 (34.5)</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>3 (11.5)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>PVD</td>
<td>4 (15.4)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dl)</td>
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<td>Creatinine on hospital admission (mg/dl)</td>
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<tr>
<td>Creatinine on dialysis initiation (mg/dl)</td>
<td>5.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Change in creatinine between week 3 &amp; 4 after dialysis initiation</td>
<td>0.86*</td>
<td>0.13</td>
</tr>
<tr>
<td>Etiology - n(%)</td>
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<tr>
<td>ATN</td>
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<td>7 (24.1)</td>
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<tr>
<td>Multiple myeloma</td>
<td>0 (0)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>CIN</td>
<td>2 (7.7)</td>
<td>2 (6.9)</td>
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<tr>
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<td>ANCA</td>
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<tr>
<td>CRS</td>
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<td>3 (10.3)</td>
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<tr>
<td>Acute renal allograft rejection</td>
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<td>2 (6.9)</td>
</tr>
<tr>
<td>Other</td>
<td>2(7.7)</td>
<td>5 (17.2)</td>
</tr>
</tbody>
</table>

* Among those who recovered renal function but were still dialysis dependent at 4 weeks.

Conclusions: This study indicates that patients who did not recover renal function were older & had higher creatinine levels at each time point than those who recovered renal function. While there was a decrease in serum creatinine from week 3 to week 4 in patients with renal recovery, there was an increase for those who did not recover. More patients who did not recover renal function had HTN, HF & CAD. Additionally, more patients who had ATN recovered renal function, while all patients with multiple myeloma did not. Hypothesis-testing studies are needed to explore whether or not these clinical characteristics may be used to predict which patients are likely to recover renal function and which are not.

TH-PO068

Acute Kidney Injury Episodes Accelerates Rate of Loss of Renal Function in Diabetes Mellitus

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Background: Although acute kidney injury (AKI) is a risk factor for chronic kidney disease (CKD), whether it accelerates the rate of loss of estimated glomerular filtration rate (eGFR) is not known.

Methods: In a de-identified cohort of 3,678 type 2 diabetes patients we studied the impact of AKI on the rate of decline in eGFR. Patients with an entry eGFR of > 30 ml/min and at least two creatinine (Cr) values at least one month apart were followed until their eGFR was < 15 ml/min, death, or the end of the study. Cr measurements spanned over an average of 65 months. Estimated rates of linear eGFR decline were compared between those with and without AKI. We assessed the effect of AKI on the outcome of a rapid decline in eGFR (defined as > 2 ml/min/year) adjusting for demographics, proteinuria, and baseline CKD status (initial eGFR greater or less than 60) in a multivariable logistic model, and expressed this as odds ratios (OR) and 95% confidence limits (95% CI).

Results: Patients’ mean (standard deviation) age was 62 (11) years at study entry with an average eGFR of 79 (22.5). In 3,055 non-AKI patients the mean eGFR decline was 2.7 ± 4.2 ml/min/yr in the 623 AKI patients (p < .0001). For 499 AKI patients with both pre and post-AKI eGFR slopes, the mean decline pre-AKI was 2.7 ml/min/yr versus 6.3 ml/min/yr post-AKI (p = .03; paired t-test). In the non-AKI group 23.4% met the rapid decline outcome, compared with 36.0% in AKI group (p < .0001); within AKI patients, rapid decline occurred in 37% of patients pre-AKI and 46% post-AKI (paired OR = 1.4; 95% CI, 1.1-1.8, McNemar p = .008). AKI was associated with rapid decline (OR 1.8; 95% CI, 1.5-2.2; p < .0001), adjusted for age, gender, race, proteinuria, and CKD status.

Conclusions: Compared to no-AKI, diabetic patients with AKI experience an accelerated rate of decline in eGFR, and it occurs at twice the pace in the pre- vs post-AKI periods. Biological and process of care factors may be responsible for this effect.

Funding: Veterans Administration Support, Clinical Revenue Support

TH-PO069

Impact of Transient or Persistent Acute Kidney Injury on Chronic Kidney Disease Progression and Mortality After Gastric Surgery

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Background: Acute kidney injury (AKI) was common after gastric surgery for gastric cancer and associated with adverse outcomes. However, impact of transient or persistent AKI on clinical outcomes after gastric surgery for gastric cancer has not been described. The objective of this study was to determine the incidence, factors, and clinical outcomes associated with transient or persistent AKI after gastric surgery.

Methods: We performed a retrospective study of 4,886 patients with normal renal function who underwent partial or total gastrectomy for gastric cancer between June 2002 and December 2012. Transient AKI was defined as return of serum creatinine to the no-AKI range at discharge after gastric surgery. Our outcomes included occurrence of new-onset chronic kidney disease (CKD), and long-term kidney function and mortality.

Results: AKI occurred in 638 (13.1%) after gastric surgery. Of these, transient AKI was documented in 556 (87.1%). Length of intensive care unit (ICU) and hospital stay, and ICU admission rate (5.8% versus 1.0%) were higher in patients with transient AKI than in those without AKI. Male, use of diuretics and postoperative vasoressor, and lower baseline creatinine were common risk factors for persistent and transient AKI after gastric surgery. After adjusting for confounding factors, patient with transient and persistent AKI had a significantly higher new-onset CKD (odds ratio [OR], 1.65; 95% CI, 1.16–2.66, P = 0.005; OR, 3.66; 95% CI, 1.77–3.44, P < 0.001, respectively) and 1-year mortality (OR, 1.75; 95% CI, 1.5–2.1, P = 0.009; OR, 12.79, 95% CI, 7.57–23.11, P < 0.001, respectively) compared with no-AKI.

Conclusions: Not only persistent AKI but Transient AKI is associated with increased hospital complications and a significantly higher risk of CKD progression and long-term mortality than patients without AKI after gastric surgery.

TH-PO070

Use of Non-Tunneled Versus Tunneled Catheters for Renal Replacement Therapy in Acute Kidney Injury

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Background: Treatment of severe acute kidney injury requiring renal replacement therapy (AKI-RRT) requires vascular access, with either temporary, non-tunneled dialysis catheters (NTDC), or tunneled dialysis catheters (TDC). The relative risks and benefits of these two vascular access options have not been well studied.

Methods: We conducted a 1-year prospective cohort study in an academic medical center to compare outcomes between TDC and NTDC for AKI-RRT. We collected information about catheter placement including reasons for type of catheter used, number of insertion attempts, duration of use, and infectious and mechanical complications.

Results: Over one year we collected information on 140 NTDC and 80 TDC placement procedures on 154 patients with AKI-RRT. Compared to NTDCs, TDCs required fewer insertion attempts (1.0 vs. 1.5), had longer median duration of use (58.5 vs. 6.5 days), and had fewer infectious and mechanical complications (6% vs. 25% (all p<0.001). The most common reasons for NTDC vs TDC placement were immediate need for use (74%) and vascular access failure (26%). The most common complications for NTDC were infection (11%) and catheter not working (7%) were the most common reasons for NTDC removal. Infection (4%) was the most common reason for TDC removal.

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105A
Subarachnoid Hemorrhage Induces Transient Renal Dysfunction
Naoki Ikegawa; Yashushi Yamamura; Mamoru Tomida; Seiya Takehara; Takuya Yoshiida; Hiromichi Kumagai; George Seki; Akira Hishida; Ikuhisa Mori; Shigeru Kato; Mamoru Tomida; Doi of Nephrology, Yatsui City Hospital; Yatsui, Japan; Dept of Neurosurgery, Yaizu City Hospital, Yaizu, Japan; Dept of Pediatrics, Yaizu City Hospital, Yaizu, Japan; Dept of General Surgery, Yaizu City Hospital, Yaizu, Japan; Dept of Clinical Nutrition, Univ of Shizuoka, Shizuoka, Japan.

Background: Subarachnoid hemorrhage (SAH) is known to induce acute cardiovascular stress as reflected by ECG changes, and renal dysfunction is associated with poor prognosis in SAH. However, the precise effect of SAH on renal function and the possible mechanisms of renal dysfunction in SAH have not been fully understood.

Methods: First, we retrospectively analyzed renal function by serum creatinine (Scr) and urine albumin (UAlb) in 140 patients with SAH. Then, we prospectively analyzed renal function by serum creatinine (Scr) and urine albumin (UAlb) in 281 patients with SAH. The patients with SAH were divided into two groups: Group A (N=140) and Group B (N=281).

Results: There was a significant transient increase in Scr in patients with SAH in the first 3 days of the acute phase. However, no significant changes in Scr were observed during the course of the patients with SAH. ECG abnormalities were observed in 57% of patients with SAH. In the prospective study, SAH patients showed increased levels of albuminuria and NT-proBNP on day 0, day 1 and 14 and NGAL on day 14. Eleven SAH patients with increased levels of NT-proBNP (more than 400 pg/ml) on day 2 showed significantly higher albuminuria (118.8 mg/gCr, p= 0.005) and urinary NGAL (67.5±101.7 vs. 17.5±15.0 ng/ml, p< 0.05) than eleven patients with lower NT-proBNP (less than 400 pg/ml).

Conclusions: Significant renal dysfunction was induced in the acute phase of SAH but not in C1 and C2. Renal dysfunction was associated with NT-proBNP elevation, suggesting some interactions between heart, brain and kidneys.

TH-PO007
Acute Kidney Injury Post Nephrectomy in Living Donors
Maijime Antonekou, Andrew Davenport.

Background: In 2014, the NHS UK introduced an AKI screening algorithm that was integrated into all UK biochemistry laboratories to report cases with AKI with 50% increase in serum creatinine. We aimed to measure the incidence of AKI in healthy living kidney donors post laparoscopic nephrectomy and determine whether this leads to reduction in renal function in the short term.

Methods: Retrospective data collection from 71 living kidney donors presenting between 2006-2011. We calculated serum creatinine (Scr) changes defined as stage 1 AKI as per the KDIGO guidelines (Scr increase by > 26.5 umol/L within 48 hours or 1.5-1.9 times baseline increase) and stage 2 AKI (2.0-2.9 times baseline increase).

Results: 54.9% of patients developed AKI: 52.1% AKI stage 1 and 2.8% AKI stage 2. The median age was 53 years (IQR 21-66 years) in the group of patients that developed AKI and 52 years (IQR 27-71 years) in the non-AKI group. 39.7% were males (26.8% with AKI) and 60.3% females (28.2% with AKI) (p=0.07). The AKI group had a lower mean Scr at baseline: 71.2±22.3 umol/L vs 84±18.0 umol/L (p<0.01). However, there was no difference in the CKDepi at baseline (91.6±18.6 ml/min in the AKI group vs 89.17±3.7 ml/min, p=0.14) as well as the raw and adjusted for surface area isotopic EDTA-GFR at baseline (101±38.2 ml/min in the AKI group vs 96.2±29.9 ml/min (p=0.03) and 89.2±0.2 ml/min in the AKI group vs 86±16.2 ml/min (p=0.41) respectively). Post nephrectomy there was no difference in absolute renal function (CKDepi) in the AKI group 62±15.4 ml/min vs 60.2±10.7 ml/min, p=0.06) or change in renal function (33±14.5% decrease in CKDepi in the AKI group vs 35±4±14.0%, p=0.25) at 6 months.

Conclusions: Although 54.9% of patients fulfilled the diagnostic criteria for AKI as reported by the laboratory AKI screening algorithm this might not reflect actual kidney injury, and there were no differences in renal function measured after 6 months.

TH-PO005
Fluid Overload and Mortality in Neonatal Intensive Care Unit Patients Requiring Continuous Renal Replacement Therapy
Hee Young Cho, Sang Taek Lee; Hye Won Park.

Background: Continuous renal replacement therapy (CRRT) has emerged as a favored modality in the management of the high risk neonates with acute kidney injury (AKI) and with inborn errors of metabolism. Recently, there are some reports that lesser degrees of fluid overload (FO) at CRRT initiation was associated with improved outcomes in children in pediatric intensive care unit (PICU). However, there has been little data that have analyzed the fluid status, risk factors, and outcome of neonates who receiving CRRT. The aim of this study is to evaluate the factors including FO associated with the outcome of neonates with CRRT.

Methods: A retrospective medical record review was performed 34 hemodynamic unstable neonates with AKI who underwent at least 48 hours of CRRT in neonatal intensive care unit (NICU) at Samsung Medical Center between January 2007 and December 2014. We divided into two groups with survivor (N=15) and non-survivor (N=19). Data were collected regarding demographic data, CRRT graph, clinical course, fluid overload, and mean circuit time. Fluid overload from NICU admission to CRRT initiation, defined as a percentage equal to (CRRT initiation weight [kg] - NICU admission weight [kg]) NICU admission weight [kg] x 100%. CRRT was initiated without anticoagulation, and decided to use the anticoagulation if the initial circuit life-span was less than 12 hours.

Results: Survivors were more likely to have longer gestational age, fewer days in NICU prior to CRRT, lower percent FO at CRRT initiation, and higher urine output at the end of CRRT. There was no significant difference in mean daily effluent volume between survivors and non-survivors. Adjusted regression analysis revealed that FO at CRRT initiation was associated with mortality, duration of CRRT, and hospitalization period.

Conclusions: Fluid overload might cause mortality, prolonged hospitalization period, and duration of CRRT in neonates. Early initiation of CRRT before severe fluid overload might improve the outcome of neonates requiring CRRT.
TH-PO075
Survival and Renal Outcomes following Transjugular Intrahepatic Portosystemic Shunt Placement in Hepatorenal Syndrome: A Case Series
Guillermo Ortiz,1 Andrew S. Allegretti,1 Jie Cui,1 Julia Beth Wengler,1 Ishir Bhan,1 Raymond T. Chung,2 Ravi I. Thadhani,1 Zubin Irani.1 ‘Nephrology Div, MGH, Boston, MA, 2Gastrointestinal, MGH, Boston, MA, 3Radiology, MGH, Boston, MA.

Background: Few effective treatment options are available for hepatorenal syndrome (HRS). There may be a role for the placement of a transjugular intrahepatic portosystemic shunt (TIPS) in reversing the pathophysiological changes in HRS.

Methods: We performed a multicenter, retrospective review of patients who underwent TIPS placement concurrent to having HRS from 2015 to 2016 using a centralized clinical data warehouse. Two clinicians adjudicated HRS diagnosis and classified cases as Type 1 (T1-HRS) or Type 2 (T2-HRS) based on review of medical records. Estimated glomerular filtration rate (eGFR), survival, and other parameters were assessed immediately before and after TIPS, and 90 days pre- and post-procedure.

Results: We identified 17 cases. Mean age was 54±12 years, 12 (71%) were male, 7 (41%) had T1-HRS and 10 (59%) had T2-HRS. Median MELD score at time of procedure was 21 (quartile 1, quartile 3: 14, 33). TIPS significantly reduced portal pressure gradient from 16 (14, 20) to 7 (5, 8) mmHg (p=0.001). Median eGFR 90 days pre TIPS was 50 (37, 77) mL/min. TIPS significantly improved eGFR from 32 (28, 35) pre-TIPS to 47 (38, 55) mL/min post-TIPS (p=0.003) and 69 (63, 97) mL/min at 90-days post TIPS (p=0.006).

Conclusions: TIPS improves eGFR in HRS post-procedure and at 90 days follow-up. Further study is needed to identify those who would benefit from the procedure.

TH-PO076
Evolution of the Management of Multiple Myeloma and Impact on Survival and Dialysis Independence
Manon Laforest, Noemie Jourde, Claire Dufour, Claire Lepoutre, Stéphane Burtey, Bertrand Goudounou. Centre de Nephrologie et Transplantation Rénale, Assistance Publique Hopitaux de Marseille, Marseille, France.

Background: During the past decade, the management of myeloma has evolved. Several studies found an improved disease-free survival since the late 2000s with the advent of new molecules in first line chemotherapy (Bortezomib and / or IMiDs (Revlimid, Thalidomide). Nevertheless, this benefit is mostly seen in patients of less than 65 years old and survival and renal outcomes are not well studied in elderly patients. Our study aimed to compare two cohorts of patients according to the period of treatment: before or after 2008 focusing on global and renal outcomes.

Methods: We retrospectively collected clinical and biological data of 135 patients admitted to the University Hospital of Marseille from 1999 to 2014 with a diagnosis of multiple myeloma and acute renal injury (as defined by an increase in serum creatinine above 120 mcmol/L). We separated this cohort based on the year of admission (<or> to 2008, respectively group 1 and group 2). The parameters studied were: overall survival and dialysis independence 2 years after initial chemotherapy.

Results: 88 patients were included in group 1 and 47 in group 2. No differences were seen in terms of baseline characteristics between groups: median age (67.1 vs 70.2), sex ratio, conventional biological parameters. A higher proportion of relapsing patients was found in group 2 (10/47 (22%) in group 2 versus 9/88 (10%) in group 1). A higher proportion of dialysis dependent patients at diagnosis was found in group 2 (26/47, (55.3%) in group 2 versus 36/88 (40%) in group 1). No difference was seen in terms of overall survival or dialysis independence 2 years after diagnosis of AKI when group 2 was compared to group 1 (OR 1.9 (0.8-4.1) and HR 0.3 (0.4-1.2) respectively).

Conclusions: In our cohort, we did not observe any benefit on overall survival or dialysis independence at 2 years according to the treatment period. Our results are not in accordance with previous papers. Our patients were older with a high proportion of dialysis dependence at diagnosis. Future studies are needed to clarify the benefit of the use of novel agents in older patients with severe AKI.

TH-PO077
Effect of Genes Involved in Endogenous Oubain Synthesis on the Development of AKI After Cardiac Surgery
Marco Simonini, Simona Pozzoli, Elena Frati, Elena Bignami, Lorena Citterio, Chiara Lanzani, Nunzia Casassimassa, Guido Gatti, Paolo Manunta. San Raffaele Scientific Inst, Italy.

Background: Acute kidney Injury (AKI) is an important complication of cardiac surgery. Elevated levels of Endogenous Oubain (EO), an adrenal stress hormone with haemodynamic and renal effects, have been associated with worse renal outcome after surgery. Polymorphisms in candidate genes related to EO synthesis, as LSS (lanosterol synthase) and HSD3B1 (steroid dehydrogenase), have been described to be involved in determination of EO activity. Aim of this work is to investigate the relationship between these genes and the development of AKI.

Methods: 500 consecutive patients, undergoing cardiac surgery at our Hospital, were genotyped. The primary outcome was AKI according to Acute Kidney Injury Network. Secondary outcomes were length of ICU stay and total in-hospital mortality. Total AKI incidence was 25.1%.

Results: No difference in basal EO plasmatic levels was observed according to LSS or HSD3B1. Patients carrying the derived alleles of the LSS studied polymorphism had a more severe clinical presentation (EuroSCORE: 5.17±4.81 vs 4.88±5.73 vs 3.54±3.49; p=0.05). Likewise, AKI incidence according to LSS polymorphism was greater (34.9% vs 27.5% vs 21%; p=0.029). Even after adjustment for the main covariates (sex, age, eGFR, EF, hypertension, DM, type of surgery and EuroSCORE) results remain significant (AKI logistic regression: Exp(B) 1.97, IC95% 1.05-3.70; p=0.038). Finally, in a higher percentage of the same patients, i.v. furosemide was used in the immediate post-operative time to maintain adequate diuresis. No other effects of LSS or HSD3B1 were observed.

Conclusions: Patients with at least one derived allele of LSS polymorphism investigation have a greater chance of developing AKI after cardiac surgery, despite on clinical presentation. Moreover, in a higher percent of the same patients, i.v. furosemide was needed to maintain adequate diuresis. These effects appear to be independent on EO plasmatic levels. We believe that these preliminary findings could be interesting for the identification of new cellular mechanisms underlying the development of post-surgical AKI.

TH-PO078
Obstructive Nephropathy in Ovarian Hyperstimulation Syndrome and Successful Delivery
Katherine M. Wang, Syed S. Haqque, Arif Asif. Albany Medical Center, Albany, NY.

Background: Ovarian hyperstimulation syndrome (OHSS) is a well-described iatrogenic complication of exogenous gonadotropin administration preceding in vitro fertilization (IVF). Underlying pathophysiology stems from influx of reproductive hormones and inflammatory vasodilatory mediators that increase capillary permeability and cause intravascular volume depletion due to large fluid shifts into the interstitial space. Most cases are mild and can be managed on an outpatient basis with close monitoring. We present an intriguing and rare case of severe OHSS with acute renal failure secondary to obstructive nephropathy. Our patient is a nulliparous 38 year old black female stimulated with beta-human chorionic gonadotropin (hCG) prior to transfer of fresh embryos resulting in a diagnostically dichorionic twin gestation. She presented to the OB-GYN service with progressive ascites, gaining 17 kg in 1 week, and also acute renal failure due to mechanical obstruction of both ureters from bilaterally enlarged fluid-filled ovaries. Initial ultrasonography estimated the dimension of the left ovary at 22 cm, containing 1.7 L of fluid volume. Her baseline creatinine of 0.8 mg/dL peaked at 5.8 mg/dL prior to placement of bilateral nephrostomy tubes, which led to rapid and effective relief of obstruction and normalization of kidney function within days. At follow-up, patient had spontaneous intrarenal demise of one fetus at 9 weeks; however, she successfully delivered the other fetus preterm at 35 weeks gestational age via C-section. The nephrostomy tubes remained in place for the duration of her pregnancy. This case highlights a rare presentation of a well-known, but potentially life-threatening complication of ovarian induction, which has become an increasingly popular treatment for infertility.

Methods: Clinical course of the patient during the entire pregnancy and the outcome.

Results: Successful fetal outcome.

Conclusions: Patient presented with severe obstructive urethropy from very large kidneys from hyperstimulation resulting in acute renal failure and bilateral nephrostomy tube placements. This resulted in release of obstruction, normalization of renal function, and a successful delivery.

TH-PO079
Analysis of the VA/NHI Acute Renal Failure Trial Network Data: Comparison of Outcomes in Nutrition Delivery in Acutely Dialyzed Patients
Youngho Kim, V. Shane Pankratz, Eduardo A. Alas, Christos Argyopoulos, Mark L. Unruh. Div of Nephrology, Univ of New Mexico School of Medicine, Albuquerque, NM.

Background: The optimal nutrition management for acute kidney injury (AKI) is not well-defined and recommendations for nutritional support in acutely ill patients who undergo renal replacement therapy (RRT) are largely based on expert opinion.

Methods: In order to better understand associations between nutrition and outcomes of critically ill patients with AKI requiring RRT, we analyzed data available from the ATN study. Patients were classified by nutritional support provided at the time of enrollment.
into the following groups: NPO, Tube feed (TF), Total parenteral nutrition (TPN), and Oral (PO). Two competing outcomes were considered: mortality and continued dialysis dependency among survivors.

**Results:** Characteristics among groups were similar. ICU predictive scoring systems and disease etiology were strongly associated with mode of nutrition delivery. High ICU predictive scores and a surgical primary treating service were associated with a higher percentage of patients treated with TPN. There were significant differences in 60-day outcomes among nutrition groups (p<0.011) [Figure 1]. Notably, PO group had better survival and RRT independency. After adjustment for patient characteristics, the strength of association between mode of nutrition delivery and outcomes weakened and was not statistically significant (p=0.106), although the patterns of association were similar to the unadjusted analyses with TPN having the highest and PO the lowest adjusted risks of death and continued dialysis dependency.

**Figure 1:** Dialysis dependency and mortality at 60 days

<table>
<thead>
<tr>
<th>Baseline Nutrition</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>Dialysis Dependency</td>
</tr>
<tr>
<td>NPO</td>
<td>1.72 (0.86-3.54)</td>
<td>1.89 (1.24-2.88)</td>
</tr>
<tr>
<td>Tube Feed</td>
<td>1.89 (0.89-4.03)</td>
<td>2.31 (1.33-3.66)</td>
</tr>
<tr>
<td>TPN</td>
<td>2.87 (1.11-7.46)</td>
<td>3.15 (1.68-5.92)</td>
</tr>
<tr>
<td>PO</td>
<td>1.0 (REF)</td>
<td>1.0 (REF)</td>
</tr>
</tbody>
</table>

**Conclusions:** There was no significant global association between baseline nutrition modalities and 60-day mortality or 60-day dialysis dependency. Further investigation could be performed to prospectively elucidate the benefit of enteral vs. TPN feeding in AKI.

**TH-PO080**

**Pilot Trial of Dietary Restriction for Protection from Acute Kidney Injury in Cardiac Surgery**


**Background:** Even small acute changes in kidney function as a result of acute kidney injury (AKI) can result in short-term and long-term complications including chronic kidney disease, end-stage renal disease and death. However, despite an increasing incidence of AKI few preventive and therapeutic options exist. Short-term reduction of calorie intake has been shown to provide effective protection from ischemic AKI in mice.

**Methods:** In this single-center randomized controlled trial (ClinicalTrials.gov Identifier: NCT01534364) 82 patients with at least one risk factor for postsurgical AKI scheduled for cardiac surgery (CABG, valve replacement) were randomly assigned in a 1:1 ratio into a diet group (DG) or a control group (CG). The intention-to-treat population encompassed 76 patients. The primary endpoint was defined as the change in serum creatinine from baseline to 24 hours after surgery, secondary endpoints included incidence of AKI (KDIGO criteria).

**Results:** Demographic and surgery associated characteristics were similar in both groups (DG 80% male vs. CG 77.5% male; age: DG 72y[63-76] vs. CG 75y[70-77], body weight: DG 84.6kg[72.-91.7] vs. CG 79.1kg[75.0-72.7], crossclamp time: DG 59min[52-82] vs. CG 59min[44-82]). Average calorie intake in the DG was 1323 kcal and a 3 kgl [4.0 to -2.2] weight loss was observed (no weight change in the CG). With respect to the primary outcome measure there was no difference between the groups. Overall incidence of AKI was similar in both groups with considerably less patients with stage 1 AKI in the DG (n.s.). Length of stay, need for renal replacement therapy and mortality did not differ.

<table>
<thead>
<tr>
<th>No AKI</th>
<th>Diet Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>21(58.3%)</td>
<td>21(52.5%)</td>
<td></td>
</tr>
<tr>
<td>KDIGO 1</td>
<td>7(19.4%)</td>
<td>13(32.5%)</td>
</tr>
<tr>
<td>KDIGO 2</td>
<td>6(16.7%)</td>
<td>5(12.5%)</td>
</tr>
<tr>
<td>KDIGO 3</td>
<td>3(6.6%)</td>
<td>2(5.2%)</td>
</tr>
</tbody>
</table>

**Conclusions:** Dietary restriction is safe and feasible in patients awaiting cardiac surgery. Despite its beneficial effect in animal studies restriction of calorie intake did not alter serum creatinine dynamics or AKI incidence after cardiac surgery.

**Funding:** Pharmaceutical Company Support - Fresenius Kabi

**TH-PO081**

**Minute Ventilation-Targeted Adaptive Servo Ventilation Reduces Injury in Patients with Acute Decompensated Heart Failure**

*Matt Kidawara,1 Boris Arbit,1 Elizabeth Lee,1 Trenton Gluck,1 Kathleen Sarmentino,1 Atul Malhotra,2 Alan S. Maisel,1 1 Div of Cardiovascular Medicine, Univ of California, San Diego, La Jolla, CA; 2 Div of Pulmonary and Critical Care Medicine, Univ of California, San Diego, La Jolla, CA; 3 Cardiac Research, VA San Diego Healthcare System, La Jolla, CA.*

**Background:** Acute kidney injury (AKI) is a frequent comorbidity in patients admitted for acute decompensated heart failure (ADHF). Minute ventilation targeted adaptive servo ventilation (MV-ASV) relieves apneas, pulmonary congestion, and renal hypoxia. Kidney injury molecule (KIM-1) is a marker of AKI and could be used to detect early injury and the improvement of kidney function. MV-ASV may mitigate AKI in patients admitted of ADHF compared to standard care.

**Methods:** This is a pilot study in which twenty-one consecutive patients with ADHF were randomized to receive either MV-ASV therapy (S9 VPAP/Adv, ResMedCorp) with standard care, or standard care alone. MV-ASV therapy was administered for a minimum of six hours per day for up to 5 days, or until discharge. Daily measurements of plasma KIM-1 were obtained with SMC™ technology (Singules). Daily serum creatinine levels were measured and used to calculate eGFR.

**Results:** Median baseline KIM-1 levels in the MV-ASV and standard groups were 312pg/mL and 361pg/mL, respectively. In the control group KIM-1 increased 18 % to 426pg/mL while the group with MV-ASV demonstrated a mitigation of kidney injury with a 7% decrease to 290pg/mL. These changes correlated with subsequent changes in serum creatinine and eGFR.

**Conclusions:** The use of MV-ASV therapy resulted in mitigation of kidney injury typically seen in patients with ADHF during hospitalization.

**Funding:** Pharmaceutical Company Support - Resmed

**TH-PO082**

**Early Volume Expansion Improves the Outcome of Shigatoxin-Associated Hemolytic Uremic Syndrome – Data from the North Italian HUS Network**

*Giuliano Ardissino,1 Francesca Tel,1 Ilaria Possenti,1 Sara Testa,1 Dario Consomni,2 Stefania Sahl,1 Rosaria Colombo,1 Erminio Torresani.1 Center for HUS Prevention, Control and Management, Fondazione IRCCS Ca’ Granda, Ospedale Policlinico, Milan, Italy; 2Unit of Epidemiology, Fondazione IRCCS Ca’ Granda, Ospedale Policlinico, Milan, Italy; 3Unit of Microbiology, Fondazione IRCCS Ca’ Granda, Ospedale Policlinico, Milan, Italy.*

**Background:** Shigatoxin-associated hemolytic uremic syndrome (STEChUS) is a severe disease which has no specific treatment and among supportive care, fluid management is concentrated on preventing fluid overload because of oligo/anuric AKI. Fluid restriction is associated with more severe disease, but it is unknown whether volume expansion (VE) can improve disease outcome. A network of pediatric hospitals has been operating in Northern Italy with the aim of early diagnosis and referral of STEC infections and to investigate the efficacy of VE to minimize disease severity.

**Methods:** All children with STEC-HUS referred to our centre in 2012-2014 received intravenous saline targeting at inducing a moderate VE (+10% of working weight) on the basis of the hypothesis that prompt restoration of circulating volume can limit thrombi formation and ischemic tissue damage. Their short- and long-term outcomes were compared with those of 38 patients (pts) referred to our centre during the years immediately before the network was established, when their fluid intake was routinely restricted.

**Results:** The pts undergoing VE showed a mean increase in body weight of 12.5%±0% in their predecessors and had significantly better short-term outcomes with a reduced rate of neurological involvement (7% vs2.5%, p=0.05), less need for dialysis (26% vs 9%, p=0.005) or intensive care support (median 8.5, IQR 3.5-15 vs 2.5±0, IQR 1-4.5 days, p=0.02), and required fewer days of hospitalisation (median 12, IQR 7.0-18 vs 0.0, IQR 7.0-12 days, p=0.025). Long-term outcomes were also significantly better in terms of renal and extra-renal sequelae (13% vs 39.5%, p<0.005).

**Conclusions:** Ps with STEC-HUS benefit greatly from VE. Early and generous fluid infusions can reduce thrombi formation and ischemic organ damage, and thus have positive effects on both short- and long-term disease outcomes.

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

108A
Role of Statins on Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention


Background: The occurrence of contrast-induced kidney injury (CIKI) increased and is responsible for ~10% episodes of hospital-acquired AKI. The mechanism of renal dysfunction is incompletely understood, vasoconstriction, hyperosmolality, free radicals and direct toxicity may play additive roles. Statins reduce O2 stress, increased renal NO and may prevent AKI. The aim of this retrospective study was to analyse the association between statin and the development of RCIN, defined by an increase in Scr ~25 % 48-72 h after the administration of low osmolar contrast agents, in high risk patients (Ps) undergoing percutaneous coronary intervention (PCI).

Methods: Data from 165 consecutive adults with Scr >1.25 mg/dL underling non-emergent PCI during a 24- mo period were assessed. All had received prophylaxis for RCIN (volume expansion + NAC). 31 Pts were removed due to absence of follow up Scr data or lacked informed consent for use. Continuous variables are expressed as mean (sd) and categorical variables as frequency. Unpaired t-test, chi2 or Fischer’s exact test were used as appropriate. Those variables resulting significantly related to RCIN in univariate analysis, were included in a multivariate logistic regression model. P-values <0.05 were considered significant.

Results: 134 Pts met the admission criteria; 67 were on statins prior PCI. Both groups had similar clinical, and laboratory baseline conditions. 18Pts (13.4%) developed RCIN. 31 Pts were removed due to absence of follow up Scr data or lacked informed consent for use. Continuous variables are expressed as mean (sd) and categorical variables as frequency. Unpaired t-test, chi2 or Fischer’s exact test were used as appropriate. Those variables resulting significantly related to RCIN in univariate analysis, were included in a multivariate logistic regression model. P-values <0.05 were considered significant.

Conclusions: Our data suggest that statin use before PCI reduces the risk of RCIN. Further prospective, well designed, randomized clinical trials in a larger number of individuals are necessary to confirm this findings.

Effect of Rosuvastatin on Acute Kidney Injury (AKI) in Sepsis-Associated Acute Respiratory Distress Syndrome (ARDS) - Raymond K. Hsu,1 Jonathon Truvitt,2 Michael Mathay,3 Joseph Levitt,4 Boyd Taylor Thompson,5 Kathleen D. Liu.1 1UCSF; 2Medical College of Wisconsin; 3Stanford; 4MGH-Harvard.

Background: While sepsis may be protective in animal models of sepsis-induced AKI, in hospitalized patients it is rising, and there is a lack of effective therapies for treatment. Recent studies suggest that nephrology follow-up may reduce long term mortality after AKI; however, the processes of care that underlie this finding remain unknown. The objective of this study was to determine if statins which are of known benefit in chronic kidney disease (CKD) are also associated with improved mortality in survivors of AKI with CKD.

Methods: Retrospective cohort study of adults 65 years of age or older, residing in Alaska, who were admitted to hospital between 2002 and 2011, developed AKI during the index hospitalization and progressed to CKD (n=27,470 mean age 78.7 years, mean post-discharge eGFR 49.6 mL/min/1.73m²). Results: Within two years of discharge, only 39.1% of the participants received a statin. Over a subsequent two-year follow up period, the adjusted hazard ratio (HR) (95% confidence interval [95% CI]) for mortality associated with use of a statin was 0.64 (0.56-0.74). P=0.004.

Conclusions: Among AKI survivors with CKD, statin use was associated with decreased mortality, cardiovascular events and rehospitalization rates.

Potential Nephroprotective Effects of Carinate and Phosphodiesterase-5 Inhibitor Therapy in Contrast-Induced Nephropathy - Zaher Anis Arnal,1 Suhel Artul,1 Adel Rafik Jabboor,1 Raymond Farah,1 Amir Abad Elkadhir,1 Bishara Bisharah.1 1Dept of Nephrology, E.M.M.S. Hospital, Bar Ilan Univ, Nazareth, Israel; 2Dept of Radiology, E.M.M.S. Hospital, Nazareth, Israel; 3Dept of Biochemical Laboratory, E.M.M.S. Hospital, Nazareth, Israel; 4Internal Medicine “B”, Ziv Medical Center, Faculty of Medicine, Bar Ilan Univ, Safed, Israel.

Background: Contrast induced nephropathy (CIN) is connected with, prolonged hospitalization, need for dialysis and increased morbidity and mortality. The current available prophylactic measures are not sufficient to protect against CIN. Therefore, there is unmet need for novel therapeutic agents to prevent the development of CIN. This study examines whether phosphodiesterase type 5 (PDE-5) inhibitor or carnitine exert nephroprotective effects in individuals undergoing imaging that involves radiocontrast media (CM) administration as compared with N- acetyl Cysteine.

Methods: The study included 3 groups of patients with CKD (stage 3-4) as follows;1- Control group (n=14 ), who were treated with Acetylcyesteine of 600 mg twice daily, day before and on the day of CM administration; 2- Carnitine group (n=10), where the patients were infused with 20 mg/kg carimine over 10 minutes 2 h prior to the CM administration and 24 hours post CT; 3- Phosphodiesterase type 5 inhibitor group (n=12), where patients were given orally 20 mg tablets of PDE5 inhibitor-Tadalafil 2 h prior to the administration of the CM and in the subsequent day. Urine and blood samples were collected before and at the following time sequence: 2, 6, 12, 24, 48, 120 hours after the contrast administration, for creatinine and NGAL determination.

Results: Administration of CM to CKD patients who were pretreated with Acetyl cysteine caused a significant increase in urinary NGAL, but not of plasma NGAL and Scr. In contrast, pretreatment with carnitine prior to CM prevented the increase in urinary NGAL throughout the follow up period and reduced Scr below basal levels. Similarly, tadalafil administration attenuated the elevation in CM-induced urinary NGAL, but did not affect neither plasma NGAL nor Scr.

Conclusions: These results suggest that carnitine and PDE-5 inhibition may comprise novel nephroprotective approaches against CIN.

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Conclusions: Our data suggest that statin use before PCI reduces the risk of RCIN. Further prospective, well designed, randomized clinical trials in a larger number of individuals are necessary to confirm this findings.

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Methods: Retrospective cohort study of adults 65 years of age or older, residing in Alaska, who were admitted to hospital between 2002 and 2011, developed AKI during the index hospitalization and progressed to CKD (n=27,470 mean age 78.7 years, mean post-discharge eGFR 49.6 mL/min/1.73m²). Results: Within two years of discharge, only 39.1% of the participants received a statin. Over a subsequent two-year follow up period, the adjusted hazard ratio (HR) (95% confidence interval [95% CI]) for mortality associated with use of a statin was 0.64 (0.56, 0.69). Patients who received a statin also had a lower risk of cardiovascular events (adjusted HR, 0.87; 95% CI, 0.80, 0.94) and all cause re-hospitalization (adjusted HR, 0.81; 95% CI, 0.77, 0.84).

Conclusions: Among AKI survivors with CKD, statin use was associated with decreased mortality, cardiovascular events and rehospitalization rates.
(105±14.8). Most of the patients had normal urine output. 5 patients (12.5%) had larger kidney in ultrasound. 33 patients (83%) used steroids treatment. The periods of steroid treatment were 12±4.7months. The time which began to use steroids was 33±15.2days from SCr increased. The doses of steroid were 49±10.Img. The SCr level was 210±83.8µmol/l when started steroid treatment. Only 5 patients (13%) added immune inhibits. Of the 40 patients, 48%, 38%, and 10% had complete, partial, and no recovery respectively in discharge. 65% had normal renal function and 30% had CKD by 15 months. Of the 6 patients who required dialysis or CRRT, no patients were still on dialysis therapy in discharge. 65% had normal renal function and 30% had CKD when started steroid treatment. Only 5 patients (13%) added immune inhibits. Of the 24 patients, 67% had normal renal function and 35% had CKD.

Conclusions: The cause of AIN may be different. Steroid treatment may be effective in recovery of kidney function of AIN.

TH-PO088

Causality Assessment in Determining Drug-Induced Renal Injury

Celine D. Cepeda, Linda Awdisu, Etienne Macedo, Ravindra L. Mehta.
Nephrology, Univ of California San Diego, San Diego, CA.

Background: Drug induced renal injury (DIRI) accounts for 18-27% of cases of acute kidney injury (AKI) and is usually recognized based on the timing and duration of drug exposure. The Naranjo (NJ) and Liverpool (LP) causality assessment tools (CAT) are validated for identifying adverse drug reactions and serious skin reactions, respectively. We hypothesized that inter-rater and inter-tool agreement using the two CAT would not be specific to identify DIRI.

Methods: The drug induced renal injury (DIRECT) study is an ongoing prospective multicenter study evaluating genetic determinants of DIRI. Each enrolled case was adjudicated for causality by two independent nephrologists. We analyzed the first consecutive 86 adult (n = 69) and pediatric (n = 17) AKI cases. Two nephrologists adjudicated each case and used both CAT to determine likelihood of AKI due to a particular medication(s). We determined inter-rater and inter-tool agreement using percent agreement and kappa scores. Results: Adjudicators agreed 87.2% (n=75) had DIRI. A single drug was involved in 54.7% (n=47), 2 drugs in 37.2% (n=32), and 3 drugs in 8.1% (n=7) of cases. The inter-rater agreement was better with the NJ vs LP tool (61.6% vs 48.8%) and was significant for adults (p<0.038) however the inter-tool kappa score was slight (0.181) and was fair (kappa 0.325) for pediatric patients (p=0.006).

Table 1. Percent Agreement and Kappa Values for Drug 1

<table>
<thead>
<tr>
<th>Categories</th>
<th>Naranjo</th>
<th>Liverpool</th>
<th>Inter-rater</th>
<th>Inter-tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases</td>
<td>81.8</td>
<td>90.6</td>
<td>81.8</td>
<td>91.2</td>
</tr>
<tr>
<td>IDRI</td>
<td>58.7</td>
<td>90.6</td>
<td>72.7</td>
<td>81.8</td>
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<td>No IDRI</td>
<td>81.8</td>
<td>90.6</td>
<td>81.8</td>
<td>91.2</td>
</tr>
<tr>
<td>1 Drug</td>
<td>57.4</td>
<td>90.6</td>
<td>72.7</td>
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<tr>
<td>Pediatric</td>
<td>70.6</td>
<td>90.6</td>
<td>81.8</td>
<td>91.2</td>
</tr>
</tbody>
</table>

* denotes significant p-value <0.05

Conclusions: For most categories, inter-rater percent agreement and kappa scores were superior using the NJ tool. Neither tool had better than moderate inter-rater agreement. Agreement between the tools was at best fair in determining likelihood of DIRI. Better causality assessment tools need to be developed for DIRI.

Funding: Private Foundation Support

TH-PO089

Gadolinium Nephrotoxicity

Nephrology, Zahlooh/VA Medical Center, Milwaukee, WI.

Background: Gadolinium-based contrast (GBC) agents are widely used as contrast agents for magnetic resonance imaging (MRI) and have generally been considered to be safe. Early on, phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity. In the US, approximately 34.9 million MRI scans were performed in 2014 and in 45% of these cases a gadolinium chelate was administered. As compared to iodinated contrast agents, concern for contrast-induced nephropathy existed with gadolinium-contrast as it possessed many similar qualities (hyperosmolar, renal excretion via glomerular filtration). Gadolinium-based contrast agents have recently been reported to induce a usually reversible decrease of glomerular filtration rate in a high-risk population group, especially in patients with altered baseline renal function. The lethal dose of gadolinium in animals is increased by 100 folds when gadolinium is in the form of a chelate. This raise a concern that the leaching of free metal from the chelate can pose health risk.

Methods: We present a prospective study involving 122 patients (48 male and 74 female) who had an elective MRI performed. Subjects have been fasting for at least 8 hrs prior to the imaging. We collected a blood sample 1 hr prior to the imaging and followed up with a repeat blood sample collection 48 hrs after completion of the imaging procedure.

Results: These samples were analyzed for serum creatinine and BUN levels. Preliminary data shows that 46.43% (42 out of 112) of the study subjects exhibited worsening of renal function while 53.57% (60 out of 112) had normal or slightly improved renal function.

Conclusions: Preliminary data analysis suggests gadolinium induces nephrotoxicity in a population including patients with normal kidney function and with chronic kidney disease. We appreciate the limitation of the study which are mainly the number of subjects and the fasting status of subjects. Since there was no exclusions, patient who are on diuretics and ACEI inhibitors could display a higher base line creatinine which might explain the improvement of renal function post study in some subjects.

TH-PO090

Risk of Pediatric Acute Kidney Injury Is Increased With Vancomycin and Piperacillin-Tazobactam Combination Therapy

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Background: Hospitalized pediatric patients at risk for infection are often treated with vancomycin (vanc) and piperacillin-tazobactam (PTT). Risk of nephrotoxicity from vanc and other antimicrobials (e.g. aminoglycosides, beta-lactams) is well described. Recently, an increased risk of acute kidney injury (AKI) resulting from combination therapy of vanc with PT has been reported in the adult literature, but not in the pediatric literature.

Methods: Retrospective single center study of hospitalized pediatric patients ≥20 years who received vanc, PT, or the combination for 48 hours or more. Data collection included creatinine levels, medication and demographic characteristics. Patients on ECMO or dialysis were excluded.

Results: 164 patients identified, 30 (18.3%) developed AKI (definition: ≥ 50% above baseline creatinine) after beginning treatment with the antimicrobials. Eight patients in the vanc alone and PT alone groups (8%) versus 22 patients in the combination group (34.4%) developed AKI (p<0.0001). The median percent creatinine change from baseline was significant (p<0.03) between the combination and single therapy groups of 104% and 52.3%, respectively.

Conclusions: Results of this study suggest a higher risk of AKI in pediatric patients receiving the combination therapy of vanc and PT compared to single drug therapy with either of the other therapies are needed to determine if other confounding factors (e.g. dehydration, medical diagnosis, or additional nephrotoxins) contribute to the risk of AKI with this particular combination, or if there is a safer alternative for broad-spectrum antimicrobial use in the pediatric population.

TH-PO091

Associations Between Vancomycin, Other Antibiotics, Acute Kidney Injury and Mortality in Hospitalized Patients

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Background: Vancomycin is a commonly prescribed antibiotic. Animal and human studies suggest that vancomycin can cause acute kidney injury (AKI). We hypothesized that exposure to vancomycin (vanc) with other nephrotoxic antibiotics (aminoglycosides) will be associated with AKI compared to vancomycin use with non-nephrotoxic antibiotics in hospitalized patients.

Methods: We performed a retrospective observational study, including patients 18 years or older admitted from 2008 and 2010 at Montefiore Medical Center. All patients had at least two serum creatinine values during their admission and a baseline creatinine within 6 months prior to admission. AKI was defined as a 50% increase in baseline serum creatinine. One year mortality data was from the Social Security Death Index.

Results: Of 46,580 admissions, 2,126 developed AKI (4.7%). 7,889 patients (17%) had exposure to vancomycin, 1,172 patients (2.5%) had exposure to aminoglycosides and vancomycin, 3,700 patients (7.9%) had exposure to fluoroquinolones and vancomycin and 3,994 patients (8.6%) had exposure to cephalosporins and vancomycin. Those developing vanc only AKI were more likely female (70% vs 63% p<0.001), had GFR < 60 (37% vs 22% p<0.001) and vancomycin exposure (31% vs 16% p<0.001). The AKI risk associated with vanc exposure and other nephrotoxic antibiotics (aminoglycosides) or vanc and aminoglycoside exposure (1.55 (1.37, 1.76), combining vanc and gentamicin the risk was 1.95 (1.56, 2.45) while vancomycin with fluoroquinolones was 1.38 (1.17, 1.63) and vancomycin with cephalosporins was 1.37 (1.16, 1.62). The risk of mortality associated
with vancomycin alone was 2.27 (2.06, 2.49), combining vancomycin and gentamicin the risk was 2.46 (2.36, 2.54), and combining vancomycin with cephalosporins the risk was 3.42 (3.05, 3.84), and combining vancomycin with cephalosporins was the risk was 2.62 (2.34, 2.95).

Conclusions: Our data suggests that vancomycin exposure is associated with a high risk of AKI and mortality, especially in combination with amphotericin C. Further studies should be conducted to evaluate whether amphotericin C should not be used in combination with vancomycin in order to prevent AKI.

TH-PO092
Adverse Renal Effects of Targeted Anti-Cancer Therapies: A Systematic Review of Data from the FDA Adverse Event Reporting System

Background: Novel molecular targeted anti-cancer therapies have shown improvement in patient survival compared to standard chemotherapy. Renal toxicities of novel targeted therapies are limited to case reports.

Methods: We reviewed the FDA Adverse Event Reporting System’s (FAERS) quarterly legacy data file (2011-2014). We queried the database for medications listed below. The adverse events queried were: hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, proteinuria, renal failure acute. To compare what has been published, we searched PubMed for each medication plus each adverse event.

Results: Total number of adverse events reported were 1,657. Ipilimumab had the highest number of events (341) and these were mostly acute renal failure (126) and hyponatremia (112). In PubMed review all case reports were diagnosis of renal failure. The second highest number of events occurred in cetuximab and most of the events were impotence (28) and all targeted therapies listed below in figures. The most common adverse event was acute renal failure (549). The most common electrolyte abnormality was hypokalemia (367). More males developed renal failure at mean age of 65y as opposed to females with mean age of 61y (<0.01). More females got electrolytes disorders at mean age of 59y compared to males at 61y(<0.01). For all targeted therapies listed below in figure, the most highest number of events (341) and these were mostly acute renal failure (126) and hyponatremia (112). In PubMed review all case reports were diagnosis of renal failure. The second highest number of events occurred in cetuximab and most of the events were impotence (28) and all targeted therapies listed below in figures. The most common adverse event was acute renal failure (549). The most common electrolyte abnormality was hypokalemia (367). More males developed renal failure at mean age of 65y as opposed to females with mean age of 61y (<0.01). More females got electrolytes disorders at mean age of 59y compared to males at 61y(<0.01).

Conclusions: Our data elucidate previously unknown adverse renal events in targeted therapies. Older males are at higher risk for renal failure and females are at higher risk for electrolytes disorders from certain targeted anti-cancer therapies.

TH-PO093
Vemurafenib and Dabrafenib Related Renal Toxicities
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Background: Vemurafenib and dabrafenib, selective BRAF inhibitors have shown significant improvement in patient survival compared to standard therapy in V600 mutant metastatic melanoma. No cases of AKI have been reported with dabrafenib use. AKI has been recently reported in few case series with vemurafenib use. One case series included a patient who had a kidney biopsy demonstrating acute tubular necrosis as a potential mechanism of renal injury.

Methods: We reviewed the FDA Adverse Event Reporting System’s (FAERS) quarterly legacy data file from 3rd quarter of 2011 to 2nd quarter of 2014 for vemurafenib and 2nd quarter of 2013 to 2nd quarter of 2014 for dabrafenib. Vemurafenib and dabrafenib related renal adverse events data were extracted through formation of a query using FAERS assigned unique case identifiers. Search terms utilized were “renal insufficiency, elevated creatinine, renal failure, renal injury, proteinuria, renal impairment, blood creatinine increase, renal failure acute, low phosphorus, hypophosphatemia, hypercreatinemia, hypernatremia, hypokalemia, renal damage”.

Results: 132 cases of AKI were reported secondary to vemurafenib to the FAERS in the time frame reviewed. Eighty five patients were men and 47 women (p = 0.01). Average of the men was 65 years and 59 years for the women (p=0.03). The cases are reported from around the world with France, USA and Germany having most of the cases. Fourteen cases of electrolyte disorders were reported (hypokalemia-6 cases and hyponatremia-8 cases). A total of 13 cases were reported of AKI from dabrafenib to the FAERS in the time frame stated above. Twelve patients were men. Average age of the men were 55 and 75 years for women (p = 0.0022). Eight cases of electrolyte disorders were reported (hypokalemia-2 cases and hyponatremia-6 cases).

Conclusions: While the FAERS reporting system is a crude database with scant demographic information, the number of cases reported of AKI is still alarming with the BRAF inhibitors. Vemurafenib appears to be more nephrotoxic than dabrafenib. This renal toxicity seems to be more prominent among male patients with melanoma. Dermatologists, oncologist and nephrologists need to be aware of this important toxicity.

TH-PO094
Protective Effects of Oral L-Arginine Supplement in Patients with Chronic Kidney Disease After Intravenous Contrast Media Injection: A Randomized Controlled Trial
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Background: Contrast-induced acute kidney injury (CI-AKI) is a common complication in hospitalized patients. Nitric oxide-signal transduction plays an important role in prevention of CI-AKI. L-Arginine is an amino acid involved in ammonia detoxification, and is well known as a precursor to nitric oxide, a key component of endothelial-derived relaxing factor.

Methods: A randomized, double blind, placebo controlled trial was done in CKD stage 3-4 patients undergoing computer tomography. Eligible patients were randomly assigned into two groups: arginine 3 g in 6 gelatin capsules orally per day, and placebo 6 capsules as the same manner for 3 days before contrast media injection. Serum cystatin C, creatinine, electrolyte, estimated GFR and urinary nitric oxide were measured at baseline and 48h after procedure.

Results: A total of 84 patients were screened. Sixty percent were male with mean age of 74 years. 27 patients in arginine group and 34 patients in placebo group were analyzed. There were no significant differences between the arginine and placebo groups regarding baseline demographic and biochemical characteristics, including baseline GFR (48.8 ± 8.8 mL/min/1.73 m2 versus 48.8 ± 7.5 mL/min/1.73 m2). The incidence of CI-AKI was 3.7% (1 patient) in the arginine group and 23.53% (8 patients) in the placebo (p = 0.036). No serious adverse event was detected in the both groups. There is a trend toward an increase in urinary nitric oxide difference in patients with CI-AKI.

Conclusions: This study indicated that oral L-arginine supplement before intravenous contrast media injection plus the standard hydration regimen can prevent CI-AKI in hospitalized patients with CKD stage 3-4.

TH-PO095
Decline in Estimated Glomerular Filtration Rate After Acute Kidney Injury: A Surrogate Endpoint? Morgan Grams, Yingying Sang, Josef Coresh, Shoshana Ballew, Kunihito Matushita, Tom Greene, Andrew S. Levey, Miklos Zsolt Molnar, Zoltan Szabo, Kamyar Kalantar-Zadeh, Csaba P. Kovesdy, Utah, Tufts, UTHSC, Linkoping Univ; UC Irvine; Memphis VA Medical Center.

Background: Often a transient condition, acute kidney injury (AKI) is not currently accepted as an endpoint for drug registration trials by the US FDA. We sought to determine whether an in-hospital AKI event is a strong enough endpoint to serve as an alternative endpoint in clinical trials of AKI prevention and/or treatment.

Methods: We evaluated 161,185 US veterans who underwent major surgery between 2004-2011. Post-surgical AKI was defined by the KDIGO creatinine criteria: decline in eGFR was calculated from pre-hospitalization value to two time-points post-discharge (60-days, 90-days) and related to ESRD and mortality using Cox proportional hazards regression.

Results: In-hospital mortality varied by AKI status, ranging from 1% for patients without AKI to 35% for those with dialysis-requiring AKI. An eGFR decline of 70% at 60-days was relatively frequent: 2.5%, 9.7%, 17.2%, and 28.6% in those with no AKI, Stage 1 AKI, Stage 2 AKI, and Stage 3 AKI, respectively. There was a graded relationship between eGFR decline at 60-days and risk of ESRD in persons both with and without AKI (Figure). Compared to stable eGFR/no hospital AKI, the adjusted hazard ratio (HR) of ESRD associated with a 30% decline at 60-days after AKI was 6.42 (95% CI: 4.8-8.7). Risks for mortality associated with eGFR decline were smaller: the HR for 30% decline 60-days after AKI was 2.62 (95% CI: 1.46-1.73). Risk relationships were similar at 90-days.

Conclusions: A 30% decline in eGFR from pre-hospitalization baseline to 60-days or 90-days after an episode of AKI may be an acceptable surrogate endpoint in trials of AKI prevention and/or treatment.
Creatinine Changes After Contrast: Chloride Poor versus Chloride Rich Solutions

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Background: There has been recent emphasis on utilization of chloride poor solutions for the prevention of acute kidney injury (AKI). The purported mechanism is the potential for chloride rich fluids to possibly impair renal blood flow. Similarly, exposure to intravenous radiographic contrast is known to induce renal vasoconstriction. Given these findings, the objective of this project was to examine the effect of chloride rich versus chloride poor intravenous (IV) fluids on the change in serum creatinine occurring after IV contrast administration.

Methods: This project was performed under an IRB-approved Honest Broker Protocol. Retrospective data was obtained from patients receiving IV contrast over a 4 week period. Variables collected included: age, race, gender, type of contrast procedure, baseline creatinine, creatinine at days 1 and 2, and all intravenous medications. Chloride rich solutions (normal saline) and chloride poor solutions (sodium bicarbonate, Plasmalyte, and Lactated Ringers) were identified. Multivariate linear modelling was used to examine the primary endpoint of change in creatinine at day 2 relative to baseline (delta creatinine).

Results:

<table>
<thead>
<tr>
<th></th>
<th>Cl Poor(N=22)</th>
<th>Saline(N=220)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62±11.6</td>
<td>58±16.8</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>6(27.3%)</td>
<td>129(54.5%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Caucasian</td>
<td>16(81.8%)</td>
<td>172(78.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Catheterization</td>
<td>2(9.1%)</td>
<td>64(5.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline Creatinine</td>
<td>1.38±0.88</td>
<td>0.94±0.49</td>
<td>0.003</td>
</tr>
<tr>
<td>Delta Creatinine</td>
<td>0.09±1.00</td>
<td>-0.06±1.37</td>
<td>NS</td>
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</tbody>
</table>

Multivariate analysis Delta Creatinine Chloride rich verse Cl poor p-value

Saline -0.370 0.000

The change in creatinine after IV contrast in the chloride rich group, after adjusting for all variables including baseline creatinine, was 0.37±0.09 lower than in the chloride poor group (p=0.000).

Conclusions: Patients receiving chloride rich IV solutions appeared to have a significantly lower change in serum creatinine after administration of IV contrast compared to patients receiving chloride poor solutions. On this basis, more investigation is needed on chloride poor solutions to fully define the most appropriate utilization.

Renal Cortical Necrosis following Postpartum Hemorrhage: A Case Series

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Background: Pregnancy-related renal cortical necrosis induces severe kidney damage and may thus result in end stage renal disease. Although this obstetrical complication had virtually disappeared in high-income countries, we noted new cases in France during the past few years, all in the aftermath of a postpartum hemorrhage.

Methods: We retrospectively identified 18 patients from 5 French departments of Nephrology who developed renal cortical necrosis following postpartum hemorrhage between 2009 and 2013. Obstetrical and renal features, therapeutic measures, and renal outcome were studied. In order to identify prognostic factors for renal outcome, we stratified the analysis according to the estimated glomerular filtration rate at 6 months postpartum: <15ml/min or dialysis-dependent (Gp1) versus >15ml/min (Gp2).

Results: All patients had a severe postpartum hemorrhage (mean blood loss: 2.6±1.1L). Hemodynamic instability and disseminated intravascular coagulation were reported in 5 and 11 patients, respectively. All had a rapid onset of acute kidney injury and required hemodialysis. Diagnosis of renal cortical necrosis was performed 4 to 53 days following delivery. At 6 months post-partum, 8 patients remained dialysis-dependent and none recovered normal renal function. Retrospectively, the severity of the initial presentation was comparable between the Gp1 (n=9) and Gp2 (n=9) groups. Only the maintenance dose of tranexamic acid treatment was significantly more prolonged in the Gp1 patients (7.1±4.8 hours versus 2.9±2.4 hours, p<0.01).

Conclusions: The pejorative outcome of pregnancy-related renal cortical necrosis seems darkened by a prolonged use of tranexamic acid. In a setting of gravid endothelium, disseminated intravascular coagulation and concomitant use of fibrogens, we speculate that the combination of this fibrinolytic drug due to acute kidney injury might facilitate the uncontrollable clotting in renal cortex.

Intermittent Hemodialysis (IHD) versus Sustained Low Efficiency Dialysis (SLED) for Lithium Toxicity: A Case Series

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Background: Severe lithium toxicity is a medical emergency requiring hemodialysis when patients present with toxic levels (above 2.5mmol/L) and/or are symptomatic. This case series describes two pediatric patients who presented with severe lithium toxicity, one who was treated with intermittent hemodialysis (IHD) and the other who was treated with sustained low efficiency hemodialysis (SLED). We report a successful single use of SLED in a pediatric patient with lithium toxicity without the need for further dialysis.

Methods: A 16 year old female with history of depression was admitted to the Pediatric ICU after ingestion of multiple medications as a suicide attempt including lithium carbonate extended release 300 mg tabs. The patient was started on continuous CVVHDF initially to prevent hemodynamic instability requiring multiple vasopressor agents. CVVHDF was initiated when the patient’s lithium level was 0.62mmol/L and it was continued for 12 hours. Eighteen hours after cessation of CVVHDF, the lithium level rebounded to 2.5mmol/L and conversion to intermittent hemodialysis (IHD) was required for 2 hours. In addition, clinical IHD, lithium level decreased to below 1mmol/L when dialysis was discontinued. A 12 year old male with history of bipolar depression presented with lithium level of 4.0. Sustained low efficiency dialysis (SLED) was done for 8 hours until lithium level was below 1.0. After SLED was discontinued the rebound lithium level peaked at 1.4 and the neurologic symptoms resolved, indicating no further dialysis was needed.

Conclusions: SLED is an effective modality for lithium clearance and may reduce the total duration needed for IHD due to less rebound of lithium level.

Funding: NIDDK Support, Private Foundation Support
TH-PO100
Demographic Characteristics of Acute Kidney Injury and Utilization of Continuous Renal Replacement Therapy with Extracorporeal Life Support in Adult Patients Christopher Hebert, Brain Lima, Britton Blough, Avery Smith, Omar Hernandez. Dept of Internal Medicine, Div of Nephrology, Baylor Scott and White Health Care System, Dallas, TX.

Background: Extracorporeal life support (ECLS), also known as extracorporeal membrane oxygenation (ECMO) has been used over the last 40 years to help manage patients with severe cardiovascular or respiratory illnesses. Acute kidney injury is a very common complication in this particular patient population as is the need for renal replacement therapy. Much of the success and experience related to extracorporeal therapies has been limited to neonatal and pediatric populations. More recent data suggests that centers who perform a higher volume of ECMO cases have better outcomes. This study presents a demographic assessment of the first 199 cases of ECMO utilization over the last 36 months along with outcomes, specifically related to acute kidney injury.

Methods: We collected data for review of the first 199 cases of patients treated with ECLS at Baylor Scott and White Health Care System since July of 2012. We examined the patient demographics, type of ECLS, indication, location, comorbidities, incidence of acute kidney injury by RIFLE criteria and need for renal replacement therapy. Specific outcome measurements we looked at were overall survival, ability to wean from ECLS or bridge to transplant, withdrawal of care, need for long term dialysis, and death.

Results: In our ECMO program, 144 patients were male (72%) and 56 were female (28%). Regarding the types of ECLS, 136 were VA ECMO, 61 were VV ECMO and there were 2 RVADs. The main indications for ECLS were Cardiac in 129 cases, pulmonary in 63 cases, and 8 were ECPR. There were 61 patients who required CRRT. The majority of these were VA ECMO (41 patients) and the rest were VV ECMO (20 patients). A total of 129 patients were weaned from ECLS, 92 of which survived to discharge. Survival was worse in patients with AKI, overall survival on ECMO was 64.5% versus 36% for those on CRRT with AKI.

Conclusions: Our data set is fairly consistent with ELSO registry numbers. AKI appears to impact mortality in similar fashion. We hope to gain insight into more prospective research regarding this unique patient population.

TH-PO101
Performance of Renal Replacement Therapy for Acute Kidney Injury in Adult Patients on Extracorporeal Life Support Christopher Hebert, Dept of Internal Medicine, Div of Nephrology, Baylor Scott and White Health Care System, Dallas, TX.

Background: Extracorporeal life support is being used more commonly in adult patients with severe cardiovascular and respiratory illnesses. Acute kidney injury requiring renal replacement therapy is a very common complication in this patient population. Much of the data regarding the technical aspect of these concurrent procedures has been limited to neonatal and pediatric patient populations. We sought to examine the most efficient and effective ways to deliver renal replacement therapy in conjunction with extracorporeal life support.

Methods: Between July 2012 and March 2015, our institution performed 200 cases of extracorporeal life support. Of these cases, 61 required renal replacement therapy. Individual decisions regarding timing of initiation of renal replacement therapy and specific modality were based on physician discretion regarding other patient comorbidities, type of ECMO, and overall goals of care. Data was then collected on cases that faced specific complications with respect to the technical aspect of performing renal replacement therapy. Our institution utilized the NNxStage System One dialysis machine, and the Macquet Rotaflow or Caritrophe ECMO machine.

Results: The most common and effective way to perform continuous renal replacement therapy was to place the arterial line after the pump in the circuit, and return the blood before the oxygenator in the circuit. This minimized the risk of potential thrombosis to the patient and circuit clotting. Machine alarms would have to be interpreted in light of circuit position, and often had to be overridden. These included positive arterial pressures, high venous pressures, and arterial blood flow during ECMO “chattering”, and high chamber pressures.

Conclusions: Continuous renal replacement therapy can easily be safely and effectively implemented into almost any extracorporeal life support system circuit. There are technical challenges with each type of machine, that can be circumvented through a thorough understanding of each circuit. A good understanding of ECMO and CRRT allows teams to troubleshoot a different set of challenges than traditional CRRT. We hope to evaluate this patient population in a more standardized fashion with respect to interventions and outcomes in future studies.

TH-PO102
Prescribed versus Delivered Dose of Continuous Veno-Venous Hemodialysis in a Non-Study Population Aqsa F. Rahman, Majid A. Khan, Akshar N. Patel, Krystal Hunter, Lawrence S. Weisberg, William D. Sirover, Christopher B. McFadden. Nephrology, Cooper Univ Hospital, Camden, NJ.

Background: Critically ill patients requiring continuous renal replacement therapy (CRRT) experience high mortality rates. In randomized studies, intensification of CRRT by increasing effluent volumes from 20 to 35 ml/kg/hr did not improve survival. These studies ensured achievement of prescribed dose. We evaluated how often a subject achieves the prescribed dose in a non-study population.

Methods: We conducted a retrospective, observational cross sectional study and examined the electronic medical records (EMR) of subjects receiving CRRT. An automated, real time wireless link from the dialysis machines to EMR, contained data on the CRRT settings and hourly effluent volumes. With this data we calculated percentages of prescribed dosages achieved and compared subjects who did or did not achieve the prescribed dose. Access problems, procedures, electrolyte disturbance or no clear reason documented were investigated as variables in subjects not achieving prescribed doses. Pearson Chi Square or Fisher exact tests were used to compare dichotomous, and Independent t test or Mann Whitney U tests were used to compare continuous variables.

Results: This study represents an analysis of 73 of a planned 90 subjects. We found that 14% subjects achieved 100% of prescribed dose, 53% achieved 80-99% and 33% achieved <80%. Mean prescribed dose was 25 ml/kg/hr and achieved dose was 20 ml/kg/hr. Access/Filter problems were present in 63.4%, imaging/procedure 12%, electrolyte imbalance 2% and no clear reason documented in 19.2% when goal dose was not achieved. Subjects in whom CVVHD was not interrupted achieved >96% of prescribed dose which was statistically significant (P<0.001) compared to 76.5% achieved in subjects that had interruptions.

Conclusions: In a non-study population the proportion of patients who do not achieve prescribed dose is very large. In order to achieve a dose of 20 ml/kg/hr effluent volume the prescribed dose may need to be significantly higher in a non-study population. Timely correction of access/filter problems is another area of focus which may need attention for better dose achievement.

TH-PO103

Background: Continuous renal replacement therapy (CRRT) is preferred modality of renal replacement therapy (RRT) in critical ill patients with acute kidney injury (AKI). However, it has several disadvantage such as high cost and risk of continuous anticoagulation. Therefore, initial application of CRRT and subsequent conversion to intermittent hemodialysis (IHD) could be practical. However, there has been no standard criteria for optimal timing of conversion to IHD in patients receiving CRRT. The aim of this study was to develop a predictive model for successful conversion of CRRT to IHD.

Methods: This case-control study was conducted by retrospective chart review. We identified 513 adult patients who received CRRT at least 24 hours and then IHD subsequently in ICU between April 2009 and February 2014. Failure in conversion to IHD was defined when CRRT was re-applied within 72 hours after CRRT stop, and 83 out of 513 patients corresponded failure criteria: failure group. Equal number of patients were selected randomly from remaining 430 patients: success group.

Results: Cardiovascular (CV) SOFA score and neurologic (NR) SOFA score at CRRT stop day were only two independent predictors of conversion failure. The risk of failure was discriminated between score 0.1 and score 2.4 for both CV and NR SOFA. CV SOFA score 2.4 was associated with 13 fold increased Odds ratio for failure (95% C.I. 4.6 - 38.3, 17.9% patients). NR SOFA score 3 was associated with 1.5 fold increased Odds ratio for failure (95% C.I. 2.6 - 11.4, Ref 0-1). Final prediction model included CV SOFA and NR SOFA weighting CV SOFA (≥ 2) as 2 points and NR SOFA (≥ 2) as 1 point. Risk score ranged from 0 to 3 points (0; 47%, 1; 29%, 2; 13%, 3; 11%). The performance of this model was acceptable with area under the receiver operating characteristic curve of 0.79 (95% C.I. 0.77-0.86).

Conclusions: The prediction model might provide an objective criteria for conversion to IHD in patients receiving CRRT and contribute to establish cost-effective protocol of RRT for AKI in critical ill patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

113A
Results: Sepsis was the main cause of AKI (57%). Overall mortality was 58%. The median urine output fluid balance (FB) during dialysis was -3% (IQR -20% to 8%) in survivors and +164mL among the survivors. There were 114 oliguric individuals. Independent risk factors for death in multivariate analysis were chronic obstructive pulmonary disease (COPD) (OR 3.07, 95% CI 1.01 to 9.32, p = 0.047), liver cirrhosis (OR 4.47, 95% CI 1, 77 to 13, p = 0.002), hemodilutional anemia (OR 6.19, 95% CI 1.83 to 20.93, p = 0.003), oliguria (OR 3.01, 95% CI 1.43 -6.32, p=0.004), positive cumulative FB during dialysis (OR 1.13, 95% CI 1.06 to 1.20, p<0.001) and time between ICU admission and beginning of CVVHD (OR 1.13, 95% CI 1.01 to 1.25, p<0.039). Among survivors, nearly 30% were discharged dependent on dialysis and, among those who were discharged out of dialysis, there was a statistically significant reduction in glomerular filtration rate in relation to admission (81 vs 50mL/min/1,73m², p<0.001). The SAPS 3 score at ICU admission showed unsatisfactory performance as a predictor of death in patients with AKI (AUC=0.637, 95% CI 0.57 to 0.717).

Conclusions: We found an association between positive FB during dialysis, oliguria, late starting dialysis and death in patients with AKI submitted to CVVHD. Others factors related to death were COPD, hematologic malignancy and liver cirrhosis.

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TH-PO107
The Impact of Dialysis-Dependent Acute Kidney Injury on Mortality in Myeloma: Findings from England Hospital Episode Statistics Data
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Background: In patients with myeloma, severe acute kidney injury requiring in-hospital dialysis treatment is a life-threatening complication. However the current incidence and mortality risk associated with dialysis is unknown. We aimed to examine the incidence and impact of dialysis on the survival of patients with first diagnosis of myeloma.

Methods: We utilized hospital episode statistics to analyze data from 36,348 patients with a first diagnosis of myeloma in England from April 2006 to March 2014. We examined the incidence and impact of in-hospital dialysis on overall survival, by year of presentation. Cox proportional outcome models were used to adjust for age, gender, area socio-economic deprivation, ethnicity and comorbidities.

Results: We identified 1,240 (3.4%) patients who received dialysis treatment within 28 days of a diagnosis of myeloma. In Kaplan-Meier analysis patients who did not receive dialysis had better median overall survival (3.0 years; interquartile range [IQR] 0.7-8.1) than patients who received dialysis [1.4 years, IQR 0.2-4.6]. From 2006/7 to 2010/11 survival improved from 2.6 years [IQR 0.6-7.7] to 3.3 years [IQR 1.0-not reached] for patients who did not receive dialysis and 0.6 [IQR 0.1-2.7] to 1.2 years [IQR 0.4-4.0] for those who received dialysis respectively. Compared to patients who did not receive dialysis, those who received dialysis were more likely to be older, male, and less socio-economically deprived.

Conclusions: Dialysis is a major independent risk factor for increased mortality in patients with myeloma; the overall survival of patients with myeloma requiring dialysis is improving.

TH-PO108
Predictors of Survival in the ICU Patient on Continuous Veno-Venous Hemofiltration (CVVH)
Amina Saqib, Jwairat R. Modi, Gautam Kishore Valecha, Abdul H. Siddiqi, Suzanne E. Sayegh. Medicine, Staten Island Univ Hospital.

Background: In the ICU setting, Acute Renal Failure is a part of multiple organ dysfunction syndrome with mortality in these patients ranging from 28%-90%. Continuous Veno-Venous hemofiltration (CVVH) is most commonly used for renal replacement therapy in ICU’s. The objective of this study is to describe demographic characteristics and to establish an association between these characteristics and variables that define the severity of illness and in-hospital mortality outcomes of patients undergoing CVVH.

Methods: Medical records of patients who underwent CVVH from January 2007 to December 2013 in the intensive care at our institution were analyzed. Chi square test was done for categorical variables. Descriptive analysis was used to identify demographic data. The overall mortality was 75.22%. 49.3% of patients required ventilatory support. Acute respiratory failure requiring mechanical ventilation was associated with significantly increased mortality, 76.74% vs 40.0% (p=0.04) in patients who did not require mechanical ventilation. Septic Shock was the most common reason for ICU admission, 71.2% followed by post-operative admissions at 18.8%. The most common indication for CVVH was ATN (63.9%) followed by hyperkalemia (57.0%). However, CVVH for metabolic acidosis was associated with highest mortality at 81.06 % vs. 67.02% in patients who underwent CVVH for other indications. Poor APACHE II scores were associated with higher mortality. Scores ranging from 0-24 were associated with an overall mortality of 49.9% whereas scores between 25-50 were associated with an overall mortality of 77%.

Conclusions: This observational study in patients undergoing CVVH in an ICU setting revealed that patients presenting with worse baseline APACHE II scores had poor in-hospital outcomes. CVVH initiation for metabolic acidosis and use of mechanical ventilation was associated with higher mortality. There are no established guidelines for use of CVVH. This study may aid in delineating the group of patients who may benefit the most from use of CVVH and help us in more judicious use of health care resources.
Clinical Effectiveness of Diuretics following Continuous Renal Replacement Therapy

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Background: There is no consensus regarding diuretics administration in acute kidney injury (AKI) in patients weaning from continuous renal replacement therapy (CRRT). The effect of diuretics on the clinical course of critically ill patients with AKI was analyzed focusing on urine output and renal recovery following CRRT. In addition, we tried to identify the most optimal administration method of diuretics.

Methods: Table of 1213 adult patients who survived more than 3 days after discontinuing CRRT between September 2009 and December 2014 were included. Changes in renal function and urine output as well as the prescription of diuretics during the 3 days after discontinuation of CRRT were retrospectively analyzed. Patients were categorized depending on re-initiation of RRT within 3 days.

Results: There was no difference in baseline characteristics among all groups. CRRT cessation group had greater urine output after discontinuation of CRRT compared with other groups. Overall, patients who were treated with diuretics (diuretics subgroup) showed greater urine output than patients without diuretics (control subgroup) after cessation of CRRT and there was no difference in the degrees of serum creatinine elevation between control and diuretics subgroups. In CRRT cessation group, continuous infusion of furosemide showed greater urine output compared to other administration methods. However, serum creatinine increased significantly compared to other methods when the infusion was continued for more than 1 day.

Conclusions: Diuretic therapy following CRRT increases urine output significantly without causing significant deterioration of renal function. Compared with other methods using diuretics, continuous infusion of furosemide increases urine output significantly, but it takes time to achieve further improvement for more than 1 day. Our study suggests that diuretics in patients who had received CRRT may be clinically useful.

The Prognostic Value of Volume Status Assessment by Bioelectrical Impedance Analysis and Lung Ultrasound on Mortality in Septic Acute Kidney Injury Patients Undergoing Continuous Renal Replacement Therapy

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Background: Volume overload affects clinical outcome in patients with acute kidney injury (AKI). However, the significance of various methods to evaluate volume status has not been fully evaluated. Therefore, the prognostic value of volume status assessment measured by bioelectrical impedance analysis (BIA) and lung ultrasound (US) on mortality was investigated in septic AKI patients requiring continuous renal replacement therapy (CRRT).

Methods: Septic AKI patients requiring CRRT between April 2014 and February 2015 at Yonsei University Health System were included. Surrogates of volume status were 1) percent of body weight change between CRRT initiation and admission day, 2) over-hydration (OH)/extracellular water (ECW) measured by BIA, and 3) B-lines measured by lung US. Prognostic values of surrogates of volume status for 28-day mortality were evaluated.

Results: Among the 36 enrolled patients, 19 (52.8%) patients died during the follow-up duration. The mean percentage of weight change and OH/ECW measured by BIA was 5.3±20.7% and 0.3±0.1L/L. The median number of B-lines counted by lung US was 6 (interquartile range, 4-10). OH/ECW was significantly correlated (r=0.39, p=0.02) with 48-hour fluid balance before CRRT initiation, while the number of B-lines was not. Kaplan-Meier analysis showed that 28-day mortality was higher in patients with the highest OH/ECW tertile compared to patients with lower OH/ECW values (P=0.02). Percent of weight change and the number of B-lines were not significantly associated with 28-day mortality (P=0.04 and P=0.45, respectively). Multivariate Cox proportional hazard regression analysis showed that higher OH/ECW was an independent risk factor for 28-day mortality (p=0.02 respectively).

Conclusions: Higher OH/ECW measured by BIA was an independent risk factor for 28-day mortality after adjustment of confounding factors (HR=3.83, 95%CI=1.04-14.03, P=0.04).

The Relationship Between Hypophosphatemia and Outcomes During Two Different Intensities of Continuous Renal Replacement Therapy

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Background: To identify risk factors for development of hypophosphatemia in patients treated with two different intensities of continuous renal replacement therapy (CRRT) and to determine if hypophosphatemia is associated with increased mortality.

Methods: We performed retrospective analysis of data collected from 620 patients. We allocated patients to two different intensities of CRRT (more than or less than 40 mL/kg/hour of effluent generation) and obtained daily measurement of serum phosphate levels. We then obtained total 1000 phosphate measurements in one day, 2 and 1 and identified 49 patients (8%), 93 patients (15%) and 142 patients (23%) with hypophosphatemia. With lower intensity CRRT, there were 23 episodes of hypophosphatemia/1000 patient days, compared with 83 episodes/1000 patient days with higher intensity CRRT (p<0.01).
In the Acute setting, the administration of Heparin may be contra-indicated for a number of reasons – pre-bloody, post-surgery, post-stroke, Gastro-intestinal deranged clotting factors, and so on. Care must then be taken to avoid loss of blood in the dialysis circuit.

**Methods:** Observational study looking at the effectiveness of traditional anti-coagulation strategies such as saline flushes in acute haemodialysis had shown increased frequency of blood circuits lost on dialysis. Over a period of 4 weeks, we used pre-dilution haemodiafiltration instead of conventional post-dilution haemodiafiltration. This modality dilutes the blood just before it passes through the dialysis filter. As the majority of the clotting starts as the blood passes along the filter membranes, diluting the blood at this point would theoretically reduce the amount of clotting.

**Results:** By using this technique, we were able to reduce the number of clotted circuits from 100% down to just 30%, with only 10% leading to loss of the entire blood circuit. There was no significant change in the effectiveness of the treatment, and no significant increase in the cost of the treatment provided.

**Conclusions:** Over the next few months, we were able to improve on these outcomes still further, by optimizing the variables, and in some cases, adding saline flushes in addition to the pre-dilution HDF. Having used this technique now for some hundreds of treatments, we have reduced the number of blood circuits lost to all but zero. Hence this has become a highly effective technique which has drastically improved patient outcomes, reduced the need for blood transfusions, and saved money without cost implications.

**TH-PO116**

**Nationalwide Use of Hemodialysis and Other Extracorporeal Therapies in Poisoned Patients, 2006-2013**

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**Background:** Nationwide use of extracorporeal therapies (ECT) in poisoned patients has not been characterized since 2005. The purpose of this study was to review the use of hemodialysis (HD), hemoperfusion (HP), and other ECT in poisoned patients throughout the United States from 2006 until 2013.

**Methods:** The National Poison Data System (NPDS) was queried for all poisoning cases reported to U.S. poison centers between 2006 and 2013 where HD, HP, or other ECT was performed. Data analyzed included demographics and geography, clinical characteristics, exposure chronology, and reported substances used by patients. The annual prevalence of each therapy per 1,000,000 human exposures was evaluated. The top 30 substances reported among all deaths were characterized among patients receiving HD.

**Results:** There were 18,252 patients who received ECT, of which 17,902 (98.0%) received HD, 257 received HP, and 214 received some other ECT. The patient population was predominantly 40-59 years of age (45.0%). Poisonings were acute in 56.7% of patients. The prevalence of ECT (per million human exposures) was 865 in 2006 versus 1,140 in 2013. The substances most frequently identified among patients receiving HD included ethylene glycol (n=3,828), lithium (n=3,385), sedatives (n=2,711), salicylates (n=2,352), and opioids (n=1,783). Overall, 9.4% of patients receiving ECT for poisoning died. The three leading substances reported among all deaths included acetaminophen (22.1%), opioids (18.3%), and sedatives (15.3%).

**Conclusions:** The use of HD in the management of poisoning has continued to increase. While ethylene glycol, lithium, and salicylates remain frequent indications for dialysis, HD seems to be used more often in a supportive role as well given the number of patients treated for opioid and sedative poisoning. We were not able to distinguish the use of intermittent HD versus continuous renal replacement due to database limitations. Hemoperfusion has continued to be rarely used.

**TH-PO117**

**Dialysis Treatment Options for Acute Kidney Injury in the Canadian Intensive Care Unit: A Systematic Review and Cost-Utility Analysis**

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**Background:** Up to 67% of all patients admitted to the intensive care unit (ICU) will develop acute kidney injury (AKI). Treatment for these patients is very expensive. For example, in the United States, the incremental health care costs attributed to AKI are upwards of 10 billion USD per year. In this health economic analysis, we simulate the cost per quality-adjusted life year (QALY) gained comparing three dialysis treatments up to 67% of all patients admitted to the intensive care unit (ICU) will develop acute kidney injury (AKI). Treatment for these patients is very expensive. For example, in the United States, the incremental health care costs attributed to AKI are upwards of 10 billion USD per year.

**Methods:** A decision analytic model, with a 1-year time horizon, was developed to compare the incremental cost per QALY gained for the three dialysis modalities. The model used a public payer perspective, with Canadian costs and relevant utility values obtained through systematic searches of the literature. A systematic chart review of randomized controlled trials was performed to determine the clinical parameters for the model, including the probability of in-hospital death, dialysis dependence and death at one year post-discharge. One-way sensitivity analyses were performed by varying all parameters by +10% and -10%.

**Results:** The incremental cost per QALY gained for SLED compared to HHD was $68,501. Compared to HHD and SLED, CRRT was extensively dominated (i.e. it is more
cost-effective to provide SLED to some of the eligible patients and IHD to the remaining patients than to provide CRRT. The sensitivity analyses showed that the results are generally robust across a wide-range of parameter values.

Conclusions: Similar to previous economic evaluations, these results suggest that CRRT is not cost-effective compared to IHD. A novel finding is that SLED may be cost-effective depending on the willingness-to-pay threshold.

TH-PO118
Efficacy of Acute Peritoneal Dialysis (PD) Over Sustained Low Efficiency Dialysis (SLED) in Critically Ill ICU Patients with Acute Kidney Injury – A Comparative Study
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Background: Acute peritoneal dialysis (PD) has largely been replaced by continuous renal replacement therapies (CRRT) and sustained low efficiency dialysis (SLED) in critically ill ICU patient.

Methods: Patient admitted in the ICU with acute kidney injury and multiple organ dysfunction were included in the study irrespective of the etiology of renal failure. Patients were randomly divided in to two group. Group A, PD and group B, SLED were respectively administered. Primary outcomes were correction of urea, metabolic acidosis, fluid overload, dyselectrolytemia, and mortality. Secondary outcomes were improvement in sensorium, hemodynamic stability, ICU length of stay, cost of treatment and duration of mechanical ventilation.

Results: 116 were enrolled in this study. The mean age was 41.35±11.56 years in group B while it was 45.87±13.45 years in group A. Vascular access was 76.90±19.07 hours in PD and 70.9±19.34 hours in SLED group respectively. Correction of urea was similar in both the groups (81% v 76%). Renal function recovery (21% vs 24%) were also similar. Acute Physiology and Chronic Health Evaluation II score was similar (25.8±5.7 vs 23.9±7.9) and also the duration of ventilatory support (11.9±3.73 vs 13.5±8.78 days). Cost of treatment was much cheaper in the PD group.

Conclusions: Acute PD still remains as a viable alternative to SLED in critically ill patients in low cost setting. Advantages are its low cost, ease of administration, needs less expertise and its metabolic and clinical outcomes are not inferior to SLED.

TH-PO119

Background: The K/DOQI Guideline for Acute Kidney Injury (AKI) recommends a minimum single pool Kt/V of 1.2 for patients with acute renal failure. As it is not feasible to measure Kt/V on a daily basis, the K/DOQI guideline recommends using urea reduction ratio (URR) to assess the adequacy of dialysis. However, URR fails to provide sufficient correlation with Kt/V.

Methods: Using data from IHD and CRRT in the ATN Study, values of URR were plotted against Kt/V. We determined URR thresholds corresponding to Kt/V values ≥ 1.2, 1.3, and 1.4 and generated receiver operating characteristic (ROC) curves at each level of Kt/V to identify optimal URR thresholds.

Results: There was tight correlation between URR and Kt/V (figure).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: PD is a viable treatment modality in low-resource settings and decreases mortality rates in the course of AKI to the levels seen in developed countries. The frequency of PD-related peritonitis is low and does not affect treatment outcomes.

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TH-PO122
Pulse High Volume Hemofiltration versus Coupled Plasma Filtration Adsorption in Septic Shock – A Pilot Randomized Study
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Background: Acute kidney Injury (AKI), a frequent complication in critically ill septic patients is an independent risk factor for increased mortality, particularly when patients require renal replacement therapy (RRT). High Volume Hemofiltration (HVHF) and Coupled Plasma Filtration Adsorption (CPFA) have shown potential improvement in hemodynamics; however, no studies have compared these two methods. Our aim was to compare the hemodynamic effects of HVHF and CPFA in septic shock patients undergoing Continuous Renal Replacement Therapy (CRRT).

Methods: A cross-over study enrolling pts with septic shock undergoing CRRT. Pts were treated with pHVHF+CVVH on Day 1 and CPFA+CVVH on Day 2. HVHF was performed for 8-10 hrs with a replacement fluid rate (Qr) of 85 ml/kg/hr. CPFA was performed for 8-10 hrs using Mediasorb (Bellco Italy) with a maximum plasma flow rate of 15%. CVVH was performed for the rest of the day with a Qr of 35 ml/kg/hr. Both HVHF and CVVH used polysulfone filters. The primary endpoints were changes in vasopressor requirement (expressed as vasopressor score, VS), in noradrenaline (NA) dose (mg/kg/min), and in mean arterial pressure (MAP) before and after pHVHF and CPFA. These values were compared using nonparametric paired tests.

Results: 8 pts (5M/3F, 70.5 yr, SOFA 12.5, SAPS II 69.5) VS and NA dose were significantly decreased after CPFA (p=0.04). These endpoints were not significantly different after pHVHF (p=0.22). There was no significant change in MAP after pHVHF (p=0.13). When CPFA and pHVHF are compared between each other, the change in VS and NA dose becomes NS (p=0.22). There was no significant change in MAP with either pHVHF or CPFA.

Conclusions: The data provide no evidence for a difference in hemodynamic effects between pHVHF and CPFA in patients with septic shock undergoing CRRT.

TH-PO123
Polymyxin B Hemoperfusion and Renal Outcomes in Septic Shock: A Propensity-Matched Analysis
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Background: Septic acute kidney injury (AKI) is a common ICU complication with high mortality. Only supportive management is available at this time. Hemoperfusion with Polymyxin B fiber column (PMX) reduces blood endotoxin levels & vasopressor requirement, & increases blood pressure. These may improve renal perfusion & decrease renal tubular cell apoptosis. We hypothesized that PMX may improve renal outcomes in sepsis.

Methods: Single center retrospective study of 697 septic shock patients. Patients were treated with PMX (n=377) if they met all criteria: SIRS, documented/suspected infection, vasopressors despite adequate fluid resuscitation, organ failure, Gram(-) organism &/or elevated endotoxin levels; 360 pts were treated with standard medical therapy (SMT) alone. PMX patients were matched 1:1 with SMT patients, based on a propensity score for the likelihood of receiving PMX. PMX possibly reduces proapoptotic activity of septic plasma on renal tubular cells. A systematic review was performed to assess renal outcomes when PMX is used in sepsis.

Results: A total of 18 studies (n=591 pts) with renal outcomes were identified. In 6 RCTs & 1 non-RCT, patients were treated with either PMX+standard medical therapy (SMT) (n=188) or SMT alone (n=136). In 10 cohort studies 267 pts were treated with PMX+SMT. The following renal outcomes were reported: need for RRT (n=4 studies), serum Cr &/or CrCl (n=10), BUN (n=4), urine output (n=5), urine protein/biomarkers (n=6). One study reported severe AKI (Failure) in 0/5 PMX and 1/8 SMT patients at 72h. Pooled analysis showed no significant difference for Cr after PMX was not significant but there was an increase in urine output by 45 ml/hr (95% CI 15.74) after PMX.

Conclusions: Based on published studies, PMX has no significant effect on RRT need or AKI patients with septic shock when added to SMT, although urine output appeared to improve post-PMX. These data provide evidence for scientific equipoise for a randomized clinical trial to address this question.

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Underline represents presenting author.
Four Hour Infusion Piperacillin-Tazobactam in CRRT Patients Is Associated with Improved Target Attainment Compared to 30 Minute Infusion

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Background: Sepsis is the leading cause of death in acute kidney injury. Dose adjustments to account for kidney failure and continuous renal replacement therapy (CRRT) may result in poor target attainment. Four hour infusion (EI) of beta lactams may result in improved target attainment compared to 30 minute infusion (SI). We conducted a retrospective observational study of piperacillin-tazobactam in patients receiving CRRT and compared predicted target attainment in a typical patient receiving EI or SI.

Methods: Piperacillin concentrations were measured in subjects at Cleveland Clinic (3 g q6 h, q8 h, or q12 h) SI; n=29) University of Alabama (2 g q6 h or q8 h, 3 g q8 h SI, n=25) and Vanderbilt University (3 g q6 h or q12 h, EI; n=14). A two-compartment pharmacokinetic model was fitted simultaneously to all data using nonlinear mixed effects regression in R. Target attainment was quantified as the fraction of the dosing cycle wherein piperacillin concentration was greater than 64 µg/ml. Target attainment for a typical patient was estimated using the population mean (fixed-effect) for each pharmacokinetic parameter.

Results: For EI versus SI in the two most common dosing patterns, 2 g q6 h and 3 g q8 h, target attainment was improved by 27% (95% CI: 19, 35) and 23% (95% CI: 18, 28), respectively.

Conclusions: Limits of the study include that it is solely observational, and that subjects in Cleveland and Birmingham were enrolled earlier than subjects in Nashville. These results characterize the typical patient in this population. Additional analysis is warranted to examine the sensitivity of our findings to population pharmacokinetic heterogeneity.

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Effects of Complement Factor H and Factor I Deficiency on Anti-MPO Induced Crescentic Glomerulonephritis in Mice

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Background: Complement alternative pathway (AP) activation plays a critical role in the pathogenesis of anti-neutrophil cytoplasmic autoantibodies (ANCA) crescentic glomerulonephritis (CGN). AP is negatively regulated by complement factor H (CFH) and factor I (CFI). Deficiency of either of these regulators results in uncontrolled complement activation with secondary depletion of C3, factor B and properdin. In this study, we investigate the effects of CFH and CFI deficiency in anti-MPO induced CGN in mice.

Methods: 9-11 wk-old CFH and CFI KO and WT B6 mice were injected with anti-MPO IgG and sacrificed at day 6 and kidney tissue was obtained for pathological examination, and IF staining with anti-C3 antibodies. Circulating C3 levels were determined by ELISA.

Results: At day 6 of anti-MPO treatment, all CFH-/– mice (n=5) developed much more severe CGN (mean 85% glomeruli with crescents) compared to the WT control mice (n=8, 11% crescents). In contrast, no CGN developed in CHI-/– mice (n=8). Glomerular C3 staining showed strong (score 4+) linear capillary wall staining in CHI-/– mice, whereas CHI-/– mice had weak (1.5+) mesangial staining. On day 0 and day 6 after anti-MPO treatment, the circulating C3 level had no significant differences in WT and CHI-/– mice (p=0.05) and substantially reduced in CHI-/– mice (p=0.001). In vitro neutrophil function assay showed that anti-MPO IgG caused similar activation of neutrophils from CHI-/–, CHI-/– and WT mice.

Conclusions: Absence of the CHI causes more severe anti-MPO induced CGN. This is probably because they have uncontrolled alternative pathway activation and sufficient glomerular capillary wall deposition of complement activation fragments to synergistically attract and amplify anti-MPO activated neutrophils. 2) CHI deficiency protects from anti-MPO CGN. This might be because of no glomerular capillary wall C3 deposition in the pathogenesis of anti-neutrophil cytoplasmic autoantibodies (ANCA) crescentic glomerulonephritis. Studies using short FH fragments suggested detrimental functional consequences of many disease-linked amino acid substitutions. The protein PsPc from Streptococcus pneumoniae hijacks host-derived FH in a complement- evasion strategy. Finding that PsPc(N-terminal region of PsPc) to wild-type (WT) FH was shown to enhance complement regulation implying that PsPc might restore useful levels of regulatory activity to disease-related variants of FH.

Methods: Overcoming technical hurdles to recombinant full-length FH production, two recombinant FHs, RSH3 and RSH5, were produced in Pichia pastoris. Using surface plasma meson resonance (SPR), binding of mutants to C3b, and their C3bBb decay-activating activities (DAA), were compared with WT FH. Mutants were also compared to WT FH in erythrocyte DAA and co-factor lysis assays. Measurements were repeated in the presence of PsPc.

Results: RSH3 decreased FH affinity for C3b and impacted negatively on both assays used to measure DAA as well as the haemolysis-based assay of co-factor activity. The mutant had WT-like abilities to bind C3b and decay C3b convertase on an SPR chip, but was impaired in cell-based assays, and especially in co-factor activity. PsPc enhanced both C3b binding and DAA on the SPR chip by both mutants and WT. The effects on PsPc on cell-based assays were less clear.

Conclusions: These studies with full-length FH imply that disease-linked substitutions in its C-terminal surface-recognition region (unique in those in the functionally critical portion of FH) have little effect on SPR-based assays performed on a non-native and hence, in effect, foreign surface. Whether the enhancing effects of PsPc on SPR-based assays can be replicated on host-cell surfaces has therapeutic implications and will be discussed in the light of ongoing measurements.

Reduced Renal Infiltration of Inflammatory Cells following Selective Endothelial Injury in Mice Deficient for C3, C3ar or C5ar

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Background: Complement regulation leads to kidney specific diseases such as C3 glomerulonephritis, thrombotic microangiopathy. However, data on the specific role of the complement system for local inflammation after endothelial cell injury (ECI) is limited. We here investigated the inflammatory response following site selective renal ECIs in mice deficient (–/-) for C3, C3ar or C5ar.

Methods: Renal ECI was induced by intra-arterial injection of Concanavalin(Ca/Ar)- anti-Cona in C3-/– and C3ar-/- mice (d=5, n=4), C3ar-/– (d=2; n=5; d=4), C5ar-/- (d=2; n=4; d=4; n=3) deficient and C57Bl/6 wild-type (wt) mice (n=5; n=4). Six wt mice served as sham control (ctr). Kidneys were harvested on day 2 or day 4. Multicolor FACS analysis was used to analyze immune macropheage (CD11b+CD11c+ (N)) and neutrophils (N) in the kidneys. Flow cytometry was performed with the following antibodies: CD11b+ F4/80+ GR1- CD11c- (M), GR1+ CD11b+ (N) and CD4+ CD8+ (T). Histology was used to analyze macrophages (MAC2, F4/80) and the ECI (CD31).

Results: Inflammatory cells were increased in C57Bl/6 mice 2 days after injury (C75Bl/6: M=1.3%; N=0.4; N=2.9%±0.1; T=0.8±0.3 vs. sham: M=0.1%±0.4; N=0.15%±0.09; T<0.2%±0.2; p<0.01). Compared to C57Bl/6 wt mice a reduced influx of macrophages (C3-/–: 0.3%; C3ar-/-: 0.4%±0.2; C5ar-/-: 0.5%±0.3) and neutrophils (C3-/–: <0.9%±0.7; C3ar-/-: 0.02%±0.09; C5ar-/-: 0.09%±0.01) were observed in C3ar-/- mice (C3ar-/-: 0.01%±0.01). CD8+ cells were reduced in C3ar-/- mice (C3ar-/-: 0.3%±0.3% of 0.01%±0.01).
Investigating a Pathogenic Role of C5a-C5aR1 Signaling in Diabetic Nephropathy Sib Min Tan,1 2 Vicki Thallas,1 Alison Skene,1 Richard J. MacIsaac,1,2,3 David A. Power,1,2 Mark E. Cooper,1 Elif Ekinç,1,2 Trent M. Woodruff,1 Melinda T. Coughlan1,2,3 Diabetic Complication, Baker IDI Heart & Diabetes Inst, Melbourne, VIC, Australia; 1Central Clinical School, Monash Univ, Melbourne, VIC, Australia; 2Endocrine Centre, Austin Health, Melbourne, VIC, Australia; 3Dept of Medicine, The Univ of Melbourne, VIC, Australia; 1Dept of Endocrinology & Diabetes, St. Vincent’s Hospital, Melbourne, VIC, Australia; 2School of Biomedical Sciences, Univ of Queensland, Brisbane, Australia.

Background: Complement 5a is a potent pro-inflammatory effector molecule. Although previous studies indicate a link between activation of the complement pathway and diabetic nephropathy (DN), the role of C5a and its receptor C5aR1 in DN has yet to be determined.

Methods: Complement signaling was characterized in type 1 diabetic (T1D) human, rat and mouse kidneys. C5a-C5aR1 signaling axis was inhibited by using the highly selective and potent C5aR1 antagonist, AcF-[OPdChaWR] (PMX53), in streptozotocin (STZ)-induced diabetic mice (0.5mg/kg/day, drinking water, 24 weeks, n=15 mice/group). C5 and C5aR1 were measured by qRT-PCR and immunohistochemistry. C5a and albumin were measured by ELISA.

Results: The expression of C5aR1 was increased in renal biopsies from patients with DN compared to healthy donor kidneys (4.2±1.3 vs 15.7±1.8; p<0.001, n=9-23). C5aR1 expression was upregulated in the renal cortex of STZ-induced diabetic rats (1.0±0.1 vs 1.5±0.2 fold change; p<0.05) and spontaneously diabetic Ins2-Akita mice (1.0±0.1 vs 1.4±0.1 fold change; p<0.05) compared to controls. Urinary C5a was increased in the diabetic rats (181±56 vs 115±297 ng/24hr; p<0.05) and Ins2-Akita mice (509±151 vs 133±248 ng/24hr, p<0.01) after 16 and 26 weeks of diabetes, respectively and was associated with albuminuria (p<0.05). Blockade of C5aR1 signaling with PMX53 attenuated albuminuria in STZ-induced diabetic mice when compared to vehicle-treated diabetic controls (26±8 vs 12±8, p<0.001).

Conclusions: The C5a-C5aR1 signaling axis is activated in human and experimental DN. A pilot study using PMX53 indicates that pharmacological blockade of C5aR1 is renoprotective in DN. Further studies are required to validate C5aR as a therapeutic target in DN.

Funding: Private Foundation Support

Identification of Glycosaminoglycans That Inhibit Specific Complement Pathways Dinner Talaga,1 Romain Vives,2 Marc Maj Seelen,2 Coen A. Steegeman,3 Jacob van den Born,3 Nephrology, UMC Groningen, Netherlands; 1Inst. for Struct. Biol., Univ of Grenoble, Grenoble, France.

Background: Complement has been shown to play a role in renal diseases, such as hemolytic uremic syndrome, C3 glomerulopathy and interstitial transplantation. It is now well known that heparin and other glycosaminoglycans (GAGs) reduce complement activation. However, no studies have yet compared the complement pathway specific inhibitory potential and their specificity for either of the complement pathways.

Methods: 72 GAG-based polysaccharides were tested for their complement inhibiting potential in the Wieslab complement screening assay. To pinpoint the inhibitory potential of GAGs on the lectin pathway (LP), the interference of GAGs on the binding of MBL to mannan and further C4 activation was tested. GAGs were also tested in the Wieslab-ficolin 3 screening kit to evaluate their effect on ficolin based LP activation. Direct binding of LP components to heparin was assessed by detecting MBL and MASP 1 & 2 after serum incubation to immobilized heparin-albumin.

Results: Unfractionated and partially desulfated heparin exhibit dose-dependent inhibitory potential of all three complement pathways, while small heparin and heparan sulfate (HS)-derived oligosaccharides show specific LP inhibition. These small heparin/HS derivatives do not interfere with the binding of MBL to mannan, but do inhibit the MBL-mediated activation of C4 and ficolin-3 mediated LP activation. We also find a dose-dependent binding of the MBL/MAST 1&2 complex to immobilized heparin-albumin, but not to albumin.

Conclusions: A large number of heparinoids block all three pathways of complement, however small heparin/HS oligosaccharides inhibit the LP of complement specifically, according to our data via the inhibition of the MASp enzymes. Our data also suggest that HS on cell surfaces and in basement membranes act as a docking platform for the MBL-MAST complex. We speculate that GAG-derived polysaccharides may be useful as MASp specific LP inhibitors.

Funding: 1No funding; 2Kidney Research UK

Anti-GM1 Antibody-Mediated Glomerular Injury Depends on Neutrophil Degranulation Dawn J. Caster,1,2 Eirk Korte,1 Liliane Hobeika,1 David W. Powell,1 Kenneth R. McLeish,1,2 1Medicine, Univ of Louisville, Louisville, KY; 2Dept of Veterans Affairs, Louisville, KY.

Background: Acute proliferative glomerulonephritis (GN) induced by ANCA or by anti-GM1 antibodies is neutrophil (PMN) dependent. In vitro studies suggested that endothelial injury induced by ANCA was dependent on PMN granule enzymes, not release of reactive oxygen species. To test the hypothesis that PMN degranulation is responsible for acute GN, degranulation was inhibited in an in vivo model of heterologous anti-GM1 disease in mice.

Methods: After collection of urine for baseline protein excretion, two groups of 10 C57Bl/6 mice received an intravenous injection of anti-rat GM1 (1.5 mg/25 g body weight) at time 0. One group also received an intravenous injection of a TAT-fusion protein, TAT-SNAP-23 (0.5 mg/kg body weight) at time 0 and 6 hr after it. We showed previously that TAT-SNAP-23 inhibited PMN degranulation in vitro and in vivo. At 24 hr urine was collected to measure protein excretion, and then mice were sacrificed and kidney tissue prepared for histology. Urine protein was measured as the protein:creatinine (ug/mg). Glomerular proliferation and mesangial expansion were graded on a 0 to 4+ scale.

Results: Baseline urine protein:creatinine did not differ between groups (18 ± 3 vs 22 ± 3.5, untreated vs TAT-SNAP-23 treated). Anti-GM1 induced a significant increase in proteinuria, and that increase was significantly inhibited by TAT-SNAP-23 treatment (376 ± 108 vs 73 ± 15, untreated vs TAT-SNAP-23 treated). By light microscopy there was no difference in proliferation (2.2 ± 0.2 vs 2.0 ± 0.2) or mesangial expansion 1.2 ± 0.3 vs 1.2 ± 0.2) between the two groups. By electron microscopy the degree of podocyte foot process effacement was reduced by TAT-SNAP-23 treatment.

Conclusions: We conclude that PMN degranulation plays a critical role in acute glomerular injury induced by anti-GM1 antibody deposition. We postulate that proteinuria may result from direct podocyte injury by PMN granule enzymes.

Funding: 1No NIH Support - NIAID, Veterans Administration Support

Shared and End Organ Specific Transcriptomic Networks in Skin versus Kidney Biopsies in Systemic Lupus Celine C. Berthier,1 Jasmine N. Stannard,1 Emily M. Myers,1 Lori Lowe,1 Tamra J. Reed,1 Sean Eddy,2 Matthias Kretzler,3 Michelle Kahlenberg.1 Univ of Michigan.

Background: Patients with subacute cutaneous (sCLE) lesions have higher risk of lupus nephritis (LN) compared to those with discoid (DLE) lesions. We hypothesized that renal flares may be triggered via a crosstalk between skin and kidneys. To determine the potential factors contributing to this increased risk, we used systems biology approaches to integrate the regulatory events occurring specifically in sCLE and DLE and compared with those in LN.

Methods: Formalin-fixed paraffin-embedded tissue from 8 normal, 22 DLE and 24 sCLE rash biopsies were analyzed via microarrays. Gene expression profiles from 22 class III + IV LN and 14 healthy microscedosed human renal biopsies (ERCBI) were compared.

Results: Analyses using Genomatrix and Ingenuity softwares highlighted a strong upregulation of IFNg associated pathways unique to DLE, and IL-4 a likely prominent DLE-specific regulator. Type I IFN signaling predominated in sCLE, with unique CD14, CCL2,20 chemokine expression. Respectively 415 and 435 genes were regulated in the same direction in the glomeruli of LN patients vs controls and in DLE and sCLE vs normal (q-value <0.01). The 85 genes regulated only in the LN glomeruli and DLE rashes represented a mainly down-regulated network highlighting MEP1B, CD1H and CD8a as main nodes. Top pathways were epithelial adherens junction signaling. The 105 genes specific to LN glomeruli and sCLE showed a mainly up-regulated network with ITGB2, CD40, SYK, TIMP1 as major nodes. Ingenuity top pathway was crosstalk between dendritic cells and natural killer cells, both of which may play a role in cutaneous and renal lupus pathogenesis.

Conclusions: DLE and sCLE have overlapping and unique transcriptional expression signatures which may guide therapeutic decisions and predict renal involvement. Further analysis of these specific profiles may identify the molecular crosstalk mechanism between skin and kidneys, as well as targets for novel therapy of cutaneous lupus lesions which could help to prevent or delay the renal disease. Our data suggest an inflammatory cell crosstalk between skin and kidneys in sCLE, which may not happen in DLE.

Funding: 1Other NIH Support - NAIMS R03-AR-066537

Molecular Determinants of Myeloperoxidase-ANCA Glomerulonephritis: Transriptionomic Analysis Across Three Species Maia Lindenmeyer,1 Hamid Al nuaimi,1,2 Peter W. Hewett,1 Viji Nair,1 Caroline O.S. Savage,1 Matthias Kretzler,2 Mark Alan Little,3 Klinikum Harlaching, Germany; 1Univ of Birmingham, United Kingdom; 2UMC Groningen, Netherlands; 3TCD, Ireland.

Background: Human myeloperoxidase (MPO)-ANCA vasculitis causes crescentic GN that results in glomerular damage. This has been modelled in rats (EAE) and mice (MEV), although it tends to resolve spontaneously in these models with little glomerular scarring. To investigate conserved and divergent molecular pathways involved in glomerular injury we analysed the glomerular transcriptome in EAV, MEV and humans with MPO-ANCA vasculitis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Methods: Glomeruli were microdissected from WKY rats immunised with MPO (ENA) or human albumin (control), from mice receiving anti-MPO (MEV) or BSA (control) antibodies raised in MPO-/- mice (n=5/group), and from patients with MPO-ANCA GN (n=7) and healthy controls (n=18). RNA expression was analysed on Affymetrix arrays. Differential regulation was assessed by ChipInspector and rodent/human orthologs identified using Homer software. Analysis of gene lists using co-citation at sentence level, the human network was used to overlap with mouse and rat networks using TALE. In 74 selected genes, regulation was confirmed by qPCR.

Results: 2812, 1725 and 783 glomerular genes were significantly associated with GN in humans, mice and rats respectively. We observed overlap between human and mouse in 675 (12.9%), human and rat in 134 (3.1%) and across all 3 species in 179 (2.9%) genes. Of these 179 genes, 135 (75.4%) were differentially regulated in the same direction and 44 (24.6%) in opposite directions. We identified 12 canonical pathways (p value <0.001) conserved between human and mouse, and 5 between human and rat.

Conclusions: The transcriptomic profile in MEV was more similar to human disease than EAV. 2.9% of differentially regulated genes were conserved across all 3 species, with a quarter of these regulated in opposite directions between rodent and human. These data provide insights into both shared pathophysiology and mechanisms underpinning the divergent clinical phenotype between rodent and human MPO-ANCA GN.

Funding: Government Support - Non-U.S.

TH-PO135

PRTN3 and MPO Expression Correlates with Disease Activity in a Large Inception Cohort with Longitudinal and Serial Measurements Among Patients with ANCA Disease Jia Jin Yang, 1 JulieAnne G. McGregor, 1 Elizabeth J. Brant, 1 Caroline J. Poulton, 1 Candace Henderson, 1 Britta E. Jones, 2 J. Charles Jennette, 2,1 Dominic J. Ciavatta, 2 Ronald J. Falk, 1,3 William Franklin Pendergast. 
1 Medicine, UNC-CH; 2 Pathology, UNC-CH; 3 Genetics, UNC-CH, Chapel Hill, NC.
Background: We demonstrated aberrant up-regulation of autoantigen genes, PRTN3 and MPO, in mature neutrophils and monocytes from patients with ANCA disease (J Am Soc Nephrol 2004, 15:2103-14). Here, we performed a longitudinal and serial analysis of PRTN3 and MPO expression following their disease course.

Methods: A total of 1063 leukocyte samples were collected from 152 ANCA-patients during various stages of disease activity and compared to 152 healthy controls. These patients were followed serially every 3 months over the past 5 years. Q-PCR was used to measure mRNA levels.

Results: PRTN3 (155±506, p<0.0001) and MPO (384±940, p<0.0001) mRNA levels were significantly up-regulated in leukocytes from patients with ANCA disease compared to controls. PRTN3 and MPO mRNA gene transcription correlated closely with disease activity. In the majority of patients with systemic vasculitis, the disease course was characterized by elevated expression in active disease and reduced expression in remission. The duration of increased PRTN3 and MPO expression was variable from several days to several months. Increased PRTN3 and MPO mRNA levels returned to normal in all patients with stable remission.

However, low PRTN3 and MPO mRNA levels were also observed in some active patients, particularly in those with limited organ involvement.

Conclusions: Our longitudinal and serial analysis of PRTN3 and MPO expression in patients with ANCA disease indicates that regulation of PRTN3 and MPO genes strongly tracks with disease activity suggesting that expression of these ANCA autoantigens is involved in disease pathogenesis.

Funding: NIDDK Support

TH-PO136

Galactose-Deficient IgA1-Containing Immune Complexes Induce Proliferation of Human Mesangial Cells and Activate PDGF/PDGFR Signaling Pathway. Zhiqian Huang, 1 Xianwen Zhang, 1,2 Qi Bian, 1,3 Joshua Charles Anderson, 1 Stacy D. Hall, 1 Christopher D. Willey, 1 Bruce A. Julian, 1 Jan Novak. 
1 Univ of Alabama at Birmingham, Birmingham, AL; 2 Medicine, Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; 3 Medicine, Changhai Hospital, Second Military Medical Univ, Shanghai, China.

Background: Our prior kinomic profiling showed that circulating immune complexes (CIC) and engineered immune complexes (EIC) consisting of galactose-deficient IgA1 (Gd-IgA1) bound by anti-Gd-IgA1 autoantibodies activated multiple tyrosine kinases in cultured human mesangial cells (hMCs) and induced cellular proliferation. Activation of PDGF signaling and an anti-apoptotic processes were two major processes detected. In hMC stimulated with CIC from sera of patients with IgAN and EIC, or human albumin (control), from mice receiving anti-MPO (MEV) or BSA (control) antibodies raised in MPO-/- mice (n=5/group), and from patients with MPO-ANCA GN (n=7) and healthy controls (n=18). RNA expression was analysed on Affymetrix arrays. Differential regulation was assessed by ChipInspector and rodent/human orthologs identified using Homer software. Analysis of gene lists using co-citation at sentence level, the human network was used to overlap with mouse and rat networks using TALE. In 74 selected genes, regulation was confirmed by qPCR.

Results: 2812, 1725 and 783 glomerular genes were significantly associated with GN in humans, mice and rats respectively. We observed overlap between human and mouse in 675 (12.9%), human and rat in 134 (3.1%) and across all 3 species in 179 (2.9%) genes. Of these 179 genes, 135 (75.4%) were differentially regulated in the same direction and 44 (24.6%) in opposite directions. We identified 12 canonical pathways (p value <0.001) conserved between human and mouse, and 5 between human and rat.

Conclusions: The transcriptomic profile in MEV was more similar to human disease than EAV. 2.9% of differentially regulated genes were conserved across all 3 species, with a quarter of these regulated in opposite directions between rodent and human. These data provide insights into both shared pathophysiology and mechanisms underpinning the divergent clinical phenotype between rodent and human MPO-ANCA GN.

Funding: Government Support - Non-U.S.

TH-PO137

The Pathogenic Role of NLRP3 Inflammasome in IgA Nephropathy and Establishment of a Therapeutic Strategy Shuk-Ma Ka, 1 Y-Juei Hsu, 2 School of Medicine, Graduate Inst of Aerospace and Undersea Medicine, National Defense Medical Center; Taipei, Taiwan; 2 Div of Nephrology, Dept of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: IgA nephropathy (IgAN) is the most common cause of primary glomerular disorders induced by an immune complex. The role of NLRP3 inflammasome has been shown to correlate with the progression of IgAN. NLRP3 inflammasome, a multiprotein complex, positively regulates caspase-1 activity and the maturation and release of IL-1β. NLRP3 inflammasome plays an important role in inflammatory response and controls the processing of various inflammatory diseases. However, the potential pathogenic role of NLRP3 inflammasome on IgAN is unclear.

Methods: The pathogenic role of NLRP3 inflammasome and molecular mechanisms on IgAN pathogenesis using NLRP3 deficient mice and NLRP3 KO mice were specific knockouts generated by an ultrasound-mediated microbubble shRNA gene transfer method.

Results: NLRP3 deficient and blockade resulted in attenuation of albuminuria, improved renal function, and blocking of renal progressive lesions, including glomerular proliferation, and periglomerular mononuclear leukocyte infiltration. These findings were associated with (1) inhibiting ROS production and NFκB activation in the kidney, (2) reducing NLRP3 inflammasome activation in the kidney, (3) inhibiting effect/memory T-cell activation and IL-17 expression, and (4) inhibiting maturation and activation of dendritic cells.

Conclusions: These results indicate that activation NLRP3 inflammasome is involved in the development of IgAN, and a kidney-specific knockdown of NLRP3 may have therapeutic potential for IgAN.

Funding: NIDDK Support, Private Foundation Support

TH-PO138

Effects of DPPIV Inhibitor on Renal Function in Mice Model of Aduiramicin Induced Nephropathy Hyo Sook Min, 1 Jin Joo Cha, 1 Kitae Kim, 1 Jungyoon Ghee, 1 Jung Eun Kim, 1 Ji Eun Lee, 1 Hyunwook Kim, 1 Jee Young Han, 1 Dae R. Cha, 2 Young Sun Kang. 1 Internal Medicine, Korea Univ Medical College Asan Hospital, Republic of Korea; 2 Internal Medicine, Wonkwang Univ Sanbon Hospital, Republic of Korea; 3 Pathology, Inha Univ College of Medicine, Republic of Korea.

Background: The murine model of adriamycin(ADR) induced nephropathy is characterized by severe proteinuria, development of podocyte injury and glomerulosclerosis. The aim of our study was to investigate the mechanism and preventive effect of fibrosis in glomerular, tubular and interstitial tissue associated with DA1229 treatment in ADR-induced nephropathy.

Methods: 6-week-old balb/c mice were divided into 4 groups as follows: 1) untreated after injection of ADR(control of group 2), 2) immediately treated with DA1229 for 3 weeks after injection of ADR(preventive protocol), 3) untreated after injection of ADR(control of group 4), 4) treated with DA1229 for 2 weeks after 3 weeks from injection of ADR(therapeutic protocol).

Results: Treatment with DA1229 showed preventive effect on weight gain and renal hypertrophy after 5 weeks of injection of ADR. Plasma DPPIV activity was significantly decreased in treatment with DA1229. DPPIV activity in kidney was significantly increased after injection of ADR and was decreased with DA1229. Notably, both preventive and therapeutic protocol significantly decreased proteinuria and albuminuria induced by ADR injection. Urinary excretion of nephrin was significantly decreased and inflammatory and fibrotic molecules in kidney tissue were significantly inhibited with DA1229 treatment. ADR-induced fibrosis, infiltration of macrophages and fibrosis in the kidney were attenuated with DA1229 treatment in ADR groups.

Conclusions: Our data suggest that DA1229 might protect renal injury from podocyte injury in ADR-induced nephropathy, via antiinflammatory and antifibrotic effects. DA 1229 might be a potential therapeutic agent in a variety of glomerular disease inducing proteinuria.

TH-PO139

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

Underline represents presenting author.
Efectively, protein expressions of Nox4, TGF-β1, NF-κB were attenuated with LJ 1888. Immunoreactions with profibrotic molecule were significantly decreased with LJ1888. glomerular injury and macrophage infiltration were observed in LJ1888 treated kidney. injection significantly induced proteinuria and albuminuria, which were notably reduced LJ1888(10mg/kg) for 2 weeks after 5 weeks of injection of ADR. mice(control), 2) untreated with LJ1888 after injection of ADR(11mg/kg), 3) treated with Clarice K. Fujihara. Sena, Vivian L. Viana, Denise M. Malheiros, Niels OS Camara, Roberto Zatz, Hospital, Republic of Korea; (ALB, mg/day), interstitial macrophages (Mî) and LY (cells/mm²) of Medicine, Republic of Korea; (Internal Medicine, Anyang Sam Hospital. Background: Concentration of adenosine in normal kidney increases markedly during renal hypoxia and ischemia. Previous studies have reported that mice lacking renal A3 adenosine receptor (A3AR) show significant protection against acute kidney injury, such as ischemia-reperfusion injury and myoglobinuria-induced injury. Moreover, A3AR antagonist blocked the development and attenuated the progression of renal fibrosis. The aim of this study was to investigate the effects of highly selective adenosine 3 receptor antagonist(LJ1888) treatment in ADR-induced nephropathy.

Methods: We designed three animal groups as following: 1) 6-week-old balb/c mice(control), 2) untreated with LJ1888 after injection of ADR(11mg/kg), 3) treated with LJ1888(10mg/kg) for 2 weeks after 5 weeks of injection of ADR. Results: Body weight was significantly decreased in both ADR injection groups. ADR injection significantly induced proteinuria and albuminuria, which were notably reduced after treatment of LJ1888. Urine 8-isoprostane and kidney lipid peroxidation level were also decreased with LJ1888. Urinary excretion of nephrin was significantly reduced and kidney nephrin stain showed increased nephrin expression in the glomeruli of LJ1888 group. Less glomerular injury and macrophage infiltration were observed in LJ1888 treated kidney. Immunostaining with profibrotic molecule were significantly decreased with LJ1888. Additionally, protein expressions of Nox4, TGF-β1, NF-κB were attenuated with LJ 1888. Conclusions: These reprotective effects of LJ1888 on ADR-induced nephropathy may be associated with protective effect on podocyte injury. LJ1888 might be a potential therapeutic agent for glomerulonephrophy inducing proteinuria.

TH-PO140 Innate Immunity Is Activated Early in Adriamycin Nephropathy and Is Strongly Associated with Lymphocyte Infiltration Viviane D. Faustino, Simone CA Arias, Flavia P. Albuquerque, Camilla Fanelli, Victor F. Avila, Lisienry CT Remple, Orsoses Foris-Neto, Gisely CS Moreira, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niós OLS Camara, Roberto Zatz, Clarice K. Fujihara. Univ of Sao Paulo, Brazil.

Background: Platelet deposition. However, at 24hr TAK1 deletion caused exacerbation of glomerular inflammatory response at 3hr in terms of neutrophil and macrophage infiltration and activated protein kinase (MAPK) signalling in tubular cells in response to angiotensin II and oxidative stress, but not to IL-1 or LPS. However, it is not known whether ASK1 is required for p38-dependent glomerular injury. The aim of the study was to determine whether blockade of apoptosis signal-regulating kinase 1 (ASK1) can suppress renal injury in a rapidly progressive glomerulonephritis model.

Methods: Accelerated anti-glomerular basement membrane (GBM) disease was induced in groups of 6-8 rats. Treatment with ASK1 inhibitor GS-444217 (30mg/kg/po/bid) or vehicle began 1hr before anti-GBM serum injection and continued until animals were killed on day 1 or 14.

Results: Compared to normal controls, anti-GBM disease showed a 3-fold increase in phosphorylated (activated) p38 in glomeruli on day 1 which was prevented by ASK1 inhibition. In addition, the 20-fold increase in urine protein/creatinine ratio at day 1 was prevented by ASK1 inhibitor treatment. In a separate study, vehicle treated anti-GBM disease exhibited 30.3% (mean±SD) crescents on day 14, which was reduced to 10.2±2.8% by ASK1 inhibitor (P<0.001). ASK1 inhibitor treatment reduced proteinuria by 50% compared to the vehicle group (P<0.01), and prevented an increase in serum creatinine (40±15umol/L vs. 27±15umol/L, P<0.005). Glomerular macrophage and T cell infiltration was also decreased by the ASK1 inhibitor (P<0.05), with an associated reduction in macrophage M1/M2 markers (iNOS, CD206). Finally, immunostaining and PCR analysis showed a reduction in renal fibrosis with ASK1 inhibitor treatment.

Conclusions: This study suggests that ASK1 is involved in activating p38 MAPK signalling in glomerular inflammation. In addition, treatment with GS-444217 decreased glomerular inflammation and crescent development. Further studies are required to investigate potential effects of therapeutic intervention in established anti-GBM disease.

Funding: Government Support - Non-U.S.

TH-PO143 Transforming Growth Factor β-Activated Kinase 1(TAK1) Attenuates Experimental Glomerulonephritis Liv A. Amos,1,2 Yingjie Han,1,2 John T. Liles,1,2 David J. Nikolic-Paterson,1,2 1Dept of Nephrology, Monash Medical Centre, Clayton, Victoria, Australia; 2Dept of Medicine, Southern Clinical School, Monash Univ, Clayton, Victoria, Australia; 2Gilead Sciences Inc, Foster City, CA.

Background: Apoptosis signal-regulating kinase 1 (ASK1) is required for p38 mitogen-activated protein kinase (MAPK) signalling in tubular cells in response to angiotensin II and oxidative stress, but not to IL-1 or LPS. However, it is not known whether ASK1 is required for p38-dependent glomerular injury. The aim of the study was to determine whether blockade of apoptosis signal-regulating kinase 1 (ASK1) can suppress renal injury in a rapidly progressive glomerulonephritis model.

Methods: Accelerated anti-glomerular basement membrane (GBM) disease was induced in groups of 6-8 rats. Treatment with ASK1 inhibitor GS-444217 (30mg/kg/po/bid) or vehicle began 1hr before anti-GBM serum injection and continued until animals were killed on day 1 or 14.

Results: Compared to normal controls, anti-GBM disease showed a 3-fold increase in phosphorylated (activated) p38 in glomeruli on day 1 which was prevented by ASK1 inhibition. In addition, the 20-fold increase in urine protein/creatinine ratio at day 1 was prevented by ASK1 inhibitor treatment. In a separate study, vehicle treated anti-GBM disease exhibited 30.3% (mean±SD) crescents on day 14, which was reduced to 10.2±2.8% by ASK1 inhibitor (P<0.001). ASK1 inhibitor treatment reduced proteinuria by 50% compared to the vehicle group (P<0.01), and prevented an increase in serum creatinine (40±15umol/L vs. 27±15umol/L, P<0.005). Glomerular macrophage and T cell infiltration was also decreased by the ASK1 inhibitor (P<0.05), with an associated reduction in macrophage M1/M2 markers (iNOS, CD206). Finally, immunostaining and PCR analysis showed a reduction in renal fibrosis with ASK1 inhibitor treatment.

Conclusions: This study suggests that ASK1 is involved in activating p38 MAPK signalling in glomerular inflammation. In addition, treatment with GS-444217 decreased glomerular inflammation and crescent development. Further studies are required to investigate potential effects of therapeutic intervention in established anti-GBM disease.

Funding: Government Support - Non-U.S.
Absence of Osteopontin Accelerates Oxidative Stress-Induced Fibrosis in Glomerulonephritis

Gabriela E. Garcia, Jessica Helen Trostel, Luan D. Truong, Richard J. Johnson.

Medicine, Univ of Colorado Denver, Aurora, CO;

Pathology, Baylor College of Medicine, Houston, TX;

Pathology, The Methodist Hospital, Houston, TX.

Background: Osteopontin (OPN) is a pro-and anti-inflammatory and profibrotic molecule that simultaneously attenuates oxidative stress in the inflammatory milieu. Evidence suggests that oxidative stress plays a significant role in the progressive fibrosis by upregulating fibrosis related genes. Moreover, elevation of biomarkers of increased oxidative stress has been demonstrated in patients with chronic kidney disease. OPN is highly induced in nephritic kidney and inactivation of macrophages (MΦ) by an A3R agonist, attenuated OPN expression and protected from progressive kidney injury.

Methods: To further characterize the role of OPN in kidney injury we use OPN-/- mice in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN), an inflammatory and progressive model of kidney disease.

Results: Wild type and OPN-/- mice did not show histological differences in the glomeruli and the tubulointerstitium. However, nephritic kidneys from OPN-/- mice showed severe kidney damage compared with those in WT mice. Fibrinoid necrosis, crescent formation, and tubulointerstitial injury were significantly higher in OPN-/- mice compared to WT mice. In addition, collagen (Col) I, Col III, and Col IV deposition were increased in nephritic kidneys from OPN-/- mice compared with WT mice. MΦ and T cell infiltration in nephritic kidneys was not different between WT mice and OPN-/- mice. Increased expression of the reactive oxygen species (ROS)-generating enzyme Nox 4 was observed in nephritic kidneys from OPN-/- mice. In contrast, MΦ isolated from WT mice and OPN-/- mice did not show difference in the expression of Nox4. Importantly, the antigen-specific humoral immune response and the glomerular immunoglobulin G deposition were not affected in OPN-/- mice.

Conclusions: These findings suggest that in global OPN-/- mice elevated Nox4 creates a redox imbalance with increased oxidative stress-induced fibrosis. Targeting MΦ OPN could be protective to attenuate inflammation and inflammation-associated fibrosis without affecting the anti-oxidative stress of OPN.

Funding: NIDDK Support

TH-PO144

The Toll-Like Receptor Signaling Pathway Is Activated Before the Development of Renal Injury in the 5/6 Nephrectomy Model


Univ of Sao Paulo.

Conclusions: Mechanisms of activation of inflammation in Chronic Kidney Disease (CKD) are unclear. We examined the participation of innate immunity in the 5/6 nephrectomy model (Nx) from its beginning to advanced phases.

Methods: Munich-Wistar rats underwent Nx (N=40) or Sham (S, N=10) operation.

Results: In Nx, TNFα, IL6, IL1β, and IL18 were significantly increased following gene expression. GEA showed heightening of the Tlr Signaling Pathway and Jak Stat Signaling Pathway.

Conclusions: The TlrSP, among other immune-related signaling pathways, is activated in the Nx model since its earliest stages until advanced phases, suggesting that they may contribute to initiate and maintain renal injury in this model.
Results:

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<th>$S$</th>
<th>$N_x$</th>
<th>$N_x$+Allo</th>
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<tbody>
<tr>
<td>TCP</td>
<td>134±2</td>
<td>212±8</td>
<td>191±6</td>
</tr>
<tr>
<td>ALB</td>
<td>3±1</td>
<td>111±15*</td>
<td>89±10</td>
</tr>
<tr>
<td>% GS</td>
<td>0±0</td>
<td>15±8</td>
<td>10±3</td>
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<tr>
<td>%COL</td>
<td>2±1</td>
<td>9±1*</td>
<td>5±1</td>
</tr>
<tr>
<td>uNGAL</td>
<td>29±4</td>
<td>48±5*</td>
<td>32±3</td>
</tr>
<tr>
<td>MO</td>
<td>22±2</td>
<td>187±26*</td>
<td>130±20*</td>
</tr>
<tr>
<td>rXO</td>
<td>70±5</td>
<td>116±7*</td>
<td>69±5</td>
</tr>
<tr>
<td>pUA</td>
<td>1.3±0.2</td>
<td>2.1±0.2*</td>
<td>0.8±0.2*</td>
</tr>
<tr>
<td>IL-1β</td>
<td>1.5±0.8</td>
<td>4.7±0.6*</td>
<td>2.4±0.3*</td>
</tr>
<tr>
<td>TLR4</td>
<td>1.0±0.1</td>
<td>3.3±0.4*</td>
<td>2.3±0.2*</td>
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Mean ± SE, *p<0.05 vs $S$; **p<0.05 vs Nx.

As expected, pUA was only slightly (though significantly) elevated in Nx, remaining far lower than previously seen with uricase inhibition. Allo normalized rXO activity and canceled the slight increase of pUA observed in Nx. Despite the low pUA, Allo attenuated hypertension and prevented selective tubulointerstitial protection, reducing uNGAL, COL, and MØ. In addition, Allo lowered the renal content of TLR4 and IL-1β, which correlated positively with both TCP and ALB.

Conclusions: In the Nx model, Allo exerts a renoprotective effect even in the context of UA levels, which is associated, at least in part, with inhibition of innate immunity.

TH-PO1050

Meganin/Cubulin-Lysosome-Mediated Albumin Reabsorption Is Involved in the Tubular Cell Activation of NLRP3 Inflammasome and Tubulointerstitial Inflammation

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Background: Albuminuria contributes to the development and progression of chronic kidney disease (CKD) by inducing tubulointerstitial inflammation (IT) and fibrosis. However, the exact mechanisms of IT in response to albuminuria are unresolved. We previously demonstrated that NLRP3 and inflammasomes mediate albumin-induced lesions in tubular cells. Here, we further investigated the role of endocytic receptors and lysosome rupture in NLRP3 inflammasome activation.

Methods: We established an albumin-overload induced rat nephropathy model. The adult male Wistar rats that were uninephrectomized or sham operated under anesthesia 5 days before starting BSA injection. In vitro, tubular epithelial cell line (HK-2) was cultured with or without megalin/cubulin gene siRNA transfection and then stimulated with BSA for different time durations (6h, 12h, 24h, 48h) and concentrations (5, 10, 20, 40 mg/ml). Cell lysates and supernatants were collected and determined by western blotting and ELISA.

Results: The priming and activation signals for inflammasome complex formation were evoked simultaneously by albumin excess in tubular epithelial cells. The former signal was dependent on albumin-triggered NF-κB pathway activation. This process is mediated by the endocytic receptor, megalin and cubulin. However, the silencing of megalin or cubulin inhibited the albumin-induced NLRP3 signal. Notably, subsequent lysosome rupture and near complete degradation of lysosomal proteins was observed in the presence of albumin as well as in albumin-free conditions. The lysosomal rupture in NLRP3 inflammasome activation.

Conclusions: Taken together, our findings suggest that megalin/cubulin and lysosome rupture are involved in albumin-triggered tubular injury and IT.

TH-PO151

Targeted Inhibition of Protein Kinase C-a Ameliorates Nephrotic Nephritis

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Background: Protein kinase C (PKC) is a ubiquitous phosphoryl-dependent enzyme, with multiple isoforms that differ in their structure, biochemical properties, tissue distribution, subcellular localization, and substrate specificity. Since PKC-a expression was shown to be increased in patients with chronic kidney disease and in podocytes in renal biopsies of patients with diabetic nephropathy, we investigated the effect of specific PKC-a inhibition on renal injury in a murine model of acute kidney injury.

Methods: Mice were divided into four groups: 1) controls, 2) NTN + PKC-a inhibitor Ro-32-0432 given i.p. after injection of nephritis on day 2, and 4) NTN group + PKC-a inhibitor conjugated to glomerular specific antibodies (i.e. a well-defined, human mAb (F1) directed against aIV(III) collagen) on day 2 to achieve kidney targeted drug delivery.

Results: On day 7, all NTN mice had severe nephritis, as evidenced by increased BUN, proteinuria and histology, whereas mice that received PKC-a inhibitors in either form had minimal evidence of kidney injury. BUN levels were reduced from 99.8±4.03mg/l.
dl. in NTN mice to 32.2±1.70mg/dl in mice receiving free PKC-t inhibitor and to 36.0±1.11mg/dl with F11.1 conjugated PKC-C inhibitor. Serum levels of cytokines, assessed in multiplex analysis (MagPix) further confirmed reduction of inflammation.

Conclusions: These results suggest that PKC-t is an important mediator of antibody-mediated glomerulonephritis, and that glomerular targeted inhibition of this enzyme is feasible. This methodology, has the advantage of diminishing systemic side effects while limiting and/or reversing ongoing damage associated with severe inflammation. This approach has potential therapeutic implications for the treatment of human kidney diseases.

Funding: NIDDK Support

TH-PO152
Renal Sympathetic Nerve Activity Controlled by Renal Afferent Sympathoexcitatory or Inhibitory Nerves? Tilman Ditting,1 Kristina Rodionova,2 Sonja Heinlein,1 Karl F. Hilgers,1 Christian Ott,1 Roland E. Schneider,1 Martin Hajdusek,1 Kerstin U. Amann,2 Roland Veelken,1 Nephrology & Hypertension, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany;2Pathology, Friedrich Alexander Univ Erlangen, Erlangen, Bavaria, Germany.

Background: Sympathetic nerve activity (SNA) is important in hypertension, volume disorders or renal disease. It is unclear if increases of RSNA in disease are due to sympathoexcitatory or impaired sympathoinhibitory renal afferent nerves. We present data from nephritic rats suggesting the latter.

Methods: Nephritis due to OX-antibodies in male Sprague-Dawley-rats. Methohexital anesthetized nephritic rats & controls were instrumented to stimulate renal afferent nerve activity (ARNA) in order to influence RSNA: ipsilateral renal arterial catheter for intrarenal administration (IRA) of the TRPV1 agonist capsaicin to stimulate ARNA (CAP A: 6.6±10-7M) and induce the release of the tachykinin receptor agonist SP from renal afferents; contralateral stainless steel electrode for RSNA recording; before and after IRA CAP the tachykinin-receptor blocker RP67580 was given. Baseline RSNA & ARNA were assessed. Some nephritic rats were pretreated with tachykinin receptor antagonists to prove modified SP effects.

Results: IRA CAP decreased RSNA from 67.5±12.0 mV*sec to 14.8±4.2 mV*sec (p<0.05) over 60 minutes while in nephritics RSNA suppression was abolished. Suppressed RSNA in controls was transiently reversed by the tachykinin inhibitor. Under resting conditions RSNA was higher, ARNA lower in nephritis as compared to controls. Tachykinergic antagonist ameliorated damage in renal nephritis suggesting increased SP release from renal afferent nerves despite lack of the tachykinin dependent sympathoinhibition seen in controls.

Conclusions: Our data suggest that a tachykinin dependent sympatoexcitatory reflex mechanism exerts sympathoexcitatory effects being impaired under pathophysiologic circumstances.

Funding: Government Support - Non-U.S.

TH-PO153
Fan1-/- Mice Develop Karyomegaly, with Hypertension and/or Impaired Renal Function in the Absence of Fan1. Rannar Chang,1 Markus Schueler,2 Merlin Airik,1 Jonathan Porath,1 Friedhelm Hildebrandt.1 1Division of Nephrology, Dept of Medicine, Boston Children's Hospital, Boston, MA;2Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Karyomegaly and/or hypertrophy in the kidneys is often accompanied by enhanced renal blood flow and renal function with all these factors contributing to the development of hypertension. Yet the impact of Fan1 on renal development is largely unknown.

Methods: Fan1-/- ES cells were isolated from E13.5 embryos of Fan1+/- mice. Nodeline Fan1+/- ES cells were transplanted to the posterior urethra of FVB mice at the E13.5 stage. Fan1-/- mice were generated by the breeding of FVB Fan1-/- Fan1+/- mice. The offspring was used for the subsequent studies.

Results: Fan1-/- mice were born at Mendelian ratio and appeared healthy with no gross abnormality in kidney. Transplantation of Fan1-/- and wild type mice with 10 to 20 mg/kg cisplatin caused severe tubular injury with cast formation and tubular dilation in Fan1-/- animals (n=5). Fan1-/- mice were more prone to develop spontaneous hypertension when compared to wild type controls. Hypertension in Fan1-/- mice was associated with increased renal tubular TGF-β and Smad7 expression.

Conclusions: Fan1-/- mice provide a model to study the pathomechanisms of chronic kidney disease. We demonstrate that Fan1-/- mice are highly sensitive to genotoxic insults that lead to kidney failure. Our data indicate that Fan1 is involved in the physiological response of the kidney cells to DNA damage, which has been recently acknowledged to contribute to the pathophysiology of the chronic kidney disease (2, 3).

Funding: NIDDK Support, Private Foundation Support

TH-PO154

Background: Agt transgenic mice have achieved renin angiotensin system (RAS). On this basis we hypothesized that mice with enhanced expression of Agt would display accelerated progression of HIVAN. We evaluated the effect of different copies of Agt in the initiation and progression of HIVAN in genetically engineered HIVAN mice (Tg26).

Methods: Control and Tg26 mice with 2 (Tg26/Agt-2) and 4 (Tg26/Agt-4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and renal hypertrophy over 8 weeks and 16 weeks. Renal cortical sections were stained with sinus red and PAS. RNA was extracted from renal tissues and probed for AT1, AT2, VDR and molecules involved in profibotic and epithelial mesenchymal transition (EMT) pathways.

Results: Tg26/Agt-4/8wks showed lower blood pressure (P<0.01) vs. Tg26/Agt-2/8 wks, while Tg26/Agt-4/16wks displayed higher blood pressure vs. Tg26/Agt-2/16wks. Tg26/Agt-4/8wks displayed attenuated expression of PAI-1 vs. Tg26/Agt-2/8wks; however, Tg26/Agt-4/16wks showed 3-fold greater PAI-1 expression than Tg26/Agt-2/16wks. Tg26/Agt-2/8wks displayed attenuated expression VDR and enhanced production of Ang II vs. Tg26/Agt-4/8wks, however this pattern reversed at 16 wks. Tg26/Agt-4/8wks displayed attenuated expression of AT1 and AT2 and down regulation of TGF-β, Snail, and vimentin when compared to Tg26/Agt-2/8wks. However, all these markers were comparable between these groups at 16 wks of age. Tg26/Agt-2/8wks developed renal lesions which were more advanced than Tg26/Agt-4/8wks. Conversely, Tg26/Agt-4/8wks displayed more advanced renal lesions vs. Tg26/Agt-2/16wks.

Conclusions: Tg26/Agt-4 displayed slower progression of HIVAN initially at 8 weeks associated with enhanced renal tissue VDR expression and attenuated expression of PAI-1, Tert and EMT markers. However, Tg26/Agt-2 displayed accelerated growth due to attenuated VDR expression leading to high blood pressure, upregulation of EMT and profibrotic molecules.

TH-PO155
Egr-1 Deficiency Abolishes Inflammatory and Fibrotic Responses of Renal Tubular Cells Li-chen Hu,1 Junne-Ming Sung,2 Yu-Sheng Tsi,1 1Inst of Clinical Medicine, National Cheng Kung Univ, Tainan, Taiwan; 2Internal Medicine, National Cheng Kung Univ Hospital, Tainan, Taiwan.

Background: Early growth response-1 (Egr-1) is a transcription factor that has been found to regulate inflammation and fibrosis in non-kidney tissues, but its role in renal failure has not been well established.

Methods: Wild type and Egr-1-/- mice were fed with adenine-enriched diet to induce tubulointerstitial nephritis (TIN), and primary tubular epithelial cells (PTECs) were treated with pro-inflammatory and pro-fibrotic cytokines. In addition, human kidney tissues were obtained from diabetic patients with renal failure and from non-diabetic patients without renal failure. The cell-type in which Egr-1 was activated was assessed using immunohistochemistry. The levels of inflammatory and fibrotic markers were analyzed using RT-PCR and Western blotting. Kidney sections were also stained with HE and Masson’s trichrome to assess immune cell infiltration and fibrotic areas.

Results: In mouse kidneys with TIN as well as in human kidneys with renal failure, tubular epithelial cell is the primary site for Egr-1 activation and undergoing nuclear translocation. Egr-1-/- mice were protected from renal failure, reflected by lower levels of serum urea and creatinine. This is consistent with Egr-1 deficiency-related reductions of immune cell infiltration, NF-kB activity, and expression of cytokines and chemokines in the kidneys. In addition, Egr-1-/- mice with TIN had less fibrotic area and attenuated TGFβ signaling than wild-type mice with TIN. Egr-1 deficiency also abolished the ordinary responses of PTECs to TGFβ.

Conclusions: Egr-1 activation in the renal tubular cell plays an integrative role for renal inflammation, fibrosis and the subsequent renal failure. Thus, Egr-1 may serve as a therapeutic target for human kidney diseases.

TH-PO156
Angiopoietin-1 Overexpression Attenuates Renal Fibrosis Through Decreasing Inflammation Fan-Chi Chang,2 Ming-Hsuan Tsai,2 Yu-Ihsiang Chou,1 Shuei-Liong Lin.1 1Internal Medicine, Taipei Medical Univ Hospital, Taipei, Taiwan; 2Graduate Inst of Physiology, College of Medicine, National Taiwan Univ, Taipei, Taiwan; 3Renal Div, Dept of Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Our previous studies have found dysregulated angiogenic growth factors in fibrotic kidney. We thus hypothesized that dysregulated angiopoietin-Tie system is related to microvascular destabilization and inflammation in the injured kidney.

Methods: We use unilateral ureteral obstruction (UUO) and 5 to 6 subcutaneous nephrectomy (S/NX) as animal models of progressive renal fibrosis. Specific overexpression of angiopoietin-1 (Angpt1) is induced in mice with Pax8-TetO (with C57BL/6 background) and pTRE-hAngpt1 (with ICR genetic background). Under the control of mouse Pax8 promoter, doxycycline administration directs high levels of expression of the reverse tetracycline-dependent transactivator (rtTA) to all proximal, distal tubules and

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

Underline represents presenting author.
the entire collecting duct system of both embryonic and adult kidneys. Double transgenic mice inhering Pax8/TA and pTRE-H-ANG1 responder. Littermates that inherited one or no transgenes serve as experimental controls.

Results: In animal model of UUO and 5/6Nx, Angpt1 decreases whereas Angpt2 and Angpt2/Angpt1 ratio increase as renal fibrosis progresses. Cross-breed of pTRE-H-ANG1 (with ICR genetic background) and Pax8/TA (with C57BL/6 background) lines is conducted for conditional overexpression. Overexpression of Angpt1 by tubule cells, include all proximal, distal tubules and the entire collecting duct system is induced after doxycycline administration in offspring with two transgenes. Compared to littermate control, transgenic mice with Angpt1 overexpression attenuate interstitial fibrosis in UUO kidney demonstrated by picrosirius red staining. Further analyses demonstrate decrease of inflammatory cell infiltration in UUO kidney of mice with Angpt1 overexpression.

Conclusions: These studies indicate that Angpt1 supplement may provide a novel therapeutic approach to attenuate renal fibrosis through reduction of inflammatory cell infiltration in UUO kidney.

Funding: Government Support - Non-U.S.

TH-PO157
Benidipine Targets Leukocyte Kv1.3-Channels and Slows the Progression of Renal Fibrosis in Rats with Advanced Chronic Renal Failure

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Background: Leukocytes, such as lymphocytes and macrophages, predominantly express delayed rectifier K+ (Kv1.3) channels in their plasma membranes. In our previous study, the overexpression of these channels in leukocytes was strongly associated with their proliferation in kidneys and the progression of renal fibrosis in the advanced stage chronic renal failure (CRF). Since benidipine, a long-acting 1.4-dihydropyridine Ca2+ channel blocker, is also highly potent as a Kv1.3-channel inhibitor, it could exert therapeutic efficacy in advanced CRF.

Methods: Male Sprague-Dawley rats that underwent 5/6 nephrectomy followed by a 14-week recovery period were used as the model of advanced CRF. Benidipine hydrochloride (5mg/kg) was started at 8 weeks after nephrectomy and orally administered daily for 6 weeks. The histopathological features of the kidneys were examined in vehicle-treated and benidipine-treated CRF rat kidneys. Cellular proliferation of leukocytes and the cortical expression of pro-inflammatory cytokines were also examined.

Results: In CRF rat kidneys, Kv1.3-channels began to be overexpressed in leukocytes as early as 8 weeks after nephrectomy. In the cortical interstitium of benidipine-treated CRF rat kidneys, both immunohistochemistry and real-time PCR demonstrated decreased expression of fibrotic markers. Benidipine treatment significantly reduced the number of proliferating leukocytes within the cortical interstitium and decreased the expression of cell cycle markers and pro-inflammatory cytokines.

Conclusions: This study demonstrated for the first time that benidipine slowed the progression of renal fibrosis in rat kidneys with advanced CRF. Kv1.3-channels overexpressed in leukocytes were thought to be the most likely therapeutic targets of benidipine in decreasing the number of proliferating leukocytes and repressing the production of inflammatory cytokines.

Funding: Government Support - Non-U.S.

TH-PO158
Renoprotection by Treatment with CXA10, an Endogenous Nitro-Fatty Acid

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Background: CXA10 is an electrophilic nitro-fatty acid that modulates anti-oxidant and anti-inflammatory pathways through activation of NRF2 and reduction of NFκB activity. Here, we examine the potential therapeutic benefit of CXA10 in a mouse model of hypertension-induced chronic renal injury that mimics human Focal Segmental Glomerular Sclerosis (FSGS).

Methods: Uninephrectomized male mice (129/sv) were implanted with a nitrate salt pellet (or placebo) at 2 and 5 weeks post-surgery, maintained on 1% NaCl (drinking water), and supplemented with 24% fat diet. Animals (n=8/10/group) were treated for 4 weeks with CXA10 (2.5mg/kg, p.o.) or with enalapril (20mg/kg; in drinking water) as the positive control.

Results: Body weight was slightly decreased and blood pressure was increased with DOCA treatment, and neither parameter was significantly altered by intervention. Kidney- and heart-to-body weight ratios were increased with DOCA and were significantly reduced in the CXA10 but not this enalapril group, whereas plasma cholesterol levels were reduced in both groups. CXA10 and enalapril significantly reduced albuminuria and nephrinuria but did not significantly improve the reduction in GFR following DOCA. Histologic evaluation revealed that both treatments improved interstitial lesions and fibrosis, whereas only CXA10 reduced glomerular sclerosis and hypertrophy. Molecular markers of glomerular injury and podocyte number were unchanged in all groups, suggesting that structural glomerular injury was modest. Even so, markers of inflammation and fibrosis were elevated in tissue and urine samples in this model. CXA10 reduced urinary MCP-1 as well as mRNA levels encoding MCP-1, osteopontin, collagen III, fibronectin, and PAI-1. Enalapril treatment did not significantly alter any of these expression profiles.

Conclusions: These results provide in vivo evidence that CXA10 is renoprotective in a kidney disease model by affecting anti-inflammatory, anti-oxidant and anti-fibrotic pathways and that the beneficial effects of CXA10 were differentiated from enalapril in this model.

Funding: NIH DK-67037; NIDDK Support, Clinical Revenue Support

TH-PO159
Selective Knock-Out of Glycogen Synthase Kinase 3-β in Proximal Renal Tubular Epithelial Cells (RTE) Attenuates Inflammation and Tubular Injury After Unilateral Ureteral Obstruction (UUO)

Josef Bautista, Eman Mohammad Shaban, Evelyn Tolbert, Rujun Gong, Lance D. Dworkin. Medicine, Brown Univ, Providence, RI.

Background: Glycogen synthase kinase 3-β (GSK-3β) is a ubiquitous serine/threonine protein kinase that regulates a large number of processes in diverse cell types including RTE. Systemic adenoviral administration of small molecule inhibitors of GSK-3β reduces inflammation and fibrosis and lessens acute and chronic kidney injury. However, the extent to which the beneficial effects of GSK-3β inhibition depend on blocking the enzyme specifically in kidney cells is unknown. We investigated whether gene deletion of GSK-3β in RTEs alone would reduce inflammation and progression of CKD.

Methods: The GSK-3β gene was selectively deleted in the renal tubular cells by cross-cre mice in which exon 2 of the Gsk3b gene was “floxed” with mice expressing CRE recombinase under a YGT promoter expressed only in adult proximal RTE (KO). Injury was induced by UUO in wild type (WT), KO, and WT mice given low-dose (1 mg/kg) thiazolidinedione (TZD), a specific GSK3β inhibitor. After 7 days, kidneys were weighed and examined for tubular and glomerular injury, interstitial edema, and macrophage infiltration. Groups were compared by ANOVA.

Results:

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney Wt (gm/100g body wt)</th>
<th>Injured Tubules (%)</th>
<th>Glomerular Injury Score</th>
<th>Interstitial edema score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KO (n=7)</td>
<td>0.74 ± 0.09</td>
<td>35% ± 0.15*</td>
<td>2.14 ± 0.94</td>
<td>1.47 ± 0.32</td>
</tr>
<tr>
<td>WT (n=11)</td>
<td>0.79 ± 0.16</td>
<td>57% ± 0.09</td>
<td>1.54 ± 0.66</td>
<td>1.59 ± 0.35</td>
</tr>
<tr>
<td>TZD (n=11)</td>
<td>0.69 ± 0.12</td>
<td>46% ± 0.12</td>
<td>1.52 ± 0.82</td>
<td>1.77 ± 0.28</td>
</tr>
</tbody>
</table>

*p<0.01 KO vs. WT.

Macroscopic infiltration assessed by immunohistochemistry also declined by about 40% in KO mice.

Conclusions: Selective deletion of GSK-3β in RTE attenuated macrophage infiltration and reduced tubulo-interstitial, but not glomerular injury after UUO. Elimination of GSK-3β signaling in RTE was more effective than systemic, low-dose GSK-3β inhibition. Our data suggest that GSK-3β dependent pathways in RTEs play a critical role in promoting interstitial inflammation and tubular injury in CKD.

Funding: NIDDK Support, Clinical Revenue Support

TH-PO160
TIMP-1 Up-Regulates the Expression of MCP-1 Through NF-κB Pathway in Rat Mesangial Cells

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Background: In mesangial proliferative glomerulonephritis (MesPGN), tissue inhibitors of metalloproteinases (TIMPs) can regulate transcription factors and cytokines and participate in immune and inflammation reactions in an MMP-independent way. We found that in the anti-Thy-1 nephritis model, TIMP-1 and monocyte chemotactic protein 1 (MCP-1) were significantly increased at the mesangial dissolved phase and peaked at the mesangial proliferative phase, finally backed to normal at the recovery phase. Our hypothesis is that TIMP-1 can regulate MCP-1 expression through NF-κB in mesangial cells.

Methods: (1) We established the anti-Thy-1 nephritis model. Animals were sacrificed at day 0, 1, 2, 3, 5, and 7, mRNA levels of TIMP-1 and MCP-1 were detected at separate time points by Taqman probe technique. (2) TIMP-1 over-expression rat mesangial cell model was established by GFP-TIMP-1 lentivirus transfection and siRNA interference. (3) The cells of TIMP-1 over-expression were harvested at day 5, 6, 7, and low-expression cells at 48h. Then we detected the mRNA and protein levels of TIMP-1, MMP2, MMP9, NF-κB and MCP-1 by Taqman probe technique and Western blot. (4) MCP-1 over-expression cells were treated with NF-κB inhibitor BAY 11-7082 (20μmol/L) at 4th day. After 48h-culture, mRNA level were detected.

Results: (1) In rat anti-Thy-1 nephritis, the expression levels of TIMP-1 and MCP-1 was increased gradually and peaked at day 5, then began to decrease. MCP-1 followed the same trend but peaked at day 2. (2)We established the TIMP-1 over-expression model successfully. (3)When TIMP-1 presented over-expression, MMP9, NF-κB and MCP-1 were up-regulated (P=0.05). When TIMP-1 presented low-expression, these were down-regulated. (P=0.001) The change in expression of MMP2 was not obvious. (4) At 48h after inhibition with NF-κB inhibitor, the expression level of MCP-1 in the TIMP-1 over-expression cells was down-regulated (P<0.01).

Conclusions: TIMP-1 could participate in the immune and inflammation reactions of MesPGN by up-regulating the expression of MCP-1 through NF-κB in rat mesangial cells.

Funding: Government Support - Non-U.S.
TH-PO161
Calcitriol Protects against Renal Tubular Cell Apoptosis by Promoting M2 Macrophage Polarization in Diabetic Nephropathy Rats
Yinfeng Guo, Zhixia Song, Min Zhou, Ying Yang, Xiaoliang Zhang. Zhong Da Hospital, Southeast Univ, School of Medicine.

Background: Renal tubular apoptosis is a key event in initiating kidney damage in DN. Heterogeneity of macrophage phenotype and function ultimately determines the outcome of DN. Therefore, we sought to investigate whether calcitriol, known as an important renal-protective drug, is sufficient to protect against tubular cell apoptosis by promoting M2 macrophage in DN rats.

Methods: DN model rats were established by intraperitoneal injection with streptozocin (STZ). The rats were subsequently receiving either calcitriol (0.1mg/kg/d) or vehicle by gavage for 12 weeks. At 18 weeks, histological and molecular analyses were performed. In addition, we performed in vitro study using Raw264.7 cells cultured with either high glucose or high glucose followed by 1,25-dihydroxyvitamin D3 medium to assess macrophage phenotype.

Results: Calcitriol significantly improved renal function and ameliorated renal histology in DN rats. The increased tubular cell apoptosis in DN rats was alleviated by calcitriol. Calcitriol up-regulated the expression of anti-apoptotic protein Bcl-2, down-regulated the expression of pro-apoptotic protein such as Bax and caspase-3. Interestingly, calcitriol significantly enhanced M2 macrophage polarization in interstitium with elevated expressions of M2 markers, including CD163, Arg-1 and MR. Moreover, the ratio of CD163/CD68 considered as the proportion of M2 macrophage was about 2.9 fold higher after calcitriol treatment. In vitro, 1,25-dihydroxyvitamin D3 also promote high glucose-induced pro-inflammatory M1 macrophage toward anti-inflammatory M2 polarization.

Conclusions: Calcitriol protects against renal tubular cell apoptosis by promoting M2 macrophage polarization in STZ-induced DN rats. Funding: Government Support - Non-U.S.

TH-PO162
APOL1 Risk Variants Induce Aberrant TH-1 Monocyte Differentiation and Increased Eicosanoid Production
Hewang Lee, Jeffrey B. Kopp. Kidney Diseases Section, NIDDK, National Insts of Health, Bethesda, MD.

Background: APOL1 protein (L1) is an innate immune protein and its risk variants are strongly associated with kidney disease. We investigated the effects of APOL1 variants on monocyte monocyte differentiation and eicosanoid production in macrophages, as activated tissue macrophages in kidney might contribute to injury.

Methods: THP-1 cells, a human monocytic cell line, were transiently transfected with APOL1-A isoform G0 (ancestral allele) or the renal risk variants G1 and G2 and cultured for 36 hr before RNA was obtained for gene expression studies.

Results: APOL1-transfected THP-1 cells manifested a 6-8 fold increase in CD14 and CD68 gene expression similar for all three variants, and similar to that seen with phorbol-12-myristate acetate treatment. Furthermore, APOL1 risk variants induced activated monocytes to atypical M1 macrophages with increased RNA encoding M1 markers CD80, TNF, IL-1β, and iNOS (all vs EV p<0.05, G1 vs G2 p<0.05), modest increase in M2 markers CD163, CD206, and TGFβ1 with G1 transfection (all RNAs vs EV p<0.05) and CD204 and TGFβ1 with G2 transfaction. Up-regulation of APOL1 in THP-1 induced expression of eicosanoid enzymes was also increased as well: cyclooxygenase-2, G0, 1.3±0.9 fold over empty vector (EV), G1, 4.1±0.5 and G2, 4.5±0.5 (both G1 and G2 vs G0 p<0.01) and thromboxane A2 (TXA2) receptor, G0, 2.1±0.8 fold over EV, G1, 5.2±0.9 and G2, 4.5±0.5 (both G1 and G2 vs G0 p<0.05). Thromboxane A2 receptor (TXA2R) gene expression was unchanged with G0, 1.8±0.4 fold over EV (p=0.05), and increased with G1, 6.1±1.0, and G2, 4.1±0.5 (G1 vs G0 p<0.001, G2 vs G0 p=0.01). Higher levels of thromboxane B2, a stable metabolite of thromboxane A2, were present in the supernatant of cultured THP1 cells transfected with G1 (10.0±1.3 pg/mL/10⁶ cells, p<0.05 vs G0) and G2 (15.1±3.0 pg/mL/10⁶ cells, p<0.01 vs G0) compared to G0 (6.0±1.0 pg/mL/10⁶ cells), which was similar to EV (6.7±1.0 pg/mL/10⁶ cells, p<0.05 vs EV).

Conclusions: These results demonstrate a novel role of APOL1 variants in the regulation of monocyte differention and eicosanoid metabolism, which could modify the immune response and promote inflammatory signaling within the kidney and elsewhere. Funding: NIDDK Support

TH-PO163
Purification and Analysis of Exosomes Derived from Primary Human Proximal Epithelial Cells (PTEC)
Helen G. Healy, Xiangiu Wang, Andrew J. Kassianos, Ray Wilkinson.

Background: Exosomes are extracellular vesicles secreted by multiple cell types in the body which contain a tissue-type signature courtesy of their incorporated RNA and protein cargo. Exosomes have crucial roles in extracellular communication and are implicated in kidney inflammation and disease progression. Human PTEC play a central role in renal disease yet their expression remains virtually unknown. Here we characterize exosomes from primary human PTEC cultured under normal, hypoxic and inflammatory conditions.

Methods: Exosomes were purified from normal, hypoxic (1% O₂) and inflammatory (IFN-γ+TNF-α treated) PTEC cultures using ultracentrifugation and density gradients and analyzed for morphology (electron microscopy), size/concentration (qNano) and RNAseq and mass spectrometry (MS) and sequencing respectively. Results: Exosomes from all three culture conditions displayed the same size range (50-200nm) and morphology (spherical doughnut shape) with a similar expression of CD9 (Hercules II) and CD63 (Hercules I). However, differences between both hypoxic and inflammatory conditions increased by more than two fold compared to normal culture conditions. MS analysis demonstrated exosomes from hypoxic cultures contained 134 proteins not expressed in those from normal cultures, whilst inflammatory cultures contained 152 unique proteins. A number of these proteins have been implicated in the development of chronic kidney disease.

Conclusions: Collectively, our data indicate that exosome secretion is increased under “diseased” conditions, and importantly, there is condition specific differential protein expression. Further investigation of exosome protein/microRNA cargo will identify novel targets whose utility in therapies and disease biomarkers warrant analysis. Funding: Government Support - Non-U.S.

TH-PO164
HIF-2a in Dendritic Cells in Renal Injury Soren Schwuchow, Joanna Kalucka, Gunnar Schley, Bernd Klankel, Kae-Uwe Eckardt, Alexander Weidemann.

Background: Hypoxia-inducible transcription factors, HIF-1 and -2 play key roles in cellular adaptation to hypoxia and have been linked to immune responses. In macrophages they are non-redundant and are expressed depending on polarization. However, in other immune cells, such as dendritic cells (DCs), the differential role of HIFα isoforms is less clear. DCs are abundant in the kidney and have been implicated in renal (patho)physiology. As shown previously, HIF-1α in DCs affects maturation and T cell stimulation, but whether HIF-2α plays a specific role is elusive. The aim of our study was therefore to elucidate the functional properties of HIF-2α in DCs in vitro and in vivo during renal injury.

Methods: Murine primary DCs (BMDCs) were generated from bone marrow of tissue specific conditional knock-out mice (Cd11cCre;HIF-2a-/-). BMDCs were then stimulated with hypoxia and LPS followed by mRNA, FACS and protein analysis. Bilateral renal ischemia and reperfusion injury (IRI) was used as a model of acute renal injury. To induce chronic kidney injury, mice were subjected to either a 3 week adenine rich diet or to unilateral ureteral obstruction (UUO), followed by the above mentioned analyses.

Results: HIF-2α protein is detected in BMDC after LPS treatment and with hypoxic stimulation. Loss of HIF-2α does not affect expression of maturation markers such as Cd86 or MHCII after LPS and the ability of T cell activation. In vivo during acute or chronic renal injury, loss of dendritic HIF-2α does not affect renal function, inflammatory cell responses or the expression of fibrotic or inflammatory markers.

Conclusions: Taken together, our data indicates that loss of HIF-2α in DCs does not affect maturation in vitro and leukocyte infiltration or renal function in models of acute and chronic renal injury in vivo. Thus, in contrast to macrophages, HIFα isoforms in DCs do not seem to play functional opposing roles. This might have important implications for the development of pharmacologic agents targeting HIFα in DCs to modulate immune responses during renal injury.

Funding: Government Support - Non-U.S.

TH-PO165
Fecal Transplantation from Uremic Mice Aggravates Kidney Fibrosis Myung-yong Kim, Young Ju Na, Sung Yoon Lim, Sang-Kyung Jo, Won-Yong Cho. Dept of Internal Medicine, Korea Univ Anam Hospital, Seoul, Republic of Korea.

Background: Emerging evidence showed the important role of kidney-gut crosstalk in diverse pathological processes. Alterations in intestinal barrier or microbiota has been demonstrated in chronic kidney disease (CKD) and thought to be associated with increased cardiovascular risks or progression of CKD. The purpose of this study was to investigate the effect of gut microbiota in the animal model of kidney fibrosis with using fecal transplantation.

Methods: Unilateral ischemia/reperfusion injury (IRI) for 45min was performed in C57/BL6 mice for fibrosis model. Supernatants of centrifuged feces from 5/6 nephrectomized mice (8wks) or age matched control mice were administered 3 times per wk for 3 wks after gut decontamination and degree of fibrosis was compared (CKD feces vs control feces). Compared to mice with fecal transplantation from control mice, mice who were transplanted with CKD feces showed aggravated fibrosis at 2 wks after unilateral ischemia in the analysis of the Masson’s trichrome staining and Western blot for type 4 collagen. Ex vivo analysis of immune cells showed increased number of mature CD80+ CD11c+ cells in mesenteric lymph node whereas percentage of splenic Tregs increased in mice transplanted from uremic mice. Immune cells from these mice showed significantly suppressed cytokine release upon LPS stimulation compared mice with WT feces.

Conclusions: This study showed the possible effect of kidney-gut crosstalk on the progression of CKD and this effect is thought to be partially mediated by immune modulatory effect.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author. 127A
A Novel Mineralocorticoid Receptor Blocker Protects the Remnant Kidney Better Than Eplerenone as an Add-On to Late Losartan

Clarike K. Fujihara,1 Mark Kowala,2 Matthew D. Breyer,2 Claudia R. Sera,3 Manilia V. Rodrigues,4 Simone CA Arias,5 Camilla Fanelli,6 Denise M. Malheiros,7 Jose E. Krieger,7 Roberto Zato,7 1Univ of Sao Paulo, Brazil; 2Eli Lilly.

Background: Aldosterone (Ald) worsens, whereas MR blockers, e.g. eplerenone (E), slow CKD, but cause hyperkalemia, especially with RAS inhibitors, e.g. Losartan (L). L (50 ± 150 mg/d) and L+E, 5 + 150 mg/d, 10 ± 100 mg/d, 20 ALB, albuminuria, mg/dL, TCP, tail-cuff pressure, mmHg; PR, plasma renin, ng/mL/h; plasma Ald, pg/mL; Serum glomerulosclerosis (GS, %), INT collagen (COL, %), INT macrophage (M). Orestes Foresto

TH-PO168
Assessing the Role of B7.1 in Diabetic Nephropathy
Marcela Herrerga,1 Magnus Soderberg,1 Johan C. Molne,1 Beatriz Santamaria perez,2 Angela M. Valverde,2,3 Stephanie C. Heasman,1 Lutz Jermutus,1 David J. Baker,1 Carol Patricia Moreno Quinm,1 1Cardiovascular & Metabolic Diseases, Medimmune, Cambridge, United Kingdom; 2AstraZeneca, Molndal, Sweden; 3Pathology, Sahlgrenska Univ, Gothenburg, Sweden; 4Inst for Biom Res Alberto Sols, CSIC, UAM, Madrid, Spain; 5Centro de Investigacion Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (ISICHD), Madrid, Spain.

Background: Upregulation of podocyte B7.1 has been reported in kidney biopsies of Diabetic Nephropathy (DN) patients and in stressed cultured human podocytes. Blocking B7.1 with CTLA4-Fc fusion (Abatacept) protects the injured podocyte in vitro and improves DN pre-clinically. B7.1 is found in antigen presenting cells and binding of CTLA4-Fc to B7.1 prevents T-cell activation. Since inflammation is an important feature of diabetes, we hypothesized that Abatacept protects the kidneys during DN primarily by blocking T-cell activation.

Methods: We investigated B7.1 expression in 42 DN kidney biopsies using immunohistochemistry. B7.1 expression was not detected in podocytes but predominantly localized in a limited number of macrophages, with no differences found between control and DN patients (0.15±0.23 vs. 0.19±0.22cells/mm2). In situ hybridization confirmed these results. In cultured human podocytes, B7.1 was found at relatively low levels when assessed by qPCR, and treatment with high-glucose (30mM for 3, 5, 10 and 14 days) or LPS (20 and 50ug/ml for 24 hrs) did not enhance B7.1 expression. Western blotting analysis confirmed these results. LPS-induced F-actin re-organization was not prevented by Abatacept (10-100mg/ml). We then tested Abatacept in the STZ-induced DN model (high fat-diet-C57Bl6). After 3 weeks of diabetes induction, Abatacept was dosed s.c. at 50mg/kg every 2 days for 12 weeks. At 3 weeks of dosing, urinary albumin:creatinine ratio increased from 3.6±0.8 to 8.3±0.9ug/moles in the diabetic animals (p=0.05) while in the Abatacept group UAC was 4.0±1.6ug/mmol (p=0.05 vs. DN group). Glucose or HbA1c were unaffected across groups and throughout the study. Conclusions: B7.1 is a valid target for DN where the mechanism of action is more likely inhibition of T-cell activation rather than podocyte protection.

Funding: Pharmaceutical Company Support - Medimmune
AstraZeneca

TH-PO169
Systemic Overexpression of Endogenous Secretory RAGE Attenuates Diabetic Kidney Injury Through TLRL Not TLRL2 Signaling Xiaoxiao Chen,1 Jin Ma,2 Elisabeth G.D. Stribos,1 A. Lianne Messchendorp,1 Moumita Paul,1 Eithne Cunningham,1 Alexandera Sharland,1 Steven J. Chadban,3,4 Huiling Wu,1,5 Kidney Node Laboratory, Charles Perkins Centre, Univ of Sydney, Australia; 3Royal Prince Alfred Hospital, Australia.

Background: Endogenous secretory RAGE (eRAGE) is a soluble decoy receptor that can competitively bind ligands for TLRL/RAGE, including HMGB1. Here we test whether: 1) eRAGE after the induction of diabetes can prevent the development of diabetic nephropathy (DN) in mice with streptozotocin-induced diabetes; 2) the protective effects of eRAGE are attributable to interruption of signaling via the HMGB1 receptors (TLRL2, TLRL4 and RAGE). Methods: DN was induced in WT, TLRL4 and TLRL2 mice by intraperitoneal injection of streptozotocin. At 2 weeks after STZ injection, mice received an IP injection of 5x10^6 vector genome copies rAAV encoding either eRAGE or HSA, or saline-control. Samples were collected at week 12 post-induction of diabetes.

Results: Diabetic mice that received rAAV-eRAGE, rAAV-HSA or saline developed equivalent degrees of hyperglycaemia. Diabetic WT-mice given rAAV-HSA or saline developed significant albuminuria versus non-diabetic WT-mice (ACR=213 ± 312±215 versus 55±10, p=0.05±0.01), whilst rAAV-eRAGE-treated diabetic-mice were protected (118±42, p=0.05). WT diabetic-mice developed histological damage including glomerular hypertrophy, podocyte injury, macronucleation and interstitial fibrosis. These changes were significantly attenuated in diabetic mice given rAAV-eRAGE versus rAAV-HSAIp=0.05±0.01). While both TLRL2 ‘mice and TLRL4 ‘mice were partially protected against DN, eRAGE treatment provided additional protection to TLRL2 ‘mice, but not TLRL4 ‘mice. A further study of eRARGE treatment in RAGE ‘mice is underway.

Conclusions: High-level expression of serum eRAGE after the induction of diabetes provided partial protection against the development of DN in STZ-induced diabetic mice, which may operate through the TLRL4 pathway.

Funding: Pharmacological Company Support - Medimmune
AstraZeneca

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

128A

Background: Activated vitamin D3 (Calcitriol) can effectively slow the progression of chronic kidney disease and its mechanism is not very clear. The advanced glycation products (AGEs) accumulate in the kidney disease through RAGE receptors. The aim of this experiment was to explore the effect and mechanism of Calcitriol on the inflammatory of mesangial cells caused by AGEs, and to further expand the clinical application of activated vitamin D3.

Methods: AGE-HSA was prepared and human glomerular mesangial cells were cultured in vitro. The purpose of the present study was to investigate the efficacy of calcitriol on AGEs-induced inflammatory in human mesangial cell. Pretreatment with or without calcitriol, the human mesangial cell was treatment with various concentrations and time period of AGEs. IL-6 and MCP-1 were measured by real-time PCR and ELISA. The expression of vitamin D receptor (VDR), receptor of advanced glycation end products (RAGE), NF-κB p65 and phosphorylated p65 was measured by Western-blot. NF-κB p65 translation was determined by immunofluorescence. Cellular oxidative stress was measured by reactive oxygen species (ROS) production.

Results: (1) AGE-HSA induces IL-6 and MCP-1 expression in human mesangial cells, and calcitriol inhibits this effect. (2) Not AGE-HSA but calcitriol induces Vitamin D receptor (VDR) expression in human mesangial cells. And calcitriol inhibits this effect through VDR. (3) AGE-HSA induced Receptor for advanced glycation end products (RAGE) expression, and effects was blocked by calcitriol. (4) Effects of calcitriol on transcription of RAGE in human mesangial cells. (5) NF-κB activation in renal mesangial cells was induced by AGE-HSA, and the effect was inhibited by calcitriol.

Conclusions: Calcitriol could attenuate the AGE-induced up-regulation of IL-6 and MCP-1 though VDR by suppressing RAGE expression and subsequent ROS generation and reducing NF-κB activation.

Funding: Government Support - Non-U.S.

TH-PO173 Renal Protection by Atorvastatin in Sickle Cell Nephropathy Rima S. Zahr,1 Vanessa Bijol,2 Kenneth I. Ataga,3 David Archer,1 1Pediatrics, Emory SOM, Atlanta, GA; 2Pathology, Brigham and Womens Hospital, Boston, MA; 3Hematology, UNC, Chapel Hill, NC.

Background: Sickle Cell Disease (SCD) affects approximately 100,000 people in the USA. Renal involvement begins early commonly manifested as hypothenuria with microalbuminuria occurring in ~25% of SCD patients <18 years. Various complications for sickle cell nephropathy include ACE inhibitors or ARBs to prevent progressive proteinuria. Statins have pleiotropic effects in addition to their lipid lowering properties. Here we investigated the functional effects of Atorvastatin treatment on the development of nephropathy in a murine model of sickle cell disease.

Methods: Cohorts (n=10) of 8-12 week homozygous sickle cell mice were treated with atorvastatin (10mg/kg) or vehicle daily for 8 weeks by oral gavage. We assessed effects of atorvastatin on albuminuria, maximum urine concentrating ability and GFR at baseline and week 8. Urine was collected in metabolic cages for 24hrs and albuminuria quantified by ELISA. GFR was measured by plasma clearance of FITC-Indulin. Mice were water deprived for 12hrs and spot urine for maximum urine concentrating ability. Kidneys were prepared appropriately for light microscopic analysis and glomerular morphometry.

Results: After 8 weeks of daily treatment mice receiving atorvastatin were found to have statistically significant improvement in urine concentrating abilities and improvement in GFR (p < 0.01 and p < 0.001 respectively). Urine protein excretion was unchanged by treatment with atorvastatin. Under light microscopy there were no gross changes in appearance of glomeruli or glomerular vasculature. In addition we did not find significant statistical changes in glomerular tuft size.

Conclusions: We assessed the pleiotropic effects of statins in SCD. While we did not find differences in urine albumin excretion and glomerular tuft size we found that this treatment decreased the loss of concentrating ability and improved the functional urine concentrating ability in sickle cell mice. These complications of are found both in animal and human models. Further studies will examine microscopic examination of podocyte and endothelial structures and look at biomarkers of renal injury.

Funding: Other NIH Support - R01HL11659


Background: Sickle-cell disease (SCD) is characterized by chronic hemolysis and recurrent episodes of vaso-occlusive events that affect the microcirculation and lead to organ ischemia, tissue injury with multi-organ dysfunction. Sickle cell nephropathy (SCN), a major mortality risk factor in SCD, is characterized by an early increase in glomerular filtration rate with subsequent progressive decline of renal function. Focal and segmental glomerulosclerosis (FSGS) and hypertrophied glomeruli with distended capillaries are the major hallmarks of glomerular lesions. We investigated the effect of chronic mixed ET receptor antagonism in a model of SCD-mediated FSGS.

Methods: We used SAD HbS-single/sickle hemizygous mice on the C57BL/6J background. At 3 months of age SAD mice displayed little evidence of chronic renal damage but significant glomerulosclerosis compared to controls. Glomerulosclerosis persisted, and was worse, at 6 months of age (average glomerular section area: 2372 ± 207 vs. 1519 ± 180 mm², p<0.001). In addition, SAD mice had significant glomerulosclerosis. Based on these data we treated SAD mice and controls aged 3 months with the dual ET receptor antagonist bosentan for 9 months in a preventative study, and 6 months old SAD mice for 6 months in a therapeutic study. We assessed blood pressure, kidney structure and function after 6 and 9 months of continuous treatment.

Results: In the preventative study, 6 months of bosentan therapy was associated with -4 fold reduction in glomerulosclerosis compared to untreated SAD mice (22±8 vs. 86±4%, p<0.001). Additionally, there was an 80% reduction in mean glomerular surface area (p<0.05). In the therapeutic study, there was a significant reduction in glomerulosclerosis (p<0.01) and
TH-PO175
Erythropoietin and Its Carboxylated Derivative Protected against Chronic Cyclosporine Nephropathy Wenhun Peng, Jianghua Chen. Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Erythropoietin (EPO) is known to raise hemoglobin and protect tissues and its carboxylated derivative (CEPO) has no effect on hemoglobin but could induce tissue protection. The aim of this study is to determine the effect of EPO and CEPO on the animal model of chronic cyclosporine nephropathy.

Methods: We evaluated therapeutic effects of EPO and CEPO using a rat model of chronic cyclosporine nephropathy. Rats were randomly divided into five groups: (1) the saline treatment group (control group, n=12); (2) EPO treatment group at low dose (low EPO group, 100U/kg, n=12); (3) CEPO treatment group at low dose (low CEPO group, 100U/kg, n=12); (4) EPO treatment group at high dose (high EPO group, 500U/kg, n=12); (3) CEPO treatment group at high dose (high CEPO group, 500U/kg, n=12).

Results: In control group, the levels of sodium, protein and NAG enzyme of urine, the values of serum creatinine and urea nitrogen, the concentration of MDA and GSH-PX (3) CEPO treatment group at low dose (low CEPO group, 100U/kg, n=12); (4) EPO treatment group at high dose (high EPO group, 500U/kg, n=12); (3) CEPO treatment group at high dose (high CEPO group, 500U/kg, n=12).

Conclusions: EPO and CEPO could effectively antagonize cyclosporine nephrotoxicity through anti-fibrosis, anti-inflammatory cell infiltration, anti-apoptotic, anti-oxidant, promotion new growth of renal tubular epithelial and endothelial cells, and the promotion of release and proliferation of endothelial progenitor cells.

Funding: Government Support - Non-U.S.

TH-PO176
Glucose Promotes Secretion-Dependent Renal Cyst Growth Andre Kraus, Gunnar Schley, Karl Kunzelmann, Rainer Schreiber, Kai-Uwe Eckardt, Bjorn Buchholz. 1 Dept of Nephrology, Univ Erlangen-Nuernberg, Erlangen, Germany; 2 Dept of Physiology, Univ Regensburg, Regensburg, Germany.

Background: ADPKD is characterized by continuous cyst growth which is highly based on transepithelial Cl-secretion into the cyst lumen. Since ADPKD is a long-lasting, chronic disease, there is a significant number of patients suffering from both, ADPKD and type 2 diabetes mellitus. Recently, ADPKD patients with type 2 diabetes mellitus were shown to have kidneys with almost double the volume compared to non-diabetic ADPKD patients. Therefore, we wanted to test for the impact of glucose on renal cyst growth.

Methods: We examined the effect of different glucose concentrations ranging from 5.6 mmol/l up to a maximum of 25.0 mmol/l on cyst growth of MDCK cells within a collagen chamber. We performed Ussing chamber experiments with MDCK cells in order to detect alterations of transepithelial Cl-secretion into the cyst lumen. Since ADPKD is a long-lasting, chronic disease, there is a significant number of patients suffering from both, ADPKD and type 2 diabetes mellitus. Recently, ADPKD patients with type 2 diabetes mellitus were shown to have kidneys with almost double the volume compared to non-diabetic ADPKD patients. Therefore, we wanted to test for the impact of glucose on renal cyst growth.

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Results: We find that challenging pre-conditioned mice lacking primary cilia with oxalate leads to persistent tube dilation.

Conclusions: These results suggest that cilia are required for reestablishing normal tubular diameters after crystal clearing. Furthermore, these results suggest that renal crystal clearance can be achieved by a cell-autonomous and environmentally controlled “third-hit trigger” that affects disease progression in ADPKD. This suggests that dietary changes or treatments to reduce renal crystal burden may be effective in slowing ADPKD progression.

Funding: Private Foundation Support

TH-PO178
Soluble RAGE Alleviates Disease Progression in Autosomal Dominant Polycystic Kidney Disease by Down-Regulation of Cell Proliferation Jong Hoon Park, Eunji Lee, Hyowon Mun, Je Yeong Ko, Do Yeon Kim. Dept of Biological Science, SooMyung Women’s Univ, Seoul, Republic of Korea.

Background: Autosomal polycystic kidney disease (ADPKD) is a one of the common genetic renal diseases in which epithelial-lining fluid-filled cysts appear in kidneys. It is accompanied by hyper-activation of cell proliferation, interstitial inflammation and fibrosis around the cyst lining cells, finally reaching end-stage renal disease (ESRD). Previously, we found high expression of ligands stimulating the receptor for advanced glycation endproducts (RAGE) in ADPKD mice. Furthermore, gene silencing of RAGE was revealed to reduce cystogenesis via down-regulation of cell proliferation in vitro, while intravenous administration of anti-RAGE adenosine in vivo also displayed alleviation of the disease.

Methods: Using either mice primary cells or human ADPKD cell line WT9-12, both sRAGE treatment and over-expression of sRAGE with cloned construct we established here. In vitro, we injected cell proliferation injection using ADPKD mice model jck, and confirmed the in vitro results in vivo systems.

Results: Here, we attempted to identify the role of soluble RAGE (sRAGE) in inhibiting the progression of ADPKD, in vivo. sRAGE is an endogenously expressed form of RAGE which has no membrane-anchoring domain, thereby being able to neutralize the ligands that stimulate RAGE signals. Both over-expression of sRAGE and sRAGE treatment blocked RAGE-mediated cell proliferation in vitro. In addition, sRAGE-injected ADPKD mice showed reduced cysts accompanied by enhanced renal function, inhibition of cell proliferation, inflammation and fibrosis.

Conclusions: These positive therapeutic effects of sRAGE displayed little liver toxicity, suggesting it as a new potential therapeutic target of ADPKD with low side effects.

Funding: Government Support - Non-U.S.

TH-PO179
Metformin Inhibits Cyst Formation in a Zebrafish Model of Polycystic Kidney Disease Mine-Yang Chang, Hoon Park, Jong Hyun Park, Chang Gung Memorial Hospital, Chang Gung Univ College of Medicine, Kueishan, Taoyuan, Taiwan.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by enhanced fluid secretion and abnormal cell proliferation in renal tubular epithelial cells. Recent research has proposed that activation of AMP-activated kinase (AMPK) is a novel treatment strategy for ADPKD. However, we examined the effect of metformin on the initiation of proenephric cysts in a PKD2 zebrafish model.

Methods: Morpholino-mediated knockdown of pkd2 was performed in wt-1b pronephric-specific GFP-expressing zebrafish embryos to induce visible pronephric cysts for observation. Pkd2 morphants were treated with metformin (2.5 to 10 mM) in the embryo medium until 48 hours post fertilization.

Results: Metformin significantly reduces the frequency of cyst formation and proenephric tubular cell proliferation in pkd2 morphant embryos. Whole mount in situ hybridization for L-plastin mRNA showed significantly reduced macrophage infiltration.
in metformin-treated pkd2 mice. RTP-PCR showed that P2X7, IL-1β and IL-10 mRNA expression were significantly inhibited by metformin. Simultaneous morpholino knockdown of AMPK α1 prevents the rescue effects of metformin on cystogenesis.

**Conclusions:** We showed that metformin decreases cyst formation through inhibiting cell proliferation and macrophage accumulation in a pkd2 zebrafish model. These results indicate that metformin reduces the earliest cyst formation in polycystic kidney disease, and its effect on progression of disease remained to be investigated.

**Funding:** Government Support - Non-U.S.

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**TH-PO180**

**Cardiac Hypertrophy and Cardiac mTORC1/2 Signaling in Rodent Models of PKD**

**Kameswaran Ravichandran,** Qian Wang, Charles L. Edelstein. *Univ Colorado Denver.*

**Background:** Cardiac disease is the commonest cause of death in ADPKD patients. Young normotensive ADPKD adults and children have higher LVMI compared to controls. Aim of study was to determine in rodent PKD models: 1) whether there is cardiac hypertrophy and increased mTORC1/2 signaling in the heart 2) the effect of mTOR kinase inhibition on cardiac hypertrophy.

**Methods:** Heart weight was determined in Pkd1 +/- mice, Pkd2ZwS25+/-(Pkd2 +/- mice) and Han:SprD (Cy/+ rats. pS6 and p4E-BP1, markers of mTORC1 and pAktSer473, marker of mTORC2, were determined by immunoblot analysis of 3 separate experiments. Pkd2 +/- mice were treated with an mTOR antisense oligonucleotide (ASO) that inhibits mTORC1 and Pkd2 from 4-16 wks of age. Cy/+ rats were treated with the mTOR kinase inhibitor, PP242, that inhibits mTORC1/2 and PKC from 3-8 wks of age.

**Results:** There was increased heart weight in 150 d old Pkd1 +/- mice, 16 wk old Pkd1 +/-, 12 wk old normotensive Cy/+ rats and Pkd2 +/- mice that are haplo-insufficient for Pkd2 and do not have hypertension. There was increased pS6, p4E-BP1 and pAkt in Pkd1 +/- hearts and increased p4E-BP1 and pAkt in Pkd2 +/- and Pkd2/+- hearts. mTOR ASO resulted in less p4E-BP1 and pAkt and less cardiac hypertrophy in Pkd2 +/- mice. mTOR kinase inhibitor, PP242, resulted in less cardiac hypertrophy in normotensive Cy/+ rats HW/TBW(%) was 0.4 in +/-, 0.52 in Cy/+(P<0.05 vs +/+) and 0.44 in Cy/+PP242 (P<0.05 vs. Cy/+).

**Conclusions:** There was increased heart weight in normotensive Cy/+ rats and Pkd2 +/- mice. There was increased mTORC1 and 2 signaling in Pkd1 +/-, Pkd2/+- (without PKD) and Pkd2/+- hearts. mTOR kinase inhibition, that blocks both mTORC1 and 2, resulted in less cardiac hypertrophy. Discovery of an agent e.g. mTOR kinase or 4E-BP1 inhibitor that decreases early cardiac hypertrophy in PKD in addition to decreasing PKD would be a significant finding and would increase the enthusiasm to use these agents in ADPKD patients.

**Funding:** Veterans Administration Support

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**TH-PO181**

**Polycystic Kidney Disease – A Case of Suppressed Autophagy?**

Kameswaran Ravichandran, 1 Charles L. Edelstein. 1Univ of Colorado Denver; 1Univ of Colorado Denver.

**Background:** Autophagy is a normal physiological process that involves the degradation of damaged cellular components. Autophagy in general promotes cell survival while apoptosis that promotes cell death. We have reported (Edelstein et al, AJP, 2011) that there are features of autophagy like autophagosomes, mitophagy and autolysosomes in normal tubules and tubular cells lining cysts in Cy/+ rats with PKD and that there is suppression of autophagic flux in cpk mice with PKD.

**Methods:** 150 day old mice with PKD due to a kidney specific Pkd1 knockout were studied. MDCK cells with a stable knockdown of PC1 was achieved by lentiviral-mediated delivery of a specific SiRNA for PKD1 were studied. MDCK cells that form tubules were used as controls. LC3-II, a marker of autophagic flux and cleared caspase-3, a marker of apoptosis, were measured by immunoblot analysis of at least 3 separate experiments. Pkd1 +/- mice were treated with bafilomycin-A1 (5 mg/kg/d IP), a lysosomal inhibitor, for 3 days. MDCK cells were treated with bafilomycin 100 nm.

**Results:** In mice kidneys there was an increase in LC3 -II compared to wild type. The increase in LC3-II in Pkd1 +/- versus wild type kidneys suggests increased autophagosome synthesis or decreased degradation in the lysosome. To investigate these possibilities, Pkd1 +/- mice were treated with bafilomycin-A1. Bafilomycin-A1 had no effect on LC3-II in PKD kidneys of Pkd1 +/- mice. To determine the direct effect of PC-1 knockout on autophagy, PC-1 +/- MDCK cells were studied. In PC-1 +/- cells, there was a decrease in LC3-II compared to control MDCK. In PC-1 +/- cells treated with bafilomycin, there was a further suppression of LC3-II, indicating decreased autophagic flux. Increased apoptosis is a feature of PKD/Nephropathic cystinosis. In the PC-1 +/- cells there was a 2-fold increase in cleaved caspase-3, a marker of apoptosis, associated with the decrease in autophagic flux.

**Conclusions:** The lack of effect of the lysosomal inhibitor bafilomycin-A1 to increase LC3-II in Pkd1 +/- kidneys and in PC-1 +/- cells suggests a defect in autophagy resulting from suppression of autophagosome formation and degradation. There was an association between suppressed autophagy and increased apoptosis in PC-1 +/- cells.

**Funding:** Veterans Administration Support

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**TH-PO182**

**Retinoid X Receptor Pathway: A Novel Signaling Cascade Responsible for Cystogenesis in Three Rodent Models of Polycystic Kidney Disease**

Daisuke Yoshishara, 1 Masanori Kugita, 1 Harold M. Aukema, 2 Tamio Yamaguchi, 2 Shizuko Nagao, 1 1Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, Toyoake, Aichi, Japan; 2Dept of Human Nutritional Sciences, Univ of Manitoba, Winnipeg, MB, Canada.

**Background:** Polycystic kidney disease (PKD) is the most common inherited renal disorder and is characterized by innumerable cysts and tubular epithelial cell proliferation. We previously speculated that retinoid X receptor (RXR) may be related to cystogenesis in the Han:SprD-Cy (Cy/+) rat, since VDR/RXR activation, LPS/IL-1-mediated inhibition of RXR function, and LXR/RXR activation were altered in diseased kidneys. RXR is known to induce cellular proliferation and is normally degraded by ubiquitin after binding to its cognate ligand. In human hepatocellular carcinoma, the degradation rate of RXR is abnormally reduced, and treatment with a RXR agonist suppressed its proliferative activity (Adachi, Hepatology 2002). We therefore determined the expression and distribution of renal RXR, and the effect of a RXR agonist in polycystic kidneys.

**Methods:** Kidneys were obtained from three rodent models: Cy/+ rats, jck and pcy mice. Expression of RXR was confirmed by western blot analyses. Co-localization of RXR with PCNA, an index for cell proliferation, was detected by standard procedures. In addition, Cy/+ rats were orally treated with 30mg/kg bexaroten (BEX), a RXR agonist, from 4 to 10 weeks of age.

**Results:** In all three models, renal RXR levels were increased compared with age-matched rats/mice with normal kidneys. Total RXR was detected in the nuclear extract of cystic kidneys, and increased RXR was co-localized with PCNA in cyst epithelia nuclei. In jck and pcy mice, BEX treatment significantly decreased RXR expression and kidney weight adjusted to body weight.

**Conclusions:** RXR was related to aberrant cell proliferation in PKD progression in three different animal models, and a RXR agonist suppressed disease progression in Cy/+ rats. These findings suggest that RXR signaling may have an important role in cystogenesis and that RXR ligands may have therapeutic potential.

**Funding:** Government Support - Non-U.S.

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**TH-PO183**

**Integrin Linked Kinase Promotes Cyst Growth and Fibrosis in ADPKD**

Changhwan Ahn, 1, 2 Gail Reif, 1, 2 Yuqiao Dai, 1, 2 Darren P. Wallace. 1Dept of Medicine and Physiology, KU Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.

**Background:** Aberrant expression of extracellular matrix (ECM) molecules and secreted factors contribute to renal cyst growth and fibrosis in ADPKD. Periostin, a matricellular protein involved in tissue development and repair, is overexpressed in kidneys of ADPKD patients and murine models of PKD. Gene knockout mice of periostin reduced renal cyst growth and interstitial fibrosis, and prolonged the survival of PKD mice. Periostin binds to a,5-integrins (αv, β3, β5) and induces cell proliferation via integrin linked kinase (ILK) activation of Akt/mTOR, a key signaling pathway involved in PKD. We have determined if knockdown/knockout of ILK prevents periostin-induced proliferation of human ADPKD cells and reduces cyst growth and fibrosis in an ADPKD mouse.

**Methods:** We knocked down ILK expression in ADPKD cells using lentiviral shRNA. Activation of the Akt/mTOR pathway was determined by measuring phosphorylation of Akt and S6 kinase (56k), a downstream target of mTOR. To determine if ILK may be a potential therapeutic target, we knocked out ILK in collecting ducts of Pkd1+/+ and Pkd1+/Cre mice, an orthogonal model of ADPKD, by breeding these mice with Ilk-/- mice. At postnatal day 25, mice were euthanized and kidney weight/body weight (%KW/BW), cystic index, interstitial fibrosis and cell proliferation were measured.

**Results:** We found that ILK knockdown blocked periostin-induced phosphorylation of Akt and S6 of human ADPKD cells. CPD-22, an ILK inhibitor, also blocked the effect of periostin on the Akt/mTOR pathway and ADPKD cell proliferation. Gene knockout of one ILK allele (Pkd1floxflox/Ilk-/-: Pkd1Cre-/-) or both alleles (Pkd1floxflox/Ilk-/-: Pkd1Cre-/-) significantly decreased %KW/BW, renal cystic index and cell proliferation. Furthermore, ILK knockdown reduced renal interstitial edema and fibrosis in PKD mice, suggesting that blockade of the ILK signaling pathway may reduce both cyst growth and fibrosis in ADPKD.

**Conclusions:** Aberrant expression of periostin stimulates ILK activation of signaling pathways that contribute to renal cyst growth and fibrosis, suggesting that ILK may be a therapeutic target for ADPKD.

**Funding:** NIDDK Support
Periostin Regulates Polycystic Kidney Cell Proliferation and Cyst Formation via CFTR and JAK2/STAT3 Signaling Pathway

Methods: Periostin expression was analyzed using immunohistochemistry and western blot analysis in ADPKD cells and normal human kidney (NHK) cells. Cell growth and western blot analysis for related molecular levels were assayed after suppression of periostin by small interfering RNA (siRNA). Finally, a three-dimensional culture was performed to understand how periostin affected cyst formation, in vitro.

Results: The periostin expression was highly increased in ADPKD cells compared to NHK cells. Transfection of ADPKD cells with periostin siRNA decreased cell growth and increased cell death. Moreover, the expression of CFTR and phosphorylated levels of JAK2/STAT3 in three-dimensional culture, addition of recombinant periostin enhanced cyst formation, whereas periostin depleted cells showed lower level of cystogenesis.

Conclusions: Periostin stimulated cyst formation via CFTR and JAK2/STAT3 signaling pathway in ADPKD.

Effect of Simvastatin on Cell Adhesion in ADPKD

Methods: The possible role of mTORC1 and TCA Cycle in Cystic Renal Cell Formation and Transformation

Background: The pathogenesis of ADPKD is still not fully understood, however, it is clear that uncontrolled cell growth and proliferation are hallmark features of ADPKD. In ADPKD, the growth factor TGF-β promotes renal cell proliferation and tumor formation. The TGF-β signaling pathway is activated in ADPKD kidneys, and inhibition of TGF-β signaling has been shown to reduce cyst growth.

Methods: In our study, we investigated the role of mTORC1 and TCA cycle in cystic cell formation using a murine model of ADPKD. We analyzed the expression of mTORC1 and TCA cycle genes in ADPKD mouse kidneys and compared them to normal mouse kidneys. We also investigated the effects of simvastatin, a drug that inhibits the TCA cycle, on ADPKD cell proliferation and cyst formation.

Results: Our results showed that mTORC1 and TCA cycle genes were upregulated in ADPKD mouse kidneys compared to normal mouse kidneys. Furthermore, simvastatin treatment significantly reduced cell proliferation and cyst formation in ADPKD mouse kidneys.

Conclusions: Our findings suggest that mTORC1 and TCA cycle play a critical role in the pathogenesis of ADPKD and that targeting these pathways may be a potential strategy for the treatment of ADPKD.

In untreated cystic tubular epithelial cells E-cadherin expression was significantly lower compared to normal control cells. Expression of E-cadherin was slightly reduced in the cystic cells after treatment with simvastatin. This cytotoxic effect on cystic cells was increased with simvastatin compared to pravastatin.

Conclusions: Simvastatin may have pleiotropic effects on cystic epithelial cells including an effect on cell adhesion. The lack of effect on normal tubular epithelial cells indicates that simvastatin may have specific therapeutic benefits in human ADPKD. Future clinical trials will be necessary to test the benefits of simvastatin on slowing cyst growth.

Funding: NIH/NIDDK Support

Identification of a Renal Pkd1/Pc1 Self-Amplification Mechanism via c-Myc in Polycystic Kidney Disease

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic disorders associated with kidney disease. The disease is caused by mutations in the Pkd1 and Pkd2 genes, which encode polycystin-1 and polycystin-2, respectively. The pathogenesis of ADPKD is complex and involves the aberrant activation of several pathways, including the Wnt/β-catenin and Notch signaling pathways.

Methods: In our study, we investigated the role of c-Myc in the pathogenesis of ADPKD using a murine model of ADPKD. We analyzed the expression of c-Myc and its downstream targets in ADPKD mouse kidneys and compared them to normal mouse kidneys. We also investigated the effects of simvastatin, a drug that inhibits the TCA cycle, on ADPKD cell proliferation and cyst formation.

Results: Our results showed that c-Myc was strongly induced in ADPKD mouse kidneys compared to normal mouse kidneys. Furthermore, simvastatin treatment significantly reduced cell proliferation and cyst formation in ADPKD mouse kidneys.

Conclusions: Our findings suggest that c-Myc plays a critical role in the pathogenesis of ADPKD and that targeting this pathway may be a potential strategy for the treatment of ADPKD.

Funding: NIH/NIDDK Support

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

Underline represents presenting author.
Results: We first determined that Pkd1 dosage-increased and -reduced mouse models lead to stimulation of renal c-Myc expression (5-10-fold) in an ADPKD renal tissues, identifying a key downstream effector and the high relevance of SBE mice. This prompted analysis of SBE mouse that showed enhanced protein expression of c-Myc full length and nick-Myc in tubular epithelial cells. C-Myc immunostaining determined intense nuclear subcellular localization. Immunostaining of cystic kidney sections of SBE mice revealed that SBE protein was increased 10-fold over non-transgenic controls. Analysis of c-Myc downstream target, the cytosolic hypoxia inducible factor 1 alpha (Hif1α) in SBE kidneys showed intense immunostaining as observed in ADPKD, particularly in epithelial cells of cystic tubules and glomeruli. Immunofluorescence microscopy displayed a marked activation of β-catenin in renal epithelium that was stimulated as well in both P1 CpG islands hypermethylated genes identified by MBD-seq, and were underlying mechanisms of DNMTs in polycystic kidney disease remain unknown. In this study, we investigated the direct involvement of DNMT1 in regulating cystogenesis.

Methods: To understand the role of DNMT1 in cyst growth in vivo, we generated Pkd1 and DNMT1 double conditional knockout Pkd1ΔPkd1Δ/DNMT1Δ/Pkd1Δ-Cre mice. To study the novel DNMT1 target genes involving in cystogenesis, we performed CHIP-seq, MBD-seq and RNA-seq analysis.

Results: We found that knockout of DNMT1 delayed cyst growth characterized by decrease of 1) cyst index; 2) the kidney weight (KW)/body weight (BW) ratio; and 3) the blood urea nitrogen (BUN) levels (p < 0.01); as well as the 1) the phosphorylation of ERK, Rb, S6 and STAT3 as well as the expression of cyclin D1 as that of these candidate genes were validated by qRT-PCR. One of these genes named Ptprm was identified as a marker gene of c-Myc, which was stimulated as well in both P1 CpG islands hypermethylated genes identified by MBD-seq, and were downregulated in cystic renal epithelial cells as analyzed by RNA-seq. The downregulation of these candidate genes were validated by qRT-PCR. One of these genes named Pmip (protein tyrosine phosphatase receptor type M) is a tumor suppressor gene which regulates the phosphorylation of proteins and is hypothesized that inactivation of ERK, Rb, S6 and STAT3 and the expression of cyclin D1 that as that in Pkd1 and DNMT1 knockout kidneys.

Conclusions: DNMT1 promotes renal cyst growth in ADPKD through methylation of Ptprm gene to inhibit its expression, leading to increase the phosphorylation and activation of PKD associated pathways.

Funding: NIDDK Support

TH-PO190

Triptolide Retarded Disease Progression in Polycystic Kidney Disease Through Reducing Polycystin-2 Over-Expression and Suppressing JAK2/STAT3 Pathway

Ming Wu, Changlin Mei. Kidney Inst, Dept of Nephrology, Shanghai Changzheng Hospital, Shanghai, China.

Background: The beneficial effect of triptolide in polycystic kidney disease (PKD) has been shown in several animal models and also in a clinical trial. It is suggested that triptolide inhibits cell proliferation in PKD by activating endoplasmic reticulum-bound calcium channel polycystin-2 (PC2) and thereby enhancing intracellular calcium level. The aim of current study was to prove a new working mechanism of triptolide in PKD that triptolide directly inhibit c-Myc mediated mitogenic signaling pathways which is independent of calcium.

Results: Triptolide inhibited ADPKD cell proliferation which was correlated with decreased PC2 protein level and reduced JAK2/STAT3 activity. Over-expression of PC2 restored triptolide suppressed cell proliferation and JAK2/STAT3 activity. Blockage of PC2 by siRNA abolished triptolide mediated inhibition on cell proliferation and reduced JAK2/STAT3 activity. Twelve weeks triptolide treated reduced BUN and creatinine level by 22% and 25% respectively in cystic Cy/+ HsPrkD rats. Administration of triptolide decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 18.6% and 12.7% respectively. Western blot analysis showed that triptolide decreased polycystin-2/p38 protein level and reduced JAK2/STAT3 activation in vivo.

Conclusions: Our study revealed a novel triptolide’s mechanism of action in PKD. Reducing PC2 over-expressed could be a new strategy for PKD treatment in the future.

Funding: Government Support - Non-U.S.

TH-PO191

Resveratrol Delayed Disease Progression in Polycystic Kidney Disease Through Attenuating P50/p65 Induced Inflammation

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Background: The natural anti-inflammatory compound resveratrol displayed beneficial effects in a variety of diseases. The current study aimed to study the efficacy of resveratrol in polycystic kidney disease (PKD) and reveal it’s underline mechanisms.

Results: Five weeks resveratrol treatment reduced BUN and creatinine level by 20% and 24% respectively in cystic Cy/+ HsPrkD rats. Administration of resveratrol decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 15% and 24% respectively. The proliferation index and the macrophage infiltration index were reduced by 40% and 43% respectively in resveratrol treated cystic kidneys in comparison to vehicle treated cystic kidneys. Resveratrol reduced protein levels of pro-inflammatory factors such as MCP-1, TNF-α and CFB in Cy/+ kidneys, which was correlated with decreased activity of NF-κB (p50/p65). Resveratrol and NF-κB specific inhibitor NQZ inhibited the expression of MCP-1, TNF-α and CFB and reduced NF-κB activity in ADPKD cells. Moreover NF-κB blockage minimized the reduction but not completely abolish the inhibitory of inflammatory factor production by resveratrol treatment.

Conclusions: NF-κB signaling pathway is activated in PKD and partly responsible for PKD inflammation. Targeting inflammation through resveratrol could be a new strategy for PKD treatment in the future.

Funding: Government Support - Non-U.S.

TH-PO192

Increased Hedgehog Signaling in jck Mice and in Human ADPKD

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by disruption of Polycystin-1 and Polycystin-2, which localize to primary cilia of renal epithelial cells. Activation of the Hedgehog (Hh) pathway relies on primary cilia. Previously, we showed that renal cystic disease in mice caused by deletion of Thm1, a cilary gene and negative regulator of Hh signaling, was attenuated by genetically downregulating the Hh pathway, suggesting a role for enhanced Hh activity in renal cystogenesis. We aim to determine whether a role for dysregulated Hh signaling extends to cystic disease in jck mutation and in human ADPKD.

Methods: We determined whether Hh activity correlated with disease progression in jck mutants. Hh signaling was downregulated in jck mice by deleting Gl2, the primary transcriptional activator of the Hh pathway, using a ubiquitous, tamoxifen-inducible Cre recombinase. To examine Hh status in human ADPKD, we compared Hh levels in normal human kidney (NHK) and ADPKD tissue and primary cells using Q-PCR, immunohistochemistry and immunofluorescence.

Results: In jck mice, expression of Hh target genes, Gl1, Gl3 and Pi2, were elevated at seven weeks of age and increased further at 18 weeks of age. Immunohistochemistry for GL1 revealed increased expression in renal epithelial and interstitial cells, suggesting both paracrine and autocrine signaling mechanisms. Further, jck/Gl2 double mutants showed decreased renal cystogenesis compared to single mutant littermates, suggesting a causal role for increased Hh signaling in increased disease. In human and ADPKD cells, Hh target gene expression was increased and GL1 protein expression was increased in both cystic epithelial and interstitial cells. Additionally, even in the absence of a Hh agonist, expression of Hh target genes was increased, supporting the role for dysregulated Hh signaling extending to cystic disease in jck mutation and in human ADPKD.

Methods: We determined whether Hh activity correlated with disease progression in jck mice, expression of Hh target genes, Gl1, Gl3 and Pi2, were elevated at seven weeks of age and increased further at 18 weeks of age. Immunohistochemistry for GL1 revealed increased expression in renal epithelial and interstitial cells, suggesting both paracrine and autocrine signaling mechanisms. Further, jck/Gl2 double mutants showed decreased renal cystogenesis compared to single mutant littermates, suggesting a causal role for increased Hh signaling in increased disease. In human and ADPKD cells, Hh target gene expression was increased and GL1 protein expression was increased in both cystic epithelial and interstitial cells. Additionally, even in the absence of a Hh agonist, expression of Hh target genes was increased, supporting the role for dysregulated Hh signaling extending to cystic disease in jck mutation and in human ADPKD.

Results: We found that knockout of DNMT1 delayed cyst growth characterized by decrease of 1) cyst index; 2) the kidney weight (KW)/body weight (BW) ratio; and 3) the blood urea nitrogen (BUN) levels (p < 0.01); as well as the 1) the phosphorylation of ERK, Rb, S6 and STAT3 as well as the expression of cyclin D1 as that in Pkd1 and DNMT1 knockout kidneys.

Conclusions: DNMT1 promotes renal cyst growth in ADPKD through methylation of Ptprm gene to inhibit its expression, leading to increase the phosphorylation and activation of PKD associated pathways.

Funding: NIDDK Support

TH-PO193

The Development of a Clinically Relevant Mouse Model for Autosomal Dominant Polycystic Kidney Disease

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Background: To perform pre-clinical studies for Autosomal Dominant Polycystic Kidney Disease (ADPKD), it is desirable that the models have an adult onset of PKD and that they show rapid PKD and deletion in adult mice leads to slow PKD. The differences in rate of disease progression are largely explained by a rather sharp developmental switch that occurs around P13 (Piontek et al. 2007). This suggests that there is limited flexibility in generating models with intermediate phenotypes. Surprisingly, in this study, Pkd1 inactivation at different ages in tamoxifen inducible Pkd1 knockout mice led to multiple models for PKD with different characteristics.

Methods: To inactivate Pkd1, tamoxifen administration was done on three consecutive days at P10, P16, P18 or P40. Disease progression was monitored by measuring Blood Urea Concentration. The cystic burden and segmental origin of the cysts was studied using PAS staining and IHC for segment specific markers.

Results: P10 mice developed PKD within 3 to 4 weeks, with large distal and collecting duct cysts and few proximal tubular cysts. The progression rate in P16 mice was highly variable. By contrast, P18 mice developed end-stage PKD at an age of 14-17 weeks, with
cysts derived from all tubular segments that contributed equally to the phenotype. P40 mice developed end-stage PKD at an age of approximately 22 weeks with predominantly proximal cysts.

**Conclusions:** Despite a sharp developmental switch at P13 that has been proposed previously (Piontek *et al.* 2007) it is possible to generate multiple models with different progression rates and different origins of cyst. Notably, Pkdl deletion at P18 reproducibly led to adult onset PKD within a time-window that is highly suitable for therapeutic testing. In addition, since cysts were derived from all tubular segments, this model will contribute to finding a clinically relevant therapy for ADPKD patients.

**TH-POI194**

**Identification of New Signaling Pathways Related to Polycystic Kidney Disease:** From Animal Models to Treatment

*Olaya Lamas-Gonzalez,* 1 Susana Bravo,* 1 Ana Belen Sanz,* 1 Ana Barca de la Iglesia,* 1 Alberto Ortiz,* 1 Terry J. Watnick,* 2 D. Sanchez* 1

**Background:** Pathogenesis of Polycystic Kidney Disease (PKD) has been related to a number of different mechanisms that make it very complex and there is no therapy for complete inhibition of cystogenesis, although there are advances in controlling cyst volume and cyst progression.

**Methods:** Taking advantage of the identified developmental window in PKD using the Pkd1 conditional KO mouse, we have identified the differential proteome of the cystic and non-cystic Pkd1 mutant kidneys. We identify TWEAK as a window-dependent regulator of cystogenesis, inhibiting cystic progression in the cystic window, and promoting cystogenesis in the non-cystic window. We perform an exhaustive proteomics analysis of each cyst developmental stage by MALDI-TOF/TOF analysis of peptides and proteins separated either by LC or 2D-PAGE.

**Results:** We studied the proteomics fingerprint of each physiopathologic condition and refined new therapeutic targets to a very short list of 12 candidate targets. During cystogenesis, cytoskeletal interactions with the extracellular matrix (focal adhesions) seemed to be altered and, thus, their downstream signaling and regulatory pathways. Cell polarity, endocytosis and trafficking of proteins to nuclei are altered as well. Processes such as a5+c3-A5, free fatty acid metabolism and their transport are downregulated. Fruuctose metabolism is also downregulated. We have targeted the identity pathways both inhibiting complete cystogenesis deriving from distal nephron segment, as well as, reducing/delaying global cystic progression.

**Conclusions:** Here, we first describe the proteome related to the developmental cystic window as well as those pathways associated to the cystic progression under inflammatory stress. We hypothesize that response to treatment and cyst progression depend on a particular developmental window, so the correct dose and timing of a drug may prevent cystogenesis and make chronic treatment unnecessary. Here, we use a mouse model in which conditional inactivation of the Pkd1 gene by Cre-mediated recombination results in adult onset PKD.

**TH-POI195**

**Cytokine Tweak as an Intermediary in Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

*Olaya Lamas-Gonzalez,* 1 Susana Bravo,* 1 Ana Belen Sanz,* 1 Maria D. Sanchez-Niño,* 1 Ana Barca de la Iglesia,* 1 Adrian Cordido-Eijo,* 1 Alberto Ortiz,* 1 Miguel A. Garcia-Gonzalez,* 1 *Health Research Inst of Santiago de Compostela, Spain;* 2*Fundación Jiménez Diaz, Spain.*

**Background:** The pathogenesis of Polycystic Kidney Disease (PKD) remains unclear, but appears to involve altered tubular cell proliferation, cell death, differentiation and polarity as well as inflammatory and pro-fibrotic factors. It has been reported that acute kidney injury (AKI) and inflammation accelerate cystogenesis. TWEAK is a TNF-like cytokine that has a key role in AKI since anti-TWEAK antibodies prevented experimental kidney injury (AKI) and inflammation accelerate cystogenesis. TWEAK is a TNF-like cytokine that has a key role in AKI since anti-TWEAK antibodies prevented experimental kidney injury (AKI) and inflammation accelerate cystogenesis. TWEAK is a TNF-like cytokine that has a key role in AKI since anti-TWEAK antibodies prevented experimental kidney injury (AKI) and inflammation accelerate cystogenesis.

**Methods:** We studied the proteomics fingerprint of each physiopathologic condition and refined new therapeutic targets to a very short list of 12 candidate targets. During cystogenesis, cytoskeletal interactions with the extracellular matrix (focal adhesions) seemed to be altered and, thus, their downstream signaling and regulatory pathways. Cell polarity, endocytosis and trafficking of proteins to nuclei are altered as well. Processes such as a5+c3-A5, free fatty acid metabolism and their transport are downregulated. Fruuctose metabolism is also downregulated. We have targeted the identity pathways both inhibiting complete cystogenesis deriving from distal nephron segment, as well as, reducing/delaying global cystic progression.

**Conclusions:** Here, we first describe the proteome related to the developmental cystic window as well as those pathways associated to the cystic progression under inflammatory stress. We hypothesize that response to treatment and cyst progression depend on a particular developmental window, so the correct dose and timing of a drug may prevent cystogenesis and make chronic treatment unnecessary. Here, we use a mouse model in which conditional inactivation of the Pkd1 gene by Cre-mediated recombination results in adult onset PKD.

**Results:** PKD1 inactivation at day 12 resulted in massive cyst growth by day 30. Under these conditions systemic TWEAK administration for 10 days significantly decreased kidney cystogenesis. By contrast, PKD1 inactivation at day 14 did not result in cyst growth by day 30. Under these conditions systemic TWEAK administration for 10 days significantly promoted kidney cystogenesis. Inflammation background, tissue remodeling and immune response to kidney injury could be playing a key role in the development and progression of ADPKD. Interestingly, liver appeared to present a different developmental window as well those pathways associated to the cystic progression under inflammatory stress. We perform an exhaustive proteomics analysis of each cyst developmental stage by MALDI-TOF/TOF analysis of peptides and proteins separated either by LC or 2D-PAGE.

**TH-POI196**

**Defects in Epithelial Morphogenesis of Fibrocystin-Deficient Cells Are Associated with Disturbed Cell Adhesion**

*Wolfgang H. Ziegler, Birga Soetje,* Lisa P. Marten, Dr. German. *Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.*

**Background:** Mutations of the Phd1 gene cause autosomal recessive polycystic kidney disease (ARPKD). Phd1 encodes fibrocystin (FPC), a type 1 transmembrane protein of largely unknown function, which has been suggested to affect adhesion signaling of epithelial cells. Cell adhesion and/or cell migration are key factors to the disease process of ARPKD to remain to be defined. Having established a link between loss of FPC function and epithelial morphogenesis in 3D cell culture, we now aim to determine FPC-mediated parameters of (i) cell contact formation and (ii) the function / orientation of the actin cytoskeleton and microtubular networks.

**Methods:** We analyze FPC function in Madin-Darby canine renal collecting duct epithelial cells (MDCK) based on Phd1 silencing. Cells are being studied on micro-patterned chips in 3D cell culture conditions, which induce formation of epithelial spheroids. To determine epithelial differences we compare the phosphorylation status of several signaling proteins in epithelial cultures of FPC-deficient cells at day 1 and 2 (4-cell stages after seeding on chips using fluorescence microscopy.

**Results:** Based on defined adhesion conditions, we quantified the impact of FPC-deficiency on size / density of adhesion sites, cell shape characteristics and initiation of an apical surface. In cells deficient for FPC, cell culture conditions supporting correct epithelial morphogenesis induced significantly reduced cell area and number of cell adhesions sites per cell, with differences originating from defects in cytoskeletal organization rather than reduced cell size. Further insight is expected from ongoing analysis of centrosome and microtubular parameters of FPC-deficient cells.

**Conclusions:** FPC silencing in MDCK cells restricts adhesion signaling and cell-cell interaction resulting in impaired epithelial morphogenesis. Using a cell-based model system, we can address molecular consequences of and analyze rescue strategies for FPC deficiency in collecting duct epithelia.

**Funding:** Private Foundation Support, Government Support - Non-U.S.

**TH-POI197**

**Identification of FUBP1 as a PKD2 mRNA 3'UTR Binding Protein That Suppresses Its Translation**


**Background:** PKD2, also called polycystin-2, a Ca2+-permeable non-selective cation channel that is mutated in around 15% autosomal dominant polycystic kidney disease (ADPKD). Increasing evidence indicates that the PKD2 protein level is important for embryonic development, cell proliferation and to enhance renal injury. Inhibition of protein translation, but appears to involve altered tubular cell proliferation, cell death, differentiation and polarity as well as inflammatory and pro-fibrotic factors. It has been reported that acute kidney injury (AKI) and inflammation accelerate cystogenesis. TWEAK is a TNF-like cytokine that has a key role in AKI since anti-TWEAK antibodies prevented experimental kidney injury (AKI) and inflammation accelerate cystogenesis.

**Methods:** Here, with dual luciferase assays, western blotting, biotin-RNA pull down, gene knockdown in zebrafish, co-immunoprecipitation and GST-pull down, we studied how FUBP1 mRNA translation is regulated by its 3' untranslated region (3'UTR).

**Results:** First, by dual luciferase assays, we identified a fragment in PKD2 3'UTR, named 3FI (3' fragment inhibitory), that negatively regulates luciferase activity. Western blotting with a luciferase antibody confirmed the data obtained from the luciferase assays. By FUBP1 MO pull down and mass spectrometry, we identified a 3R-binding protein, called far upstream element binding protein 1 (FUBP1) that was originally found to transcribe of oncogene c-Myc. Over-expression and knockdown of FUBP1 decreased and increased the PKD2 protein level, respectively, without altering the mRNA level. Further insight is expected from ongoing analysis of centrosome and microtubular parameters of FPC-deficient cells.

**Conclusions:** Therefore, our data indicate that FUBP1 inhibits PKD2 translation through anchoring to PKD2 mRNA 3FI and interacting with 4EBP1.

**Funding:** Government Support - Non-U.S.

**TH-POI198**

**Towards Understanding the Structure-Function Relationships of Polycystin-1**

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**Background:** Appropriate levels of functional polycystin-1 (PC1), product of the PKD1 gene, are the key determinant preventing the development of renal cysts in ADPKD. Recent work revealed the existence of hyponorphic missense mutations of PKD1 and the positioning of the proper biogenesis and trafficking of PC1, and spill cells that use non-specific therapies could potentially be designed to correct the biogenesis of mutant PC1. These advances underscore our lack of knowledge regarding PC1 structure and emphasize the importance of understanding PC1 structure-function relationships. As such, we seek to generate a plausible tertiary structure model of human PC1.

**Methods:** A combination of comparative protein structure modeling along with validation by biochemical analyses is being used to predict and refine a human PC1 structure model. Our initial goal is to generate a 3D model of the arrangement of the 11 transmembrane (TM) segments in the context of extracellular loops, cytoskeleton and cytoskeletal and microtubular networks.

**Conclusions:** Firstly, we show that PC1 structure is highly dynamic and is likely to be influenced by the presence or absence of extracellular loops, cytoskeletal and microtubular networks.

**Funding:** Private Foundation Support, Government Support - Non-U.S.
prediction of transmembrane domain bundling, and experimental biochemical analyses to validate predicted models. Use of the predicted secondary structure or template-modeled tertiary structure of loops is used to constrain and refine TM segment arrangement.

Results: Initial work has focused on TM segments connected by shorter loops. Thus far, N-linked glycosylation scanning experiments have confirmed the de novo modeling results for TM segments 9 and 11. Glycosylation analyses for TM segment 10 are not entirely consistent with the predicted model, due to an extension of the length of the domain. Such discrepancy may result from the inherent membrane-associated property of this loop region of PC1, as described in earlier published work.

Conclusions: Preliminary, proof-of-concept work has resulted in a coarse model of the last 3 TM segments of PC1. These analyses will provide important knowledge for understanding structure-function relationships of PC1 and for the development of new ADPKD treatments.

Funding: Other NIH Support - KU-NIH Center of Biomedical Research Excellence in Protein Structure and Function

TH-PO201

Activation of the Polycystin Complex by WNT Ligands Seokho Kim,1 Hongguang Nie,1 Vasyl Nesin,2 Uyen Tran,2 Patricia Outeida,2 Chang-Xi Bai,2 Jacob Keeling,1 Dipak Maskey,3 Terry J. Watzick,4 Oliver Wessely,2 Leonidas Tisokas,1 Cell Biology, Univ of Oklahoma HSC, Oklahoma City, OK;1 Cellular and Molecular Medicine, Cleveland Clinic, Cleveland, OH;2 Medicine/Nephrology, Univ of Maryland School of Medicine, Baltimore, MD.

Background: PKD1 (Polycystin 1) is considered an orphan, atypical G protein coupled receptor complexed with TRPP2 (Polycystin 2 or PKD2), a Ca2+-permeable ion channel. Inactivating mutations in their genes cause autosomal dominant polycystic kidney disease (ADPKD), one of the most common genetic diseases. However, the molecular identity of the extracellular ligands activating the Polycystin complex is unknown. WNT ligands induce Ca2+ signaling on target cells. Here, we tested whether WNTs can bind and activate the Polycystin complex.

Methods: Experimental approaches include electrophysiology, protein-protein interactions using co-immunoprecipitations, directed cell migration assays, and embryological experiments in Xenopus laevis.

Results: Our data show that secreted WNTs bind to the extracellular domain of PKD1 and induce large whole cell currents and Ca2+ influx dependent on TRPP2, but independent of Frizzled (FZD) receptors. Pathogenic PKD1 or PKD2 mutations that abrogate complex formation, compromise cell surface expression of PKD1, or diminish TRPP2 channel activity suppress activation by a WNT protein. PKD2 fibroblasts lack WNT-induced Ca2+ currents and are unable to polarize during directed cell migration. In Xenopus embryos, PKD1 acts independently of FZD8, but within the same pathway with Dishevelled 2 to preserve normal kidney tubulogenesis.

Conclusions: These data define PKD1 as a new class of WNT (co)receptors and implicate defective WNT/Ca2+ signaling as one of the causes of ADPKD.

Funding: NIDDK Support

TH-PO202

Caffeine Consumption Contributes to Cyst/Kidney Enlargement and Progression of Polycystic Kidney Disease in a Pkd1-Deficient Mouse Model Renata Meca,1 Bruno E. Balbo,2 Milene Subtil Ormanji,1 Luiz F. Onuchic,3 Ita Pfefferman Heilberg,1 Nephrology Div, Fed Univ of Sao Paulo, Sao Paulo, SP, Brazil;1 Nephrology Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic renal disease, characterized by progressive cyst formation and growth, which ultimately leads to renal failure. In cultured cells from ADPKD patients, caffeine increased the levels of cyclic AMP and induced apoptosis and proliferation. We aimed to examine the in vivo effects of Caffeine on cyst growth and progression of renal disease using a murine model orthologous to human ADPKD.

Methods: Male and female Pkd1flox/floxNestin/Cre/Cystic mice and Pkd1flox/flox (Non-Cystic - NonCysCaf) mice consumed caffeine (3mg/day, in drinking water), from conception to 12 weeks of life. Caffeine was orally administered to the mother until puppy weaning (5 weeks) and thereafter directly supplemented in drinking water.Cistice control animals consumed water (CysCtrl) for the same period.

Results:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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Conclusions: Present findings demonstrate that caffeine induced an increase in renal volume and accelerated the progression of polycystic kidney disease in Pkd1-deficient mice. Funding: Government Support - Non-U.S.

TH-PO203

Changes in Urine Metabolites in PCK Rat Induced by dDAVP
Administration


Background: V2 receptor agonist-1-deamino-8-D-arginine vasopressin (dDAVP) aggravates the cystic disease of PCK rats by increasing renal cAMP without inducing cystic changes in wild-type rats (WT). We aimed to investigate the urinary metabolic changes in 1) PCK vs WT, and 2) response to dDAVP in PCK and WT rats.

Methods: PCK and WT rats were treated with 20 ng sc of dDAVP b.i.d. from p7 to p21, increasing to 40 ng sc b.i.d. from p22 to p35 inclusive or sc injections of isotonic (0.15 M) saline (S) at identical intervals. Abdominal MRI was performed at p10, p21 and p35 for kidney volume (KV). -H-NMR-based metabolomics analysis was performed from 24h urine collections at p30. The urine spectra were normalized to creatinine.

Results: Administration of dDAVP significantly aggravated the disease in PCK rats as evidenced by KV at p10, p21 and p35 (p<0.04, -0.001 and -0.001), but did not increase significantly KV or generate a cystic phenotype in WT rats (Fig1A-B). BUN levels were not significantly different between groups at p35. Thirty seven urination metabolites were identified. Thirteen metabolites were significantly different between PCK (S) and WT (S) (Fig1C). dDAVP induced significant changes in 5 metabolites in PCK but only 1 in WT rats. For example, urinary concentration of betaine, an important osmoregulatory compound, was significantly increased in PCK (S) compared to WT (S) and increased even further with dDAVP only in PCK rats.

Conclusions: -H-NMR-based metabolomics analysis identified 13 significantly different metabolites between PCK(S) and WT(S) rats. dDAVP aggravated the cystic disease and induced significant changes of urinary metabolites in PCK rats. Measurements of kidney tissue and plasma metabolites, in progress, will assist in the interpretation of these findings. Funding: NIDDK Support

TH-PO204

Localized Changes in MicroRNAs Are Critical to the Development of Fibrosis in PKD

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Background: ADPKD is characterized by proliferation and growth of tubular cysts and development of progressive interstitial fibrosis. These phases are consistently reproduced in the Pkd1+/+/- mouse, an orthologous model of Pkd1. In this mouse model, as in human ADPKD, the progression of fibrosis, rather than cyst size, leads to ESRD. MicroRNAs (miRNAs) are small noncoding RNAs that act as potent regulators of gene expression. In ADPKD, the progression of interstitial fibrosis in distinct patterns suggests that crosstalk between cystic epithelia and interstitial cells create a "pro-fibrotic" microenvironment. We hypothesize that changes in miRNA expression are critical to development of fibrosis in ADPKD.

Methods: Laser capture micro-dissection (LCM) of trichrome positive interstitium and, adjacent cystic tubular epithelia were profiled separately for local miRNA expression with QIAGEN miScript 384 HC miRNA PCR arrays at four distinct time points during which fibrosis is initiated and progresses. The miRNA profile was compared to age-matched whole kidney miRNA profiles, correlated with fibrosis pathway arrays, and immunohistochemical analysis.

Results: From PN1 to 28, interstitium and adjacent cystic epithelia demonstrated significant changes in miRNA expression (20 upregulated, 15 downregulated). These changes correlated with: a shift in the site of proliferation; a change in macrophage subtypes and number; significant increase in Tgf-B1,2,3, p-Smad2 and col3a1 and significantly decreased BMP7 expression. miRNA expression exhibited a variable expression with initiation and then progression of the disease.

Conclusions: 1. Compartmental changes in miRNA expression seen with LCM were not seen in the whole kidney analysis, demonstrating the value of the approach. 2. Pro-fibrotic and Anti-fibrotic miRNAs predicted to regulate TGFBR1, 2 and 3, collagen 3a1, 4a1, 4a4 and 4a5 and most interestingly EGRF, and STAT3 are significantly altered in peri-cystic interstitium. 3. We speculate that such compartment specific changes in miRNA expression are critical to development of fibrosis in ADPKD and may provide therapeutic targets to halt the progression of ADPKD.

Funding: Pharmaceutical Company Support - Taiho pharmaceutical ltd., Private Foundation Support

TH-PO205

miR-21 Promotes Cyst Growth in Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the presence of numerous fluid-filled cysts in the kidney. MicroRNAs (miRNAs), short noncoding RNAs that regulate gene expression, have emerged as promising new therapeutic targets for many common diseases. The goal of this study was to identify miRNAs that represent new drug targets for ADPKD.

Methods: Microarrays, Q-PCR, and ISH were performed to determine miR-21 expression in PKD. ChIP and promoter lucerase reporter assays were performed to understand the mechanisms that underlie miR-21 regulation in cystic kidneys. To study the role of miR-21 in ADPKD, miR-21 was inactivated in Pkd1+/Crc;Pkd2+/KO mice, an orthologous mouse model of ADPKD. RNA-Seq was performed to elucidate the differential gene expression pattern between Pkd2-KO and Pkd2-mir-21-/- KO mouse kidneys.

Results: miR-21 expression was increased in multiple mouse models of PKD, including two orthologous models of PKD. Upregulation of miR-21 was primarily localized to mouse kidney cyst epithelial cells. Increased miR-21 expression was also seen in cysts of human ADPKD tissue samples. cAMP-CREB signaling transactivated the miR-21 promoter in kidney cells. Inactivation of miR-21 in Pkd2-KO mice reduced kidney size, cyst number, and prolonged survival. RNA-Seq and subsequent pathway analysis identified cell death as the main biological effect of miR-21 deletion. Accordingly, compared to Pkd2-KO mice, Pkd2-mir-21-/- KO mice exhibited increased apoptosis of cyst epithelial cells without any change in proliferation. Expression of Pdcd4, a pro-apoptotic miR-21 target, was increased in cysts of Pkd2-mir-21-/- double knockout mice, indicating that miR-21 inhibits Pdcd4 in cystic kidneys.

Conclusions: Upregulation of miR-21 in a common feature of mouse and human forms of PKD. Deletion of miR-21 attenuates cyst burden and prolongs survival. miR-21 may promote cyst growth in ADPKD by preventing apoptosis of cyst epithelial cells through direct suppression of Pdcd4. Our studies suggest that inhibiting miR-21 may be a useful therapeutic strategy for ADPKD.

Funding: NIDDK Support, Other NIH Support - NIH institutional T32 grant, Private Foundation Support

TH-PO206

Macrophages Programmed by Polycystic Kidney Disease Cyst Cells Produce Soluble CXCR2 Ligands That Promote Cyst Cell Proliferation

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Background: The presence of renal macrophages in animal models of PKD has been shown to promote disease progression. The mechanisms underlying this phenomenon are incompletely understood but are likely due to reciprocal interactions between infiltrating macrophages and cyst epithelial cells: cyst cells stimulate macrophage differentiation to an M2-like, pro-proliferative phenotype and, in turn, these now "programmed" macrophages secrete factors that promote disease progression. Efforts are underway to identify the specific CXCR2 ligands produced by programmed macrophages that are responsible for this pro-proliferative effect. These factors and their signaling pathways could provide new targets for the development of therapies to slow PKD progression.

Funding: Other NIH Support - NCATS and NIGMS

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

Underline represents presenting author.

136A
PKD2-Related Autosomal-Dominant Polycystic Kidney Disease (ADPKD): Mutation Spectrum, Clinical Presentation, and Diagnosis

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Background: The milder severity of PKD2 related ADPKD (*) 15% of the pedigrees) as compared to PKD1 is well acknowledged, but population-based studies, enabling to depict the exact burden of the disease, are currently lacking. In this study, we aimed to describe the clinical presentation and the mutation spectrum in a large cohort of PKD2 patients.

Methods: Genekyst is a cross-sectional cohort which aims to include all consenting ADPKD patients followed in 23 Nephrology centers from the western part of France. Clinical data were collected and a comprehensive molecular analysis of PKD1 and PKD2 genes was undertaken.

Results: A total of 70 different PKD2 mutations were identified in 248 patients from 172 pedigrees (i.e. 20.2% of the mutation-positive pedigrees from Genekyst). A recurrent 28-kb deletion involving exons 10-15 was identified in 45 patients from 23 pedigrees confined in an area of ~3500 km², which represents to our knowledge the first case of founder mutation in ADPKD. Median age at diagnosis in the total cohort was 41.5 yrs. At age 70, cumulative probability of ESRD obtained by Kaplan Meier analysis was 37.4%, 28-kb deletion involving exons 10-15 was identified in 45 patients from 23 pedigrees.

Conclusions: This large cohort confirms that PKD2 patients typically present with a mild disease and therefore a vast majority of them may not require emerging targeted therapies. Funding: Government Support - Non-U.S.

Gene Discovery for Autosomal Dominant Polycystic Liver Disease (ADPLD)

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Background: ADPLD involves identical polycystic liver disease to that seen in ADPKD, but without clinically relevant kidney cysts. While mutations in PKD1 lead to ADPKD, mutations in genes that directly affect Polycystin 1 (PC1) expression or function cause ADPLD. Study of two identified ADPLD genes, SEC63 and PRKCSH, has shown the importance of co-post-translational modifications in the ER for PC1 function, and demonstrated the critical role of PC1 dosage in cyst pathogenesis. We hypothesize that discovery of additional ADPLD genes in patients will identify other functional modulators of PC1.

Methods: We have established a cohort of 161 unrelated individuals and families with ADPLD. Those without known mutations (Discovery Cohort) underwent whole exome sequencing together with linkage analysis where sufficient family material existed. Initial evaluation focused on candidate genes with rare heterozygous loss of function mutations. We established an in vitro bioassay to test a subset of candidates by evaluating PC1 expression and cilia trafficking following knockout of the candidate gene by CRISPR in cell culture.

Results: We found that 65/161 (40%) of ADPLD probands have mutations in SEC63 (18%) or PRKCSH (22%). Initial analysis of exome sequencing of our Discovery Cohort identified three candidate genes that function in ER biogenesis pathways related to the known genes and explain a total of 10 unrelated cases. We have generated cell knockout of one of these new candidate genes and shown a decrease in PC1 expression and as well activation of XBP1s, similar to our earlier findings in sec63 knockouts.

Conclusions: ADPLD gene discovery using whole exome sequencing coupled with in vitro bioassay of PC1 function in an unbiased and achievable approach to identify necessary proteins and pathways for PC1 function, and thus help to better define cyst pathogenesis in ADPLD and ADPKD. Funding: NIDDK Support.

Morpholino and Mutant Studies of Pde3a and Pde1a in Renal Cystogenesis Using Zebrafish

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Background: Numerous studies demonstrate the role of CAMP in cyst development and Polycystic Kidney Disease (PKD) progression. Studies in zebrafish using morpholinos show that Phosphodiesterase (Pde) 1A modulates renal cyst development and associated phenotypes, consistent with its hydrolysis of cAMP.

Methods: MOs were used to assess effects of Pde3A on renal cyst development and associated phenotypes, hydrocephalus and otolith defects. Additionally, we have generated 3 Pde1a mutant zebrafish lines using TALENs. Phenotypes were evaluated blinded, and data were analyzed using chi-square on embryos summed within treatments from 3-4 experiments.

Results: Depletion of Pde3A using two splice-blocking MOs increased the incidence of renal cysts at 2 days post-fertilization (dpf). Both MOs targeted exon 12 of pde3a, the first exon of the hydrolytic domain, encoding the conserved HD required for hydrolysis. Splice acceptor MO induced cysts with dose dependence at 2.5 ng (22%) and 5 ng (33%) vs. 5 ng control MO (0%) (p<0.003, n≥40 embryos/treatment). Splice donor MO induced cysts with dose dependence at 2.5 ng (13%) and 5 ng (59%) vs. 5 ng control MO (0%) (p<0.003, n≥40 embryos/treatment). The splice-donor MO also induced hydrocephalus at 2.5 ng (25%) and 5 ng (60%), and otolith defects at 2.5 ng (38%) and 5 ng (79%) vs. 5 ng control MO (0%) (p=0.06, n≥40 embryos/treatment). The splice-donor MO also induced hydrocephalus at 2.5 ng (25%) and 5 ng (60%), and otolith defects at 2.5 ng (38%) and 5 ng (79%) vs. 5 ng control MO (0%) (p=0.06, n≥40 embryos/treatment). Splicing of cystic embryos showed altered splicing at the targeted exon. Similar to MOs, Pde1a TALENs were generated targeting the exon encoding the conserved HD. We have obtained 3 unique mutant lines which disrupt the HD. In initial studies, Pde1a-/- fish are found at expected frequencies in adult populations, indicating survival equivalent to that of Pde1a+/+ fish.

Conclusions: MO studies of Pde3A suggest its involvement in renal cystogenesis and associated phenotypes, similar to previous studies using Pde1A MOs. TALENs effectively induced function-blocking mutations in Pde1a, which will allow studies of Pde1a-/- fish. Funding: NIDDK Support, Private Foundation Support.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Transcriptional Repression of PKD1 by Gene-Body Hypermethylation Induces Renal Cyst Development in ADPKD


Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common human genetic disease characterized by the formation of multiple fluid-filled cysts in bilateral kidneys. Although mutations in polycystic kidney disease 1 (PKD1) are predominant, responsible for ADPKD, the sporadic and familial sporadic of individual cystogenesis suggests another molecular mechanism such as epigenetic alterations.

Methods: To determine the epigenomic alterations in ADPKD and their functional relevance, ADPKD and non-ADPKD individuals were analyzed by unbiased methylation profiling genome-wide and compared with their expression data.

Results: Intriguingly, PKD1 was hypermethylated in gene-body regions, and its expression was downregulated in ADPKD. Hypermethylation of PKD1 gene-body was associated with recruitment of methyl-CpG-binding domain 2 (MBD2) proteins. Moreover, treatment with DNA methylation inhibitors retarded in vitro cyst formation, accompanied with the upregulation of PKD1 expression.

Conclusions: These results are consistent with previous studies that knock-down of PKD1 was sufficient for cystogenesis. Therefore, our results reveal a critical role for hypermethylation of PKD1 and cystogenesis-related regulatory genes in cyst development, suggesting epigenetic therapy as a potential treatment approach for ADPKD.

Funding: Government Support - Non-U.S.

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Age- and Sex-Dependent Salt Sensitivity in Pkd1+/− Rats
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Background: Most forms of hypertension are influenced by gender and salt sensitivity. However, interplay of these two factors and their functional consequences in PKD-associated hypertension are incompletely understood. Thus, we tested the hypothesis that age and male sex would pre-dispose animals with Pkd1+/− to hypertension and risk of renal injury.

Methods: We used Pkd1+/− rat model of autosomal recessive PKD to study sex difference in blood pressure in response to high salt (HS) diet. Two-month and eight-month-old male and female Pkd1+/− rats were surgically implanted with telemetry transmitters and allowed to recover for at least one week before obtaining baseline mean arterial pressure (MAP). Rats were then fed a high salt (HS; 4% NaCl) diet for 3 weeks. At the end of the study, rats were placed in metabolic cages and a 24 hr urine sample was collected before allowing to recover for at least one week before obtaining baseline mean arterial pressure.

Results: In the 2-month old Pkd1+/− rats, blood pressures were in a normal range and there were no differences between animals with Pkd1+/− and Pkd1+/+. However, in eight-month-old male and female Pkd1+/− rats, blood pressure was increased in male compared to female animals. Female, 3 weeks on a high salt diet had no effect on 24 hr MAP. In 8-month-old rats, again there were no sex differences between animals on normal rat chow. MAP was progressively increased in both male and female rats after 3 weeks of HS diet, after which physiological effects were studied. In male sex would pre-dispose animals with PKD to hypertension and risk of renal injury.

Conclusion: These results are consistent with previous studies that knock-down of PKD1 was sufficient for cystogenesis. Therefore, our results reveal a critical role for hypermethylation of PKD1 and cystogenesis-related regulatory genes in cyst development, suggesting epigenetic therapy as a potential treatment approach for ADPKD.

Funding: Other NIH Support - NHLBI

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Sodium Intake versus Disease Progression in Experimental Polycystic Kidney Disease
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Background: Vasa, a known determinant of disease severity and progression in ADPKD, increases in response to an increase in plasma osmolality, of which sodium is the most important osmol. We hypothesized that lowering sodium intake reduces vasa expression and thereby may improve disease progression in ADPKD.

Methods: We used a tamoxifen-inducible kidney epithelium-specific Pkd1-deletion mouse model. All mice were treated for 3 weeks with either a low sodium (LS; 0.39 g/kg) or high sodium (HS; 15.2 g/kg) diet, after which physiological effects were studied and mice were sacrificed.

Results: The attached table summarizes the results after the dietary intervention. A higher water intake was seen in Pkd1−/− mice in comparison with healthy controls (HC), in line with the impaired urine concentrating capacity occurring in PKD. For both HC and Pkd1−/− mice water intake was higher in HS groups, in line with the physiological effects of sodium intake. In contrast to our hypothesis, a LS diet did not result in improved disease progression as total kidney weight (TKW), TKW per body weight (TKW/BW), cyst ratio and renal function (creatinine) were similar in all Pkd1−/− mice, regardless of the diet.

Conclusions: A low sodium diet results in less water intake, but does not improve disease progression in Pkd1−/− mice.

Funding: Veterans Administration Support

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Kidney-Specific Inactivation of the Exocyst Gene Sec10 in Mice Leads to Primary Cilia Defects and a Cystic Kidney Phenotype

Background: The primary cilia is a sensory organelle that projects from the apical surface of renal epithelial cells, and has been implicated in the pathogenesis of polycystic kidney disease. The exocyst complex is essential for ciliogenesis, and is regulated by Cdc42. Our previous studies showed that Cdc42 deficiency disrupts renal ciliogenesis and causes PKD in zebrasfish and mice, and that Tuba is also necessary for ciliogenesis in cultured MDCK cells.

Methods: Tuba knockdown MDCK cells were grown on Transwell filters and in three dimensional (3D) collagen gels, and zebrafish embryos were generated in which tuba was knocked down using antisense morpholinos. Ciliary and kidney defects caused by tuba deficiency were analyzed at molecular, histological and phenotypic levels.

Results: Tuba depletion resulted in an absence of cilia with impaired apical polarization of MDCK cell cysts. In heterozygote factor-depleted tubulogenes, we found that Tuba knockdown significantly inhibited tubule formation. In zebrafish, tuba was expressed in ciliated organs, including the brain, eye, neuremasts, and kidney. Tubas morphants phenocopied cdc42 morphants, with ciliary mutant phenotypes that included: a curly tail, hydrocephalus, and abdominal fluid accumulation. In tuba morphant kidneys, pronephric cilia were short and disorganized, and glomeruli were disorganized. Moreover, tuba morphants showed defects in cardiac laterality, consistent with ciliary dysfunction. Following co-injection of small amounts of tuba and cdc42 morpholinos, that alone had no effect, a severe phenotype was observed, suggesting that tuba and cdc42 act in the same pathway.

Conclusions: Our study showed that Tuba plays a critical role in ciliogenesis and kidney development in MDCK cells and zebrafish. We are generating tuba knockout zebrafish and tuba-null mouse models, using CRISPR and the Cre-lox binary mouse system, respectively. These animal models will allow us to better understand the pathogenic mechanisms of PKD, and could lead to novel treatments.

Funding: Other NIH Support - NHLBI
tubules of Sec10 mutant and control mice. Sec10-knockout tubules showed a 38.5% average overall cell death compared to 13.4% in control tubules. This suggests that Sec10-knockout tubules were much shorter than those in the control littermates (p<0.0001). Furthermore, significantly elevated blood urea nitrogen levels in knockout animals compared to controls suggested impaired kidney function.

Conclusions: Findings from our mouse model provide the first in vivo evidence of the exocyst’s involvement in mammalian primary cilia assembly and links Sec10 and the exocyst to the pathogenesis of polycystic kidney disease. Funding: NIDDK Support, Other NIH Support - NIGMS, Private Foundation Support

TH-P0216 Whole Exome Sequencing (WES) Resolves ARPKD-Like and Meckel Syndrome (MKS)-Like Pedigrees Unresolved by Sanger/Ciliopathy Panel Screening Katharina Hoop, Sarah J. Koon, Christina M. Heyer, Vicente E. Torres, Peter C. Harris. Mayo Clinic.

Background: ARPKD and MKS have phenotypic and genetic overlap with other ciliopathies, with many unresolved pedigrees after Sanger sequencing of commonly mutated genes (ARPKD – <10% of severe and –50% of mild cases; MKS – 45% of cases).

Methods: We performed WES (Agilent SureSelect, Illumina HiSeq 2000) on 18 Sanger screened, unresolved pedigrees, of which 13 were also assessed by targeted next-generation sequencing (NGS, 258 ciliopathy/cilia genes). Identified variants were filtered/scored based on quality, population frequency, segregation and substitution/gene significance.

Results: Screening for homozygous, compound heterozygous, and de novo variants identified disease-alleles in 4 pedigrees. Ped 1, ARPKD diagnosis at 4y, was homozygous for a novel BBS9 mutation (c.437-438insA), although the proband lacked key Bardet-Biedl Syndrome (BBS) features (retinitis pigmentosa, obesity, polydactyly, learning disability). The variant was missed by the targeted NGS panel due to preferential WT allele enrichment. Ped 2, 2 MKS diagnosed fetuses with PKD, polydactyly, hepatic fibrosis, but no CNS abnormalities, inherited two novel BBS7 variants (c.1405delC/trp470delC and p.V266E [scored as pathogenic]). Of note, BBS rarely causes embryonic lethality. Ped 3, a 15w MKS-like fetus with occipital encephalocele, sloping forehead and bifid tongue, inherited two C2CD3 mutations (c.1114=-, caused ex18 skipping, and p.V99M [scored as pathogenic]). This verified findings of the targeted NGS panel and excluded additional genetic disease causes. C2CD3 is linked to oral-facial-digital syndrome 14 but the fetus lacked key Bardet-Biedl Syndrome (BBS) features (retinitis pigmentosa, obesity, polydactyly, learning disability). The variant was missed by the targeted NGS panel due to preferential WT allele enrichment.

Conclusions: We show here the value of WES for resolving Sanger/NGS panel unresolved ciliopathy pedigrees, although with low detection rates. In addition, we show BBS genes associated with a broad ciliopathy disease spectrum, reporting for the first time BBS9 mutations in an ARPKD-like case and BBS7 mutations in a MKS-like pedigree. Funding: NIDDK Support, Private Foundation Support

TH-P0217 IFT81, Encoding an Intrflagellar Transport Protein, as a Rare Cause of a Ciliopathy Phenotype Jan Halbritter, Isabelle Perrault, Jonathan Porath, Xavier Gérard, Daniela A. Braun, Heon Yung Gee, Hanan Fathy, Richard P. Lifton, Jean-michel Rozen, Friedhelm Hildebrandt. Medicine, Boston Children’s Hospital, Boston, MA; 1Imagine Inst, Paris Descartes, Paris, France; 2Pediatric Nephrology, Univ of Alexandria, Alexandria, Egypt; 3Genetics, Yale Univ, New Haven, CT.

Background: Bidirectional intrflagellar transport (IFT) consists of two major protein complexes, IFT-A and IFT-B. In contrast to the IFT-B complex, all components of IFT-A have recently been linked to human ciliopathies when defective. We therefore hypothesized that mutations in additional IFT-B encoding genes can be found in patients with multisystemic ciliopathies.

Methods: We screened 1,628 individuals with reno-ocular ciliopathies by targeted next-generation sequencing, including all IFT-B encoding genes.

Results: Consequently, we identified a homozygous mutation in IFT81 affecting an obligatory donor splice site in an individual with nephropathies and polydactyly. Further, we detected a loss-of-stop mutation with extension of the deduced protein by 10 amino acids in an individual with neuronal ceroid lipofuscinosis-1 (CLN1). This proband presented with retinal dystrophy and brain lesions including cerebellar atrophy, a phenotype to which the IFT81 variant might contribute. Cultured fibroblasts of this latter affected individual showed a significant decrease in ciliated cell abundance compared to controls and increased expression of the transcription factor GLI2 suggesting deranged sonic hedgehog signaling.

Conclusions: This work describes identification of mutations of IFT81 in individuals with symptoms consistent with the clinical spectrum of ciliopathies. It might represent the rare case of a core IFT-B complex protein found associated with human disease. Our data further suggest that defects in the IFT-B core are an exceedingly rare finding, probably due to its indispensable role for ciliary assembly in development.

TH-P0218 Loss of Aatf in Murine Tubular Cells Leads to a Neorophosphinosis-Like Phentype Manaswita Jaiswal, Heide Irene Heinen, Heike Goebel, Bernhard Schermer, Thomas Benzinger, Katja Hoeckper. 1Internal Medicine II, Univ Hospital Cologne, Cologne, Germany; 2Dept of Pathology, Univ Hospital Cologne, Cologne, Germany.

Background: Genomic integrity is continuously being challenged by DNA damage of endogenous or exogenous sources. Aatf is a key regulator of the tumor suppressor p53 in the DNA-damage response signaling cascade. Aatf inhibits the ability of p53 to transactivate pro-apoptotic target genes. The conventional knockout of Aatf in mice is pre-implanationally lethal. A central role of DNA-damage signaling in tubular cells and cystic kidney diseases has been suggested. Here we show that deletion of Aatf in developing distal tubular and collecting duct cells leads to a degenerative, cystic phenotype, much alike juvenile nephronophthisis.

Methods: Conditional knockout mice, histology, phenotypic analysis.

Results: Aatf was knocked out using the Ksp/Cre mouse line in a floxed Aatf genetic background. The homozygous Aatf deletion results in weight loss and kidney failure at the age of 6-10 weeks. The mice show polyuria, polydipsia and have a reduced urine osmolarity. Their kidneys are small, pale and show small cysts predominantly at the cortico-medullary border. Histological examination shows tubular and glomerular cysts and interstitial fibrosis as well as an increased rate of apoptotic cell death.

Conclusions: Alternating the outcome of the p53-driven DNA-damage response in the Ksp/Cre;Aatf knockout leads to clinical and histological signs of juvenile nephronophthisis that links DNA damage response signaling to cystic kidney disease. Funding: Government Support - Non-U.S.

TH-P0219 Role for the Primary Cilium in Regulation Interstitial Macrophage Proliferation and Polarization During Kidney Maturation and Injury Cheng Jack Sung, Kurt Zimmerman, Michal Mrug, Bradley K. Yoder. 1Pediatric Developmental cell and Integrative Biology, Unv of California at Irvine, Irvine, CA; 2Pediatric Developmental cell and Integrative Biology, Unv of California at Irvine, Irvine, CA; 3Pediatric Developmental cell and Integrative Biology, Unv of California at Irvine, Irvine, CA; 4Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL.

Background: Induction of cilia loss in juvenile mice results in rapid cyst development while induction of cilia loss in adult mice causes a much slower rate of cyst progression. Rapid cyst formation can be initiated in the adult-induced IFT mutants by ischemic reperfusion (IR) injury suggesting a possible role for inflammation in cyst development. This was recently confirmed by liposome clodronate (LC) mediated depletion of phagocytic macrophages that reduced cyst severity and improved renal function. However, the crosstalk between primary cilia located on epithelial cells and the interstitial macrophages during cyst progression is unknown. Here, we investigate potential connections between primary cilia associated cystogenesis and changes in macrophage populations.

Results: Our preliminary data suggest the presence of a kidney resident macrophage population, likely derived from the yolk sac, which are present in juvenile mice and re-immerge in adult-induced cilia mutants following IR injury. Renal Resident macrophage demonstrates rapid proliferation following IR injury in adult-induced IFT88 mutant mice as early as 3 days following injury and persists for at least day 21. In contrast, resident macrophages from control mice show peak proliferation 3 days following IR injury that then abates at days 7-21.

Conclusions: This work suggests communication between the cilia on epithelial cells and the resident macrophages is important for kidney maturation and repair after injury. Our prediction is that defects in this communication will result in persistent resident macrophage proliferation that contributes to the rate of cyst formation. This work will provide possible targets for therapeutic intervention. Funding: NIDDK Support

TH-P0220 Ciliary Trafficking of Polycystin-1 and Polycystin-2 Is Interdependent Chong Luo, Manqiong Wu, Wassim El-jouni, Jing Zhao. Harvard Center for Polycystic Kidney Disease Research and Renal Div Dept of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background: Mutations in PKD1 account for over 85% cases of autosomal dominant polycystic kidney disease (ADPKD). About 30% of the PKD1 mutations are missense mutations which likely produce full-length proteins that are defective in trafficking to the primary cilia. It remains to traffic to the primary cilium in cells depleted of PC1. The proteolytic cleavage at the GPS site of PC1 is not required for its ciliary trafficking.

Methods: A set of deletion/mutation constructs in mouse PC1 including those corresponding to ADPKD1 frame-shifted mutations, as well as chimeric constructs with different mPC1 C-terminal motifs were developed. Transient transfection and immunostaining methods were used.

Results: We found that all pathogenic mutations tested were defective in ciliary trafficking. Ciliary localization of full-length PC1 or its mutants was completely abolished in PKD1 knockdown cells. However, this defect can be rescued by co-expression of PC2 in a dose dependent manner. Overexpression of PC2 even drives the C-tail-less PC1 mutant to traffic to the primary cilium in IMCD-3 cells. This promotion doesn’t rely on the previously identified ciliary targeting Vps39 motif at the N-terminus of PC2. The ciliary targeting of PC2 is also
regulated by the dose of PC1. Analyses of the C-tail of PC1 also led to the identification of a potential ciliary targeting sequence, consistent with the C-terminal tail of PC1 in addition to the previously identified VxPs motif. This sequence is sufficient to drive a chimeric construct to the cilia in IMCD-3 cells and is independent of the presence of PC2.

**Conclusions:** Ineffective ciliary trafficking of PC1 may represent a pathogenic mechanism in ADPKD. The mechanisms of polycystins trafficking to the primary cilia are complex involving multiple motifs and factors. Ciliary trafficking of full-length PC1 and PC2 are interdependent, they mutually promote each other to traffic to the primary cilia.

**Funding:** NIDDK Support

**TH-PO221**

**Anoctamin 6 Is Localized in the Primary Cilium of Renal Tubular Cells and Is Involved in Apoptosis-Dependent Cyst Lumen Formation**

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**Background:** Anoctamin (ANO) 6 is a member of a novel family of Ca2+-activated Cl- channels. Although ANO6 is the most widely expressed paralogue, only little is known about its subcellular localization. Recently, we could show that ANO6 together with ANO1 is expressed in renal cyst-lining cells. Unlike ANO1, which was involved in cyst expansion, the role of ANO6 remained elusive. Therefore, we analyzed the localization of ANO6 in renal tubular cells and tested for a role in cyst formation.

**Methods:** We stained polarized MDCK cells for ANO6 in comparison to stably ANO6-deficient cells. In addition, we analyzed human collecting duct (HCD) cells and primary human tubular cells to test for species- and segment-specific expression. We also examined the effect of ANO6 deficiency on MDCK cyst formation and performed Ussing chamber experiments to test for changes in transepithelial Cl- secretion. Additionally, we stained kidney sections comprising healthy and cystic tissues from ADPKD patients for ANO6.

**Results:** ANO6 was localized in the primary cilium of all tubular cells irrespective of species or segment. Furthermore, the localization of ANO6 could be detected in human kidneys. ANO6 knockdown resulted in loss of cilary ANO6 signals but had no effect on ciliary dystroglycan or MDCK cyst growth. In line with these data, ANO6-deficient MDCK cells revealed no alteration in Ca2+-dependent Cl- secretion. However, lumen formation was markedly disturbed in ANO6-deficient cysts which could be referred to an increased number of cells situated within the cyst lumen which normally would get removed by apoptosis. However, ANO6-deficient cells showed a strong reduction of Ca2+-dependent phospholipid scrambling as well as TUNEL- and Caspase3 signals. In addition, apoptotic cyst cells in human ADPKD were characterized by strong co-expression of ANO6.

**Conclusions:** ANO6 is a cilary protein and involved in apoptosis-dependent cyst lumen formation.

**Funding:** Government Support - Non-U.S.

**TH-PO222**

**Regulation of Cilia Function by Protein Palmitoylation**

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**Background:** Cilia are microtubule based protrusions of the plasma membrane which serve sensory and signaling functions. Abnormalities in cilia cause diseases known as ciliopathies, which include autosomal dominant polycystic kidney disease and nephropathies. Many ciliopathies involve abnormal trafficking of proteins to cilia. Trafficking of proteins may be affected by cysteine palmitoyltransferase, the reversible post-translational attachment of the lipid palmitate to proteins. Since numerous cilia proteins which serve sensory and signaling functions. Abnormalities in cilia cause diseases.

**Methods:** We stained polarized MDCK cells for ANO6 in comparison to stably ANO6-deficient cells. In addition, we analyzed human collecting duct (HCD) cells and primary human tubular cells to test for species- and segment-specific expression. We also examined the effect of ANO6 deficiency on MDCK cyst formation and performed Ussing chamber experiments to test for changes in transepithelial Cl- secretion. Additionally, we stained kidney sections comprising healthy and cystic tissues from ADPKD patients for ANO6.

**Results:** ANO6 was localized in the primary cilium of all tubular cells irrespective of species or segment. Furthermore, the localization of ANO6 could be detected in human kidneys. ANO6 knockdown resulted in loss of cilary ANO6 signals but had no effect on ciliary dystroglycan or MDCK cyst growth. In line with these data, ANO6-deficient MDCK cells revealed no alteration in Ca2+-dependent Cl- secretion. However, lumen formation was markedly disturbed in ANO6-deficient cysts which could be referred to an increased number of cells situated within the cyst lumen which normally would get removed by apoptosis. However, ANO6-deficient cells showed a strong reduction of Ca2+-dependent phospholipid scrambling as well as TUNEL- and Caspase3 signals. In addition, apoptotic cyst cells in human ADPKD were characterized by strong co-expression of ANO6.

**Conclusions:** ANO6 is a cilary protein and involved in apoptosis-dependent cyst lumen formation.

**Funding:** Government Support - Non-U.S.
Reversal of Podocyte Loss in Mice with Membranoproliferative Glomerulonephritis (MPGN) by Iyoda, Tomasz A. Wietecha, Kelly L. Hudkins, Charles E. Alpers.


TH-PO228

Discovery of Mesencephalic Astrocyte-Derived Neurotrophic Factor as a Urine Biomarker for Endolymphatic Stluxium Retinopathy-Related Diseases

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Background: Accumulating evidence has highlighted the important role of endolymphatic retinopathy stress in the pathogenesis of a variety of kidney diseases. Thus, it is imperative to develop non-invasive biomarkers for detecting ER stress in podocytes or tubular cells in the incipient stage of disease, when clinically a kidney biopsy is not yet indicated. Moreover, restoration of ER homeostasis before irreversible kidney cell injury may hold significant promise as an attractive therapeutic strategy. Here for the first time we discovered mesencephalic astrocyte-derived neurotrophic factor (MANF) as a potential urine biomarker for detecting ER stress in associated kidney diseases.

Methods: We used mouse models of human nephrotic syndrome (NS) caused by podocyte ER stress and of acute kidney injury (AKI) triggered by the ER stressor tunicamycin or ischemia/reperfusion (IR)-induced tubular ER stress.

Results: In our NS mouse model carrying the C321R laminin j2 (LAMB2) mutation in podocytes, podocyte ER stress was induced. The mutants exhibited MANF induction in podocytes at P24, when proteinuria was minimal, compared with controls. In vitro, secretion of MANF by mutant primary podocytes was increased as compared to that by control podocytes. Most importantly, MANF was easily detected in the crude urines of C321R mutants in the incipient stage of disease as compared to the controls. Meanwhile, in tunicamycin or IR-induced AKI mouse models, urinary MANF excretion concurrent with tubular ER stress preceded clinical or histological manifestations of acute tubular injury.

Conclusions: MANF can potentially serve as a urine biomarker to help stratify disease risk and predict disease progression in the ER stress-related kidney diseases. In addition, MANF can help identify subgroups of patients who can be treated with ER stress modifiers and monitor treatment response in a highly targeted manner.

Funding: NIDDK Support, NIH Support - UL1TR000488, Private Foundation Support

TH-PO229

Identification of Differentially Expressed Genes in Rat Purumycin Aminonucleoside (PAN) Nephropathy, a Micm of MCNS with Next-Generation Sequencing

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Background: To explore the novel therapeutic targets of nephrotic syndrome resulted from podocyte dysfunction, we intend to identify the molecules of which gene expression is changed in rat nephrotic models by the Next-Generation Sequencing analysis.

Methods: The profile of gene expression of PAN nephropathy was analyzed by next generation high-throughput RNA sequencing (RNA-Seq) with Solid system 5500. 581 molecules, whose mRNA was clearly altered (more than 5 times increase or less than 20% decrease to normal level), were identified. 20 molecules, which were expected to play a role in maintaining podocyte function, were selected, and the kinetic of the mRNA expression of these molecules were precisely analyzed in several nephrotic models including anti-nephrin antibody (ANA)-induced nephropathy, a proteomic model caused by the disappearance of the Sidr1 gene, and in ADK nephropathy, a mimic of FSGS, as well as PAN nephropathy.

Results: In PAN nephropathy, mRNA expression of 153 genes were increased (>5 times) at 1 h when abnormal proteinuria was not detected yet. mRNA expressions of 121 genes were increased on day 10 when proteinuria peaked. mRNA expressions of 37 genes were decreased at both before times point. 297 genes, whose mRNA expression was lowered to less than 20%, were identified. mRNA expressions of 186 genes were decreased similarly on day 10, and those of 121 genes were decreased at both 1h and day 10. For further analyses Phosphosipase A2, group IID (Pla2gd2) and proto cinchalin alpha 5 (Pcdha5) were focused. mRNA expression of Pla2gd2 was decreased to 11% at 1h and 13% on day 10 of PAN nephropathy. mRNA expression of Pcdha5 was decreased to 2.7% at 1h and 1.5% on day 10 of PAN nephropathy and 15% on day 5 of ANA nephropathy, whereas the mRNA expression was clearly increased on day 5 of ADK nephropathy.

Conclusions: RNA-Seq is a powerful tool for profiling gene expression and the detection of differentially expressed gene in proteomic state. It is assumed that the decrease in the mRNA expression of Pla2gd2 and Pcdha5 is involved in the development of proteinuria.

Funding: Government Support - Non-U.S.

TH-PO230

Comprehensive Polysonse Analysis in Injured Podocytes

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Background: Podocyte injury is the key event for progressive renal failure. It is difficult to isolate mRNA of podocytes from the kidney, which is made up with multiple-type cells. Therefore, we used mouse models of human nephrotic syndrome mouse line (established by Dr. Amieux F. P.S), in which Harvey (HA)-tag is inserted into the C-terminus of Rpl22, a component of the ribosomal protein, in the presence of CRE recombinase. Ribotag line was mated with nephrin-Cre and Nep25, an immunotoxin-inducible podocyte-selective injury model.

Funding: Government Support - Non-U.S.

TH-PO227

Role of Epithelial Membrane Protein 2 in Nephrotic Syndrome

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Background: Mutations in the human gene EMP2 (Epithelial Membrane Protein 2) have recently been linked to childhood-onset nephrotic syndrome. Its gene product, a tetraspan integral membrane protein, affects various cell behaviors including regulation of cell adhesion, migration, proliferation, apoptosis and tumorigenesis. EMP2 protein modulates the expression of GPI-anchored proteins, caveolin-1, integrin, and the growth factor VEGF. EMP2 is also necessary for embryonic implantation and chondral infidelity. We studied the renal expression pattern of EMP2 and generated a conditional EMP2 knockout model and examined its phenotype in vivo. We intended to have a new tool to study the role of EMP2 in glomerular diseases.

Methods: We created a floxed Emp2 (Emp2floxflox) mouse containing a LacZ reporter gene controlled by the endogenous Emp2 promoter. We assessed Emp2 expression in kidneys using whole-mount β-galactosidase (β-gal) histochemistry. To complement this analysis, we used an antibody against EMP2 to assess its localization by immunofluorescence (IF). Podocyte-specific KO mice (Emp2floflo) were generated by breeding Emp2floxflox mice to the Nphsl-Cre driver strain and were used for experiments.

Results: β-gal staining reveals that Emp2 is prominently expressed within major vascular bundles and a distinct band of cells within the cortex and renal papilla. Double-label IF using an EMP2 antibody and Lotus lectin suggests that the Emp2 expression within the renal cortex is in proximal tubules. The EMP2 antibody did not stain the renal papilla or renal vasculature. Whether this disparity is due to cell-specific post-translational modification (e.g. glycosylation) remains to be addressed. However, in both β-gal and IF assays Emp2 within the glomerulus was not seen. By 3 months of age, Emp2floxflox do not have proteinuria.

Conclusions: In contrast to a previous report, we did not observe Emp2 expression in podocytes. The discrepancies might be due to different genetic deletions of Emp2 in tubular and endothelial compartments will provide additional insights regarding the etiology of renal dysfunction in patients with EMP2 mutations.

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

Underlines represent presenting author.
Glomeruli were isolated before or after induction of podocyte injury. Podocyte-specific polysome was yielded by immunoprecipitation with anti-HA antibody and analyzed by Agilent’s 15K66K microarray (n=12) and qRT-PCR (n=8).

Results: In a baseline condition, microarray analysis revealed 5070 (9.1%) probes were significantly and more than 2-fold enriched in podocytes within the glomerulus, which include most known podocyte genes. qRT-PCR confirmed that Nphs1 and Nphs2 RNAs were concentrated in podocytes (15 and 8.6-fold), while mesangial and endothelial RNAs were diluted. Seven days after immunotoxin injection, 3130 (5.6%)/1938 (3.5%) probes were significantly and more than 2-fold up-regulated in podocytes from the baseline condition. Podocyte-specific genes Pdpn1 and Vps17 were decreased (0.37, 0.39, 0.28 and 0.16-fold), Des, Relb, Gadd45b and Cxcl1 were markedly upregulated (8.1, 1.6, 9.2 and 2.16-fold), which were confirmed by qRT-PCR. These changes were significantly correlated with those in Actn4 KO podocytes reported in TRAP study (R=0.520; p<0.001), suggesting that these changes represent common pathogenic responders. Separately, we reviewed the published studies of candidate genes identified by GWAS, thirteen, including Vegfa, were found to be concentrated in normal podocytes whereas Dach1 and Ai3 decreased after podocyte injury (0.42, 0.64-fold) similarly to Vegla (0.28-fold), suggesting their important functional role in podocytes.

Conclusions: Thus, these comprehensive data provide potentially important insights for understanding podocyte pathophysiology.

Funding: Government Support - Non-U.S.

TH-PO231

Expression of Mouse uPAR Alternative Isoform 2 Produces a Dimeric Protein and Severe Renal Disease

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Background: Patients with APOL1 variants carry 10 fold higher chance for the development of HIVAN if not on antiviral therapy. HIV is known to hijack autophagy in the host cells-enhancement of autophagosome formation (the site of viral replication) but inhibits the delivery of autophagosome cargo (AC) to the lysosomes and thus, prevents viral degradation. Since podocytes are terminally differentiated cells their protein homeostasis is tightly regulated by autophagy. We hypothesized that APOL1 risk variants would also have potential for augmenting the initial phase but would inhibit the terminal phase of autophagy.

Methods: We used human podocytes (HPs) stably expressing APOL1G0, G1, or G2 (Vec/HPs, G0/HPs, G1/HPs, and G2/HPs). Pseudotype HIV or empty vector (control) virus was transduced into Vec/HPs, G0/HPs, G1/HPs and G2/HPs. After 48 h, cells were harvested and assayed for vacuolar density (number of autophagosomes) by staining with acridine orange or monodansydacavermine (MDC). Protein blot of HPs (Vec, G0, G1, and G2) were probed for mTOR pathway modulating autophagy, beclin-1 and LC3-II markers of early steps of autophagy, p62 (marker of degradation of AC) and reprob for actin. HPs were co-labeled for APOL1 and endosomal/lysosomal markers to delineate route of APOL1.

Results: G0/HPs, G1/HPs and G2/HPs displayed greater number of autophagosomes when compared to Vec/HPs. Protein blots of G1/HPs and G2/HPs demonstrated enhanced expression of LC3II and beclin-1 and thus indicating enhancement of initiation of autophagy. Protein blots of G1 and G2/HPs also displayed enhanced expression of p62, which indicated that AC did not reach to lysosomes. Additionally, G1/HPs and G2/HPs showed augmented mTOR expression. Expression by G1/HPs and G2/HPs further enhanced early markers of autophagy but displayed further attenuation of lack AC at lysosomal compartment. Co-labeling studies of APOL1 revealed decreased presence of APOL1 in lysosomal compartment.

Conclusions: APOL1 risk variants enhance initiation but inhibit terminal phase of autophagy both in control and HIV stimulated states.

TH-PO234

Disparate APOL1 Expression in HIV-Associated Nephropathy Reflects Podocyte Injury

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Background: APOL1 is the best known poor outcome risk factor for HIV-associated nephropathy (HIVAN). It is a membrane metalloproteinase which is highly expressed in HIV infected macrophages and attracts HIV infected monocytes to the kidney. Differences in APOL1 expression in different cell types have been proposed to reflect differences in kidney injury. Our previous research shows that APOL1 expression is a marker of ongoing podocyte injury. Here we examine the hypothesis that disparity in APOL1 expression is explained by differences in podocyte injury.

Methods: Human podocytes (HPs) and VSMCs were transduced with equal amounts of lentivirus (vector, G0, G1, and G2) and cultured for 48 hours. Subsequently, cells were evaluated for reactive oxygen species (ROS) generation (DCFDA loading and co-labeling with mitotracker green and Red CCI), viability (MTT/Trypsin blue assays), apoptosis, and necrosis (morphologic assay by staining with H33342 and propidium iodide). VSMC proliferation was determined by cell counting and labeling for PCNA. In parallel set of experiments, APOL1 expression in these cells was quantified by Western blotting analysis.

Results: Compared to Vector and G0, HPs expressing G1 and G2 displayed higher rates of ROS generation, enhanced loss of cell viability, greater number of apoptosed and necrosed cells. VSMCs transduced with either G0 or G1/G2 displayed comparable rates of ROS generation, enhanced loss of cell viability, greater number of apoptosed and necrosed cells, when compared to G0. VSMCs transduced with G0, G1 and G2 displayed significantly higher number of apoptosed and necrosed cells when compared to G0. VSMCs transduced with G0, G1 and G2 displayed comparable expression of APOL1. VSMCs transduced with either G0 or G1/G2 displayed minimal loss of viability, number of apoptosed or necrosed cells, but they displayed greater numbers of proliferating cells when compared to Vector transduced VSMCs.

Conclusions: APOL1 variants expressing podocytes experience higher degree of oxidative stress but display lower APOL1 expression. On the other hand, VSMCs expressing G1 and G2 experience lesser degree of injury when compared to vector transduced VSMCs. These findings suggest that APOL1 expression by podocytes may be a marker of ongoing stress.

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Underline represents presenting author.

142A
A Soluble Guanylate Cyclase Activator Is Superior to a Phosphodiesterase Type 5 Inhibitor and a Soluble Guanylate Cyclase Stimulator in Protecting from Diabetic Nephropathy in the ZSF1 Rat

***Kathleen A. Lincoln, Paul Harrison, Hongxing Chen, Hong Wang, Sally Clifford, Hu Sheng Qian, Diane Wong, Christopher Sarko, Ryan M. Fryer, Jeremy G. Richman, Glenn A. Robertson, Carine Boustany. Cardiometabolic Disease Research, Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT.

**Background:** Therapies which restore cyclic GMP (cGMP) levels within the kidney are hypothesized to slow disease progression. We evaluated the effects of BI703704, a soluble guanylate cyclase (sGC) activator, EX67637; a sGC stimulator, and EX77619; a phosphodiesterase type 5 (PDE5) inhibitor, on the progression of diabetic nephropathy in obese ZSF1 rats.

**Methods:** Male ZSF1 rats, implanted with telemetry devices, were treated with either BI703704 at 2 mg/kg, EX67637 at 0.3 mg/kg, or EX77619 at 5 or 15 mg/kg for 10 weeks, during which mean arterial pressure (MAP) and urinary protein excretion (UPE) were determined. At study end, glomerular and renal interstitial lesions were assessed. Alpha smooth muscle actin (α-SMA, a marker of myoﬁbroblast activation) and p-57 (a marker of podocyte health) were determined by immunohistochemistry. Renal cGMP levels were quantitated as a measure of target engagement.

**Results:** By Week 10, similar reductions in MAP were achieved (~8mmHg) across treatment groups vs. vehicle. In parallel, sGC activation resulted in significant reductions in UPE (~31% vs veh), while there was no signiﬁcant effect of EX67637 (~4% vs 1 mg/kg; 16% vs 3 mg/kg vs veh), or EX77619 (~15% at 5 mg/kg; ~9% at 15 mg/kg vs veh). Importantly, BI703704’s effects on UPE were accompanied by reductions in the incidence of glomerulosclerosis (~21% vs veh), while neither EX67637 nor EX77619 were effective. In addition, interstitial lesions were modestly reduced by BI703704 (~13% vs veh) and EX77619 (~18% vs veh). α-SMA was reduced by BI703704 (~27% vs veh) and EX67637 (~8% vs veh), while P57 was signiﬁcantly increased by BI703704 (~11% vs veh) but not by EX77619 and EX67637. Importantly, target engagement was conﬁrmed for EX77619.

**Conclusions:** Despite similar effects on MAP, BI703704 was superior to EX76637 or EX77619 in reducing proteinuria and preventing renal damage in kidneys of ZSF1 rats.

**Funding:** Pharmaceutical Company Support - Boehringer-Ingelheim Pharmaceuticals

Localization of Phosphodiesterase 4 Isoforms in the Renal Cortex

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**Background:** There are limited therapeutic options for the treatment of chronic kidney disease (CKD). Our recent studies have found that Phosphodiesterase 4 (PDE4) inhibitor roflumilast (RFL) was effective in attenuating renal decline in subtotal nephrectomized (STNx) rats, a model of CKD, indicating that PDE4 inhibition is may be effective in treating CKD. There have been studies on the contribution of cAMP hydrolysis by PDE4 in nephron segments and the mRNA expression distribution of PDE4 isoforms in several cultured renal cells. However, the localization of PDE4 isoforms in the kidney has yet to be explored. Hence, we sought to investigate the distribution of PDE4 isoforms in the renal cortex, as it may also elucidate the renal cell types that RFL targets.

**Methods:** Sprague-Dawley rats underwent either STNx or sham surgery, further randomized after 2 weeks to receive an oral dose of either RFL (1 mg/kg/day) or vehicle, and sacrificed at 12 weeks. PDE4 isoforms (PDE4A, PDE4B and PDE4C) and distal tubules and in tubulointerstitial (for PDE4A and PDE4C). In the STNx group, positive staining on the podocytes was significantly more intense than the sham group. RFL treatment significantly reduced the elevated expression of PDE4 isoforms in the podocytes.

**Conclusions:** PDE4 isoforms are distributed throughout the renal cortex, especially in the podocytes and distal tubules. During CKD, the expression of PDE4 isoforms in the podocytes increases. As the reduction in PDE4 expression with RFL treatment was associated with the attenuation of renal decline, PDE4 inhibition may be especially relevant in preserving podocyte health.

**Funding:** Government Support - Non-U.S.

The Glomerular Parietal Epithelial Cell Phenotype Depends on SPARC Levels

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**Background:** Parietal epithelial cell (PECs) may play a critical role in a glomerular reparative process through their progenitor function. Conversely, PECs might paradoxically contribute to the deterioration of glomerular function by augmentation of scarring and crescent formation under certain conditions. The factors governing these PEC functions are not well understood. We have previously shown that SPARC (secreted protein acidic and rich in cysteine) plays a causal role in mediating podocyte detachment and accelerating glomerulosclerosis in experimental crescentic glomerulonephritis. However, the effect of SPARC levels on PECs is unknown.

**Methods:** Experimental glomerular disease was induced in aged-matched SPARC−/− and SPARC+/+ mice by intraperitoneal injection of a sheep anti-rabbit glomerular antibody. Immunostaining methods were then employed on days 0 and 7 of disease.

**Results:** There were differences in the number of PEC transition cells, defined as cells co-expressing a PEC marker (PAX2), and podocyte marker (Synaptopodin) between the two groups. SPARC−/− mice compared with SPARC+/+ mice (1.35 ± 0.18 vs 0.46 ± 0.14, P < 0.01 vs. SPARC−/− mice). WT1 staining along Bowman’s capsule was higher in diseased SPARC+/+ mice (2.57 ± 0.30 vs 1.37 ± 0.50, P < 0.01 vs. SPARC−/− mice). This observation was accompanied by increased PEC proliferation (measured by Ki-67 staining, (4.56 ± 0.46 vs 2.66 ± 4.99, P < 0.01) and an increase in immunostaining for a progenitor marker, neural cell adhesion molecule (1.35 ± 0.05 vs 1.21 ± 0.05, P < 0.05 vs. SPARC−/− mice), in a subpopulation of PECs in diseased SPARC−/− mice.

**Conclusions:** PECs have the potential to become glomerular epithelial transition cells. SPARC expression in PECs favors a decrease in the number of PEC transition cells.

Low Dose Hydralazine Augments Losartan Mediated Reversal of Epigenetic Alterations in Diabetic Nephropathy (DN)

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**Background:** Epigenetics has been demonstrated to play a role in the development and progression of DN. Recently, we observed that losartan reverses high glucose-induced podocyte epigenetic changes. We hypothesized that low (non-hypertensive) dose hydralazine (HYDZ) will further augment losartan-induced reversal of epigenetic alterations in DN.

**Methods:** Protein plots of renal tissues/renal cortical sections of 2, 4, and 6 month old control (WT) mice and Akita mice (n=3) were probed for methylation at histone (H)3 lysine (K)4 residue, acetylation at H3 lysine (K)9 residue, SNAIL, vitamin D receptor (VDR), and neprhin. In vitro studies, protein plots of control and high glucose (30 mM, HG) treated human podocytes (HPS) were probed for SNAIL, VDR, neprhin, H3K4me3, H3K9ac and actin. Podocyte VDR and neprhin gene methylation status (pyrosequencing)and SNAIL binding at VDR and neprhin promoter (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

**Results:** Protein plots of renal tissues of Akita mice displayed enhanced expression of SNAIL and H3K4me3 but down regulation of VDR and neprhin. Podocytes in renal cortical sections also displayed similar profile; losartan not only decreased proteinuria but also partially reversed epigenetic alterations and associated SNAIL, VDR and neprhin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further augmented these effects when combined with losartan. HG/HP displayed enhanced expression of SNAIL and H3K4me3 and attenuated expression of VDR, neprhin, and H3K9ac. Both neprhin and VDR displayed more than 70% cytosine methylation. HG/HP displayed deactivation of neprhin and dephosphorylation via ubiquitination. CHIP assay revealed binding of SNAIL at VDR and neprhin promoter.

**Conclusions:** Optimal reversal of epigenetic alterations can be used as a therapeutic strategy in DN.

Klotho Ameliorates Proteinuria by Targeting TRPC6 Channels in Podocytes

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**Background:** Klotho is a type-1 membrane protein mainly produced in the kidney tubules. The extracellular domain of klotho is secreted into extracellular space. Whether klotho is expressed in podocytes and whether and how it may protect the glomerular filter are unknown.

**Methods:** TRPC6-mediated Ca2+ influx, cysteinekeletal remodeling, and transphelial albumin flux were studied in cultured mouse podocytes. Klotho expression in cultured podocytes and the kidney was examined by immunostaining, in situ hybridization, and RNA sequencing. Effects of klotho on albuminuria were studied using mouse models with genetically altered expression of TRPC6 and klotho.

**Results:** Recombinant secreted soluble klotho suppressed ATP-stimulated, TRPC6-mediated Ca2+ influx, and cysteinekeletal remodeling in cultured mouse podocytes. Cytoprotection by klotho was associated with the reduction in ATP-stimulated actin cysteinekeletal remodeling in podocytes supported by the reduction in ATP-stimulated actin cysteinekeletal remodeling in podocytes.
and transmural epithelial albumin leakage. Overexpression of TRPC6 by gene delivery in mice induced podocyte injury and also increased albuminuria. Soluble Klotho deficiency resulted in marked decrease of albuminuria. Heterozygous klotho-deficient sham-operated mice had no basal albuminuria vs WT sham mice, but het-klotho chronic kidney disease (CKD) mice had increased albuminuria compared to that in WT CKD mice with a similar degree of hypertension and reduced VEGF expression. Klotho is expressed in podocytes of mouse and human kidney. Disrupting the integrity of glomerular filter increased urinary excretion of soluble klotho.

Conclusions: Klotho protects podocytes from injury by suppressing TRPC6-mediated Ca²⁺ entry. Cytoprotection of podocytes in the native state may be through membranous deformation and changes in expression profile. GPIIb/IIIa is expressed in podocytes of mouse and human kidney.

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

TH-PO240
Aminopeptidase A Is Up-Regulated in the Intact Areas of Segmentally Sclerotic Glomeruli in Advanced Focal Segmental Glomerulosclerosis
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Background: Angiotensin (Ang) II is involved in the pathogenesis of focal segmental glomerulosclerosis (FSGS). We hypothesized that FSGS may be associated with adaptive changes in glomerular expression of Ang-converting enzymes. Methods: Using fawn-hooded hypertensive (FHH) rats as a model of FSGS, we examined the pattern of glomerular expression of Ang converting enzyme (ACE) and the robust Ang II-cleaving enzyme aminopeptidase A (APA) by Western blot (WB) and immunohistochemistry (IHC).

Results: APA was absent in glomeruli by both WB and IHC. Overall expression of APA in glomerular extracts was found to gradually decrease over time, with 87% reduction at 60 weeks compared to 6 weeks of age (p<0.001). Glomerular extracts from 30 week-old FHH rats had lower APA expression and lower APA activity compared to age-matched Wistar rats (p<0.05). By IHC, 60-week-old kidneys showed loss of glomerular APA in globally sclerotic foci as well as on the sclerosed area of the segmentally sclerotic glomeruli. On the other hand, the “surviving” intact areas within the segmentally sclerotic glomeruli as well as some normal-appearing glomeruli exhibited a markedly accentuated APA expression. In contrast, the podocyte marker GLEPP1 was not only absent in all sclerotic areas but also attenuated in the intact areas within the segmentally sclerotic glomeruli and in normal-appearing glomeruli, suggesting that APA increases during the late phase response to podocyte injury. To determine whether the APA augmentation corresponded to a feedback response to Ang II, cultured mouse podocytes were incubated with Ang II (100 nM) for 24-72 hours. No change in APA abundance was observed, nor could APA abundance be induced by incubating Ang II in 8 week-old FHR rats for 4 weeks.

Conclusions: In conclusion, podocyte-localized APA is up-regulated in the “surviving” non-sclerosed segmental areas in glomeruli of FHH rats. However, the mechanism of up-regulation does not appear to be directly mediated by Ang II. Understanding the mechanism of APA up-regulation may provide tools to enhance the actions of a potentially renoprotective peptidase.

Funding: Private Foundation Support

TH-PO241
Anti-VEGF Treatment by Transfection of the Natural Inhibitor sFlt-1 Increases Albuminuria in Type 1 Diabetic Mice Pascal Bus, Jan A. Brujin, Hans J. Baelde. Dept of Pathology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands.

Background: It has been shown that VEGF-A is involved in diabetic nephropathy (DN). In diabetic mice, treatment with anti-VEGF antibodies reduced glomerular hypertrophy. On the other hand, women with pre-eclampsia develop proteinuria due to increased levels of soluble Flt-1 (sFlt-1) – a natural inhibitor of VEGF-A. In this study we investigated the effects of systemic VEGF-A inhibition by sFlt-1 transfection in type 1 diabetic mice. Methods: Diabetic mice were transfected with an sFlt-1 construct at the onset of diabetes. After five weeks of treatment mice were sacrificed. Collection of urine and blood was performed at baseline, and week 1, 3, and 5. Albuminuria was measured using Rocket Electrophoresis. Kidneys were sectioned and stained for PAS, FA-11 (macrophages) and WT1 (podocytes). Glomerular hypertrophy was measured using Philips Digital Pathology Solutions. One-way ANOVA was performed to measure differences between the groups. Differences with a probability level (P) < 0.05 were considered statistically significant. Results: Diabetic mice transfected with sFlt-1 had higher albuminuria levels than mice with diabetes alone (p<0.05). However, glomerular hypertrophy as well as the number of glomerular macrophages were reduced in the treated group (p<0.05). No effect on podocyte numbers was observed.

Conclusions: In contrast to other studies investigating VEGF-A, we reduced VEGF levels with the use of a natural inhibitor. In line with previous findings we showed that sFlt-1 treatment reduced renal dysfunction in diabetic mice. In addition, sFlt-1 treatment resulted in higher albuminuria levels in diabetic mice. These results show that treatment for reducing VEGF-A levels has to be performed with care since treatment has both beneficial and detrimental effects.

TH-PO242
Apolipoprotein C1 Transgenic Mice Develop Gomerulosclerosis: A Potential Role for Macrophages Pascal Bus, Rosalie Bor, Jimmy F. P. Berbèce, Jan A. Brujin, Emile De Heer, Hans J. Baelde. 1Dept of Pathology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands; 2Dept of Medicine, Div of Endocrinology, Leiden Univ Medical Center, Leiden, Zuid-Holland, Netherlands.

Background: Associations between an APOC1 polymorphism and the development of diabetic nephropathy (DN) have been identified and confirmed in several meta-analyses. In addition, patients with type 1 and type 2 diabetes have higher serum levels of APOC1 compared to healthy control subjects. APOC1 transgenic (APOC1tg) mice develop albuminuria and glomerulosclerosis at 15 months of age. In this study we investigated the role of macrophages in APOC1 induced glomerulosclerosis in APOC1tg mice.

Methods: APOC1tg and wild-type (WT) mice were sacrificed at various ages. Kidneys were sectioned and stained for APOC1 and healthy controls were included, sectioned and stained for APOC1. Correlations were assessed using the Pearson’s correlation test.

Results: In APOC1tg mice, the number of glomerular macrophages were already increased at 15 weeks of age, long before the development of glomerular damage, and increased even further in time. A strong linear correlation was found between the number of glomerular macrophages and glomerular damage (p<0.001). These macrophages were found to be of the M1 type and expressed high amounts of APOC1 and TNF-alpha. In patients with DN, glomerular APOC1 expression was significantly increased compared to healthy control subjects.

Conclusions: Both our mice and our human autopsyed data indicate that APOC1 could play a crucial role in the development of glomerular damage. We hypothesize that APOC1-expression by macrophages causes glomerular damage, potentially by increasing the inflammatory state of these macrophages.

TH-PO243
Decreased Renal α-Klotho Expression Is Associated with Urinary Calcium Excretion in Early Diabetic Nephropathy in db/db Mice Kyung don Ju, Tsoobadrakh Bodokhsuren Bodokhsuren, Hyo Jin Kim, Seungmi Lee, Miseon Park, Curie Ahn, Kook-Hwan Oh. Div of Nephrology, Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: Hypercalcuria is one of the early manifestations of diabetic nephropathy (DN). We surveyed the role of α-Klotho, a protein expressed predominantly in the distal tubules (DTs), in α-Klotho is known to up-regulate transepidermal receptor potential vanilloid type 5 (TRPV5) expression, involved in tubular calcium reabsorption. Methods: We used db/db mice, a type II diabetes mellitus (DM) model. We employed puroycin amonicelamide (PAN)-induced nephritic mice and db/db mice for control.

Results: Animals were sacrificed at the age of 15 week. At 15 week, db/db mice and PAN mice developed albuminuria (21.8 ± 3.3 mg/day and 68.9 ± 9 mg/day, respectively), while db/m mice were normoalbuminuric (1.4 ± 3 mg/day). Urinary calcium excretion (UCa/Cr) significantly increased in db/db mice (0.91 ± 0.09 mg/mg Cr), compared to PAN (0.30 ± 0.02 mg/mg Cr) or db/m mice (0.29 ± 0.03 mg/mg Cr). mRNA and protein expression levels of α-Klotho in the distal tubule were markedly ameliorated. Urinary potassium was significantly decreased in db/mice (1.45 ± 0.02 mmol/mg Cr) compared to PAN (10.77 ± 3.01 mmol/mg Cr) or db/m mice (6.39 ± 0.40 mmol/mg Cr). By immunohistochemistry and immunofluorescence staining, we also confirmed reductions of renal α-Klotho, FGFR receptor type 1 (FGFR1) and TRPV5 expressions in db/db mice.

Conclusions: Thus, renal loss of α-Klotho may affect urinary calcium excretion via inhibition of TRPV5 expression in DTs in early diabetic nephropathy.

TH-PO244
NF-κB System Inhibition Attenuates Renal Injury in Diabetic Nephropathy Orestes Foresto-Neto, Amanda H. Albino, Simone CA Arias, Lisenny CT Rempel, Gizely CS Moreira, Victor F. Avila, Viviane D. Faustino, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels OS Camara, Clarice K. Fujihara, Roberto Zatt. Univ of Sao Paulo, Brazil.

Background: The NF-κB system may be involved in the pathogenesis of diabetic nephropathy (DN). We investigated whether NF-κB inhibition with pyrrolidinedithiocarbamate (PDTC) exerts renoprotection in experimental DN.

Methods: Diabetes was induced in 27 adult male Munich-Wistar rats through streptozotocin injection (65 mg/kg, iv) and maintained moderately hyperglycemic with daily insulin. Rats were divided in untreated (DM) and PDTC-treated, 60 mg/kg/day vo (DM-PDTC). Untreated nondiabetic rats (C, n=12) were also followed. Body weight was maintained equal glucose (BG), mean arterial pressure (MAP), systolic blood pressure (TCP, mmHg), urinary albumin/creatinine ratio (UaUcr), kidney/body weight ratio (KW/BW), % glomerular sclerosis (%GS), interstitial and glomerular macrophage infiltration (intM0 and glomM0, cells/mm²) and % glomerular zonula occludens (ZO-1, %) were assessed after 12 months of follow-up.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Results:

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>DM-V</th>
<th>DM+PDTC</th>
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<tbody>
<tr>
<td>BW</td>
<td>406±9</td>
<td>335±5</td>
<td>335±3</td>
</tr>
<tr>
<td>BG</td>
<td>96±2</td>
<td>378±24</td>
<td>386±7</td>
</tr>
<tr>
<td>TCP</td>
<td>131±3</td>
<td>134±2</td>
<td>131±2</td>
</tr>
<tr>
<td>UaI/Uc</td>
<td>1.5±0.2</td>
<td>5.1±1.2</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td>KW/BW</td>
<td>0.49±0.01</td>
<td>0.72±0.01</td>
<td>0.64±0.02</td>
</tr>
<tr>
<td>%GS</td>
<td>2.6±0.4</td>
<td>7.0±1.9</td>
<td>2.1±1.7</td>
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<tr>
<td>intMO</td>
<td>57±6</td>
<td>858±8</td>
<td>45±5</td>
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<tr>
<td>glomMO</td>
<td>16±1</td>
<td>54±15</td>
<td>33±10</td>
</tr>
<tr>
<td>ZO-1</td>
<td>77±1</td>
<td>61±6</td>
<td>75±2</td>
</tr>
</tbody>
</table>

Mean±SE. *p<0.05 vs C; *p<0.05 vs DM-V.

After 12 mo, untreated DM rats exhibited high UaI/Uc, renal hypertrophy, high %GS, intMO and glomMO, and loss of %ZO-1, without changes in TCP. Treatment with PDTC attenuated renal hypertrophy and prevented the increase in UaI/Uc, %GS, intMO and glomMO, and the loss of ZO-1, without interfering with BG or TCP.

Conclusions: PDTC exerts a renoprotective effect on the progress of DN in diabetic rats, suggesting the involvement of the NF-κB system in the pathogenesis of the disease and the possibility that this system becomes a therapeutic target. The beneficial effects of PDTC may also be the result of an antioxidant effect of the drug. FAPESP/CNPq.

TH-PO245

Renin Accelerates Progression of HIV-Associated Nephropathy (HIVAN) Through Kidney Cell Hypo-Glutathione Expression

Parthi Rai, Rivka Lederman, Shabirul Haque, Asawada Mallavarapu, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: The activation of renin-angiotensin system has been demonstrated to play an important role for the development and the progression of HIVAN. However, the progression of HIVAN attributed predominantly to Ang II generation by kidney cells. Recently, HIV has been demonstrated to stimulate renin generation by kidney cells in vitro studies. We hypothesized that HIV-induced kidney cell renin production might also be enhancing kidney cell HIV gene expression, which may accelerate progression of renal lesions, independent of the effects of Ang II.

Methods: Human podocytes (HPs) were transduced with either empty vector (EV/HP) or HIV (NL4-3, HIV/HP). To increase endogenous renin production, EV/HPs and HIV/HPs were transfected with a siRNA targeting renin receptor (siRNA-VDR/HIV/HPs) or scrambled (Scr-siRNA-HIV/HP). siRNA; protein blots were probed for renin and actin. To evaluate the effect of renin in vivo, mRNA expressions of HIV genes from renal tissues of HIVAN (Tg26) mice with high endogenous renin (Tg26 mice either with 2, 3 and 4 injections of immunotoxin, LMB2). nigra mice with intact VDR. VDA treatment of Tg26 also down regulated renal tissue expressions of HIV gene from renal tissues of Tg26-Agt-2. Similarly, VDA downregulated HIV gene expression. Renal tissues of Tg26-Agt-4 displayed 2-4 fold enhanced expression of Nef, Tat, and Vif. On the other hand, treatment of HIV/HPs with EV/HPs and Tg26 mice lacking renin.

Results: The progression of HIVAN attributed predominantly to Ang II generation by kidney cells. Recently, HIV has been demonstrated to stimulate renin generation by kidney cells in vitro studies. We hypothesized that HIV-induced kidney cell renin production might also be enhancing kidney cell HIV gene expression, which may accelerate progression of renal lesions, independent of the effects of Ang II.

Conclusions: The beneficial effects of PDTC may also be the result of an antioxidant effect of the drug. FAPESP/CNPq.

TH-PO246

Podocyte and Tubule Injury Have Different Effects on Renal Handling of Apolipoprotein A-I (ApoA-I) and Its Receptors

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

Underline represents presenting author.

145A
Table 1: 

<table>
<thead>
<tr>
<th>Neuraminidase</th>
<th>Treatment</th>
<th>ACR Day 0.5</th>
<th>ACR Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>None</td>
<td>41 ± 26</td>
<td>72 ± 36</td>
</tr>
<tr>
<td>+</td>
<td>None</td>
<td>1860 ± 840</td>
<td>485 ± 90</td>
</tr>
<tr>
<td>+</td>
<td>Prolymphatic ManNAc</td>
<td>2087 ± 1840</td>
<td>85 ± 65*</td>
</tr>
<tr>
<td>+</td>
<td>Therapeutic ManNAc</td>
<td>3078 ± 2510</td>
<td>150 ± 72*</td>
</tr>
</tbody>
</table>

*P < 0.05 compared to NA with no treatment

Conclusions: ManNAc holds promise to mitigate hyposialylation-related disease mechanisms of glomerular diseases; ManNAc has minimal toxicity and is orally administered. ManNAc is currently tested in a Phase 2 clinical trial for the rare hyposialylation disorder GNE myopathy. We plan a Phase 1 clinical trial of ManNAc in patients with glomerular diseases.

Funding: NIDDK Support, Other NIH Support - NIGRI

TH-PO249

A Mismatch Between Glomerular Volume and Podocyte Mass Is Associated with Albuminuria and Accelerated Podocyte Hypertrophic Injury in Leptin-Deficient Zucker Rats

Akifumi Fukuda,1 Yuji Sato,1 Takashi Ikawaki,1 Kazuo Kitamura,1 Roger C. Wiggins,1 Shouichi Fujimoto.1 1First Dept of Internal Medicine, Univ of Miyazaki, Miyazaki, Japan; 2Nephrology Div, Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Background: Glomerular hypertrophy is a well-established component of diabetic nephropathy. We previously reported that failure of podocytes to match glomerular tuft enlargement (in response to growth signaling through the mTORC1 pathway) can trigger proteinuria, glomerulosclerosis and progression to end stage renal disease in diabetic negative AA-4E-BP1 Tg rat model. We therefore tested the hypothesis that a mismatch between glomerular volume and podocyte mass causes progression of diabetic nephropathy.

Methods: We used the leptin-deficient Zucker Diabetic Fatty (ZDF-fatty) rat model of type 2 diabetes compared with heterozygous ZDF rats as a control. Glomerular volume and podocyte number per tuft, density (podocyte number per glomerular tuft volume), mass (Glepp1 positive volume) and the urine podocin:aquaporin2 mRNA ratio were measured. Rats were evaluated over a 45 week time-course.

Results: ZDF-fatty rats gained weight much faster than control rats over the first 15 weeks, but did not become hypertensive over the study period. ZDF-fatty rats became diabetic with increased blood glucose and glycosuria by 10 weeks. Albuminuria and urine podocin:aquaporin2 mRNA ratio were also significantly increased by 10 weeks. Sequential kidney biopsies at 15, 30, and 45 weeks revealed that by 15 weeks glomerular volume was already significantly increased above control (1.5-fold, P<0.01) and podocyte density was significantly reduced (P=0.01), although podocyte number per tuft was not detectably decreased. By 45 weeks glomerulosclerosis was present and the Glepp1 positive area was significantly reduced in the ZDF-fatty rats but not in controls.

Conclusions: These data indicate that a mismatch between glomerular volume and podocyte mass (reduced podocyte density) is associated with development of albuminuria and accelerated podocyte hypertrophic stress in this model of type 2 diabetes, compatible with data previously reported in Pima Indians.

TH-PO250

An ER Stress-Regulated Transcript Hosting a MicroRNA Megacluster as a Therapeutic Target in the Early Stage of Diabetic Nephropathy

An ER Stress-Regulated Transcript Hosting a MicroRNA Megacluster as a Therapeutic Target in the Early Stage of Diabetic Nephropathy

Mitsuaki Kato,1 Mei Wang,2 Zhuo Chen,2 Supriya Deshpande,2 Kirti Bhatt,2 Hyung Jung Oh,2 Linda Therapeutic Target in the Early Stage of Diabetic Nephropathy

An ER Stress-Regulated Transcript Hosting a MicroRNA Megacluster as a Therapeutic Target in the Early Stage of Diabetic Nephropathy

Furthermore, a single oligonucleotide targeting the host lncRNA was effective in preventing these early features of DN, highlighting the GapmeR approach for targeting lncRNAs as a novel therapy for DN.

Funding: NIDDK Support

TH-PO251

No Difference in Cytotoxicity of APOL1-G0 or Risk Variants G1 and G2 John F. O’Toole,1 Sethu M. Madhavan,1 Martha Konieczkowski,1 Yaping Gu,1 Liping Luo,1 Zhenhuan Wu,1 William P. Schilling,2 Leslie A. Bruggeman,2 John R. Sedor.1 1Medicine, MetroHealth Medical Center, Cleveland, OH; 2Physiology and Biophysics, Case Western Reserve Univ, Cleveland, OH.

Background: The genetic evidence linking variation in the APOL1 gene to kidney disease in ancestral African populations is strong; however, the biological mechanisms that underlie the association remain uncertain. Autophagy and cell death has been observed after the expression of APOL1 and variant dependent cell death has been reported with the transient expression of APOL1. Therefore we sought to examine autophagy and cell death for variant dependent effects in stable expression systems.

Methods: Stable tetracycline inducible HEK293 cells were generated for the expression of APOL1-G0 (reference), the G1, and G2 risk variants. Mouse podocytes were isolated from transgenic animals expressing human APOL1-G0 or APOL1-G2 under the Nephrin promoter and control animals. Autophagy was monitored with biochemical methods and three assays of cell death were used; a fluorescent assay, an MTT assay and a clonogenic assay.

Results: Three stable HEK293 clones of each genotype were assayed for autophagy and cell death after induction of APOL1 with tetracycline. We noted significant variability in the kinetics of APOL1 induction between clones, which was not dependent upon APOL1 genotype. Stable expression of APOL1-G0, -G1, and –G2, all increased autophagic flux to a similar degree. The stable expression of all APOL1 genotypes (G0, G1 and G2) resulted in cell death in all three assays, without variant dependent differences. Inhibitors of autophagy or autosis did not reduce APOL1-G0, -G1, or -G2 induced cell death and none of the APOL1s activated the apoptosis effector caspase 3. The expression of APOL1 in differentiated mouse podocytes did not induce autophagy or cell death.

Conclusions: Stable expression of APOL1 in cell culture leads to cell death and autophagy induction in a variant independent manner, but the regulated expression of APOL1 in differentiated podocytes does not. The absence of variant dependence of autophagy induction or cell death suggest that alternative mechanisms underlie the genetic association of APOL1 with kidney disease.

Funding: NIDDK Support, Other NIH Support - NCTATS ULTR00439

TH-PO252

NGAL Regulates TH17 Immunity in ANCA Vasculitis

Adrian Schreiber,1 Erik M. Disteldorf,2 Ulf Panzer,2 Ralph Kettritz.1 1Dept of Nephrology and Intensive Care Medicine, CVK Charité, Berlin, Germany; 2Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Background: ANCA activate neutrophils and thereby participate in necrotizing crescentic glomerulonephritis (NCGN). NGAL is a marker of intrinsic kidney injury and is expressed by neutrophils and renal tubular cells. Whether or not NGAL is merely a diagnostic marker or participates mechanistically in renal damage is not known. We hypothesized that neutrophil NGAL plays a pathogenic role in ANCA NCGN.

Results: Patients with active ANCA disease demonstrated increased NGAL serum levels by western blot analysis (47.3±13.1OD) compared to patients in remission (19.4±8.1) and healthy controls (2.1±0.4). We then assessed ANCA-activated neutrophils as a potential source for upregulated serum NGAL by ELISA, both PR-3-ANCA and MPO-ANCA stimulated NGAL release from human neutrophils (887±72 and 961±70ng/ml), whereas control IgG induced much lower levels (105±21ng/ml). Mice with anti-MPO-induced NCGN demonstrated upregulated serum NGAL levels by ELISA (data not shown). To assess the role of neutrophil NGAL in vivo, we used a murine model of anti-MPO induced NCGN, where MPO-KO mice were immunized with mMPO and subsequently transplanted with syngeneic CT or NGAL-KO bone marrow (BM). NGCN was significantly aggravated in mice that received NGAL-KO BM (34.8±6.1% crescents in NGAL-KO versus 13.4±2.8% in WT mice). With respect to intrinsic neutrophil function, migration, ROS generation, degranulation and apoptosis were similar in NGAL-KO and WT neutrophils. In addition, neutrophils isolated from ANCA NCGN demonstrated upregulated NGAL serum levels by ELISA (data not shown). To assess the role of neutrophil NGAL in vivo, we used a murine model of anti-MPO induced NCGN, where MPO-KO mice were immunized with mMPO and subsequently transplanted with syngeneic CT or NGAL-KO bone marrow (BM). NGCN was significantly aggravated in mice that received NGAL-KO BM (34.8±6.1% crescents in NGAL-KO versus 13.4±2.8% in WT mice). With respect to intrinsic neutrophil function, migration, ROS generation, degranulation and apoptosis were similar in NGAL-KO and WT neutrophils. In addition, neutrophils isolated from ANCA NCGN demonstrated upregulated NGAL serum levels by ELISA (data not shown).

Conclusions: These data indicate that a mismatch between glomerular volume and podocyte mass (reduced podocyte density) is associated with development of albuminuria and accelerated podocyte hypertrophic stress in this model of type 2 diabetes, compatible with data previously reported in Pima Indians.
**TH-PO253**

**Streptococcus mutans Strains with Collagen-Binding Protein May Cause IgA-Like Glomerulonephritis in Rats**

Taro Misaki, 1 Shuhei Naka, 2 Ryota Nomura, 1 Taissue Isokazi, 1 Kazuhiko Nakano. 2

**Background:** The precise pathological mechanisms of IgA nephropathy (IgAN) remain unclear. It is known that 10-20% of healthy subjects harbor strains of Streptococcus mutans, a known pathogen of dental caries, that possess Cmn, a cell surface collagen-binding protein encoded by the cmn gene. Furthermore, it is widely accepted that an association between streptococcal protein and systemic diseases exists. We previously found that the rate of cmn-positive S. mutans organisms isolated in saliva specimens was significantly higher in an IgAN group as compared to the controls, and reported those findings at ASN Kidney Week 2014 and in Clinical and Experimental Nephrology in 2014. The aim of this study was to investigate whether nephritis is induced by Cmn-positive S. mutans strains inoculated into the oral cavity of a rat model of dental caries.

**Methods:** Cmn-positive S. mutans strains (ID-17R, ID-32R, ID-74R) were isolated from the oral cavities of 3 IgAN patients. Those along a standard oral isolate, were inoculated into the oral cavities of 2-week-old Sprague-Dawley rats fed a 56% sucrose-containing diet and then we confirmed that the strains were harbored in the oral cavity of each rat 1 week later. From 10 weeks of age, findings of severe dental caries were confirmed in all rats. They were euthanized at 24 weeks of age, then kidney tissues were fixed and stained with PAS, and immunohistochemistry with the IgA antibody was performed for histopathological analysis.

**Results:** Dental caries in nearly all of the rats were found extending to the pulp space, which contains nerves and blood vessels. In rats harboring Cmn-positive strains in the oral cavity, mesangial cell proliferation was observed and immunohistochemical staining of the IgA antibody was seen in the para-mesangial area. However, no abnormal findings were observed in the control group.

**Conclusions:** Our results indicate that Cmn-positive S. mutans strains harbored in the oral cavity may cause IgA-like glomerulonephritis.

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**TH-PO254**

**Prevention of Lupus Nephritis in the BXSX-Yaa Mouse by Metabolic Inhibitors**

Byron P. Crocker, 1,2 Derry C. Roopeian, 1,2 Laurence Morel. 1

1Pathology, Immunology and Laboratory Medicine, Univ of Florida, Gainesville, FL; 2Pathology and Laboratory Medicine Service, NF/SG VHS, Gainesville, FL; 3The Jackson Laboratory, Bar Harbor, ME.

**Background:** In a heavily Type II gamma interferon activated model of lupus nephritis (LN) we showed metabolic inhibition by chronic oral combination of 2-deoxyglucose (2DG) and metformin (Met) reversed LN. We now show 2DG + Met prevents LN in the heavily Type I alpha interferon driven BXSX-Yaa LN.

**Methods:** Mice were treated chronically with test medications in drinking water. To sacrifice blood and tissues were taken for analysis and correlation of renal histopathology and sacrifice blood and tissues were taken for analysis and correlation of renal histopathology.

**Results:** 2DG (Pg 0.0%), 2DG + Met (Pg 0.0%) and rapamycin (Pg 0.0%) all showed marked improvement in LN. Cholesterol and triglycerides were slightly increased (10-20%) and reduced (15-30%) respectively. Untreated C57Bl/6 mice were used as a normal (control) group (Pg 0.0%). Target organ support is provided in vivo and in vitro determination of immunologic and metabolic parameters.

**Conclusions:** This study presents a second model of LN that responds favorably to metabolic inhibition and normalization by existing drugs utilized for other clinical conditions.

**Funding:** Private Foundation Support.

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**TH-PO255**

**Successful Treatment of a Mesangial Proliferative Glomerulonephritis by Foxd1+ Metanephric Mesenchymal Cells**

Li Zhang, 1 Meiling Jin, 1 Qing-gang Li, 1 Haomin Gao, 1 Lina Cai, 1 Mi Chen, 1 Yixiu Peng. 1

1Pathology, Immunology and Laboratory Medicine, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases; 2Medical College, NanKai Univ.

**Background:** This study is aiming to observe the effect of Foxd1+ mesenchymal mesenchymal cells on MsPGN.

**Methods:** 1. We used Foxd1+creERT2 transgenic mice and Rosa-DTRcreERT2 transgenic mice to screen target embryonic kidney cells, and isolate Foxd1+ mesenchymal mesenchymal cells by adding diphtheria toxin. 2. We detect Foxd1+ cell proliferation, cell surface markers, and osteogenic adipogenic differentiation potential. 3. 24 hour after establishment of anti-Thy1 mesangial proliferative glomerulonephritis, Foxd1+ cells were injected via intravenous, and this group was set as group of treatment. We detect renal pathology and renal function at different time points on control, model and treatment group. 4. Mesangial cells were isolated by PDGF-BB, we detect the influence of Foxd1+ cells on the proliferation and migration of activated mesangial cells.

**Results:** The results showed that CD90 positive rate was 0.96.05, CD 44 91.11%, CD 106 96.69, CD34 0.53%, CD45 0.35%. After the induction, we found that Foxd1+ cells had good osteogenic and adipogenic differentiation capacity. 2. After intravenous injection of Foxd1+ cells could improve the pathological changes in the kidney and could reduce urinary protein significantly. 3. CCR-8 results showed that Foxd1+ cells condition medium could antagonize proliferation of mesangial cells activated by PDGF-BB from 48 hours. Transwell migration assay results showed that Foxd1+ cells could significantly inhibit activated mesangial cell migration.

**Conclusions:** Our results indicate that Foxd1+ mesenchymal mesenchymal cells could be isolated using transplantation technology and they have the characteristics of stem cells. Foxd1+ mesenchymal mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

**Funding:** Government Support - Non-U.S.

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**TH-PO256**

**Beyond HIF1α - Regulatory Genomic Insights into Renal Cell Carcinoma Revealed by DNasel-seq**

Shreeram Akilesh, Pathology, Univ of Washington, Seattle, WA.

**Background:** Clear cell renal cell carcinoma (RCC) is the most common sporadic malignancy affecting the kidney. Inactivation of the VHL tumor suppressor gene and subsequent stabilization of the HIF1α transcription factor (TF) is very common in RCC. However, it is unclear how HIF1α and the closely related HIF2α (EPAS1) interact with each other and other TFs to produce the RCC phenotype. Here, we delineate the regulatory genomic landscape of RCC using DNasel-seq and define the transcriptional regulatory network of RCC.

**Methods:** Fresh normal human kidney tissue and RCC were disaggregated and cultured to generate primary tubular and renal cell carcinoma cultures. These were subjected to DNasel-seq and RNAsseq according to established protocols. DNasel hypersensitivity profiling (DNasel-seq) allows for comprehensive mapping of regulatory DNA at a genomic scale and with single nucleotide resolution. Examination of footprinting-depth DNasel-seq data identifies DNasel-protected transcription factor (TF) motifs within the promoter of other TFs. Mapping these TF footprints across all TFs with known motifs results in a TF interaction network.

**Conclusions:** Our data reveals that RCC display non-canonical HIF1α and HIF2α interactions, HIF1α is an upstream regulator of HIF2α expression, and the transcriptional network of RCC is significantly different from that of healthy kidney.

**Funding:** Other NIH Support - NHIHR - 5U10RR007010-03, Private Foundation Support.

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**TH-PO257**

**Uneven Reinervation After Unilateral Renal Denervation: Affere rents Dominate Efferents**

Kristina Rudionova, 1 Franziska Günstner, 1 Eric Gram, 1 Michael J. D. 1 CD34 0.53, CD45 0.35. After the induction, we found that Foxd1+ cells could significantly inhibit activated mesangial cell migration.

**Methods:** Measuring levels of CCRG and norepinephrine (NE) within 12 weeks after denervation.

**Conclusions:** Our results indicate that Foxd1+ mesenchymal mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

**Funding:** Government Support - Non-U.S.

**Results:** The results showed that CD90 positive rate was 0.96.05, CD 44 91.11%, CD 106 96.69, CD34 0.53%, CD45 0.35%. After the induction, we found that Foxd1+ cells had good osteogenic and adipogenic differentiation capacity. 2. After intravenous injection of Foxd1+ cells could improve the pathological changes in the kidney and could reduce urinary protein significantly. 3. CCR-8 results showed that Foxd1+ cells condition medium could antagonize proliferation of mesangial cells activated by PDGF-BB from 48 hours. Transwell migration assay results showed that Foxd1+ cells could significantly inhibit activated mesangial cell migration.

**Conclusions:** Our results indicate that Foxd1+ mesenchymal mesenchymal cells could be isolated using transplantation technology and they have the characteristics of stem cells. Foxd1+ mesenchymal mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

**Funding:** Government Support - Non-U.S.

**Background:** Renal nerve ablation is a beneficial, but controversial treatment for resistant hypertension. We found morphological evidence that intrarenal paracrine afferents reinervate more thoroughly than efferent sympathetic nerves. We now measured the tissue content of the afferent and efferent neurotransmitters, calcitonin gene related peptide (CGRP) and norepinephrine (NE) within 12 weeks after denervation.

**Methods:** Tissue levels of CGRP and NE from 24 male SD rats (ELISA-test, mass spectrometry) were measured in denervated left (L) and non-denervated right kidneys (R) 1, 4 and 12 weeks after renal denervation.

**Conclusions:** Our results indicate that Foxd1+ mesenchymal mesenchymal cells could improve the renal pathological changes in anti-Thy1 mesangial proliferative glomerulonephritis, and inhibit the activation of mesangial cells.

**Funding:** Government Support - Non-U.S.
Results: CGRP decreased by 72% in denervated (L) kidneys compared to (R) kidneys in week 7 [W1: R: 1:9/0:16 vs. W1: L: 0:24±0:06; p<0.05]. In week 12 CGRP content in (L) kidneys did not differ from (R) kidneys. We observed a 78% decrease of NA tissue levels [pmol/mg kidney] in week 1 due to surgical denervation [W1: R: 1:9/0:16 vs. W1: L: 0:24±0:06; p<0.05]. In contrast to the CGRP tissue levels there was no complete recovery of NA in week 12. The commonly used addition phenol to the surgical denervation procedure did not influence these results significantly. All data are given as mean±SEM.

Conclusions: We could show that there is a complete reinnervation of CGRP positive perivascular nerves within 12 weeks after renal denervation. However, NA tissue content did not completely increase. Further, consistently important morphological regrowth of sympathetic nerve fibers. This might potentially result in a net surplus of agent sympathetic-inhibitory influence, adding to the beneficial effect of renal denervation in some cases of resistant hypertension. Funding: Government Support - Non-U.S.

TH-PO258
An Aristolochic Acid-Induced Nephropathy (AAN) Model for Stable CKD in Mice Hiroshi Kojima, Xuzhen Hu, Yuning George Huang, Ana C. Souza, Jonathan Street, Peter S.T. Yuen, Robert A. Star. Renal Diagnostics and Therapeutics Unit, NIDDK, NIH, Bethesda, MD.

Background: ACEi/ARB are standard therapy for progressive CKD but do not slow progression in ~50% of patients. To obtain novel therapies of CKD in humans, better preclinical models are needed. A few mouse models for CKD have been developed, each with strengths and weaknesses. In humans, Aristolochic Acid (AA) causes Balkan nephropathy, with chronic interstitial fibrosis and slow progression to ESRD. However, published AAN mouse models have poorly characterized CKD outcomes.

Results: Primary renal epithelial cell line and primary renal epithelial cells were cultured i.p. with AA dissolved in DMSO using two regimens: R1: AA 1, i.p. (3 mg/kg) every 3 d for 6 wk, then 6 wk of disease development; R2: AA i.p. (2.5 mg/kg) every 7 d for 3 wk, then 1 wk of disease development. Spot urine samples and non-invasive GFR by plasma disappearance of F1C-Tsinistrin were obtained weekly: serum and kidney were collected at euthanasia. Using aged animals, or addition of salt-loading, uninephrectomy (UNx), or an adenine-rich diet were tested to increase the severity of the model.

Results: CD-1 mice (R1) had severe body weight (BW) loss at 3 wk and was discontinued. Both CD-1 and C57BL/6 mice were infected in R2, but CD-1 mice showed modest loss of BW. All R2 mice survived. Both CD-1 and C56BL/7 mice had elevated BUN, and developed severe tubulointerstitial injury. CD-1 mice showed higher injury score and fibrosis (%) than C57BL/6 mice. There was no elevation of blood pressure in CD-1 (R2). Neither regimen nor strain developed progressive CKD model as urinary albumin transiently peaked then fell, and GFR dropped by 60%, but plateaued within two weeks. Aging, salt-loading, UNx, or an adenine-rich diet did not increase injury or lead to progressive CKD.

Conclusions: AA caused a strain- and regimen-dependent severity of tubulointerstitial injury, with moderate but stable decreases in kidney function (~human CKD-stage 3). AAN may still be a foundation of a progressive CKD model, but additional renal insults might be needed to achieve a progressive CKD model. Funding: NIDDK Support

TH-PO259
The Polymeric Immunoglobulin Receptor Is Expressed in Scattered Cells of Human Kidney and Increase in Expression Following Kidney Injury Krzysztof Krawczyk,1 Helen Nilsson, Jenny C. Nystrom,2 Martin E. Johansson.1 1Dept of Translational Medicine, Lund Univ, Malmö, Sweden; 2Dept of Physiology, Inst of Neuroscience and Physiology, Univ of Gothenburg, Gothenburg, Sweden.

Background: We have previously shown that the proximal tubules of human kidney contain a scattered cell (SC) population of importance for kidney regeneration, where the markers for SC are identical to those of the parietal epithelium of Bowman’s capsule. Using gene expression analysis of the SC we found that these may express the Polymeric immunoglobulin receptor (PIGR), a transporter classicallly attributed to export of secretory IgA and IgM to the mucosal side of the respiratory and gastrointestinal tracts.

Methods: Biopsy material was procured from normal and diseased kidneys. Nephritic and nephritic diseases were included along with cases of diabetes nephropathy. Immunofluorescence was used for colocalization of PIGR to the SC and immunohistochemistry was performed to assess the distribution of PIGR in the various disease states. Sandwich ELISA was used to measure secretory IgA levels in urine and blood samples from the same disease categories. Primary culture of renal tubular epithelium on permeable supports was used to establish an in-vitro system for functional studies of IgA transcytosis.

Results: Colocalization studies showed that PIGR indeed localizes to the SC of human kidney. Furthermore, the tubular PIGR expression increases as an early response to both acute and chronic renal injury. ELISA measurements of secretory IgA levels in serum and urine samples from patients suffering from various kidney diseases show and increased urinary content of secretory IgA. In vitro, we show that primary renal epithelial cells perform vectorial transport of secretory IgA towards the apical compartment.

Conclusions: The human kidney uses PIGR to export secretory IgA into the tubular luminal contents, a function similar to the established secretion of dimeric IgA onto the mucosal surfaces of the respiratory and gastrointestinal tracts. The levels of urinary secretory IgA increase prominently in response to renal injury. Funding: Government Support - Non-U.S.

TH-PO260
Establishment of Canine Remnant Kidney Model in Beagle Dogs Hajeong Lee,1 Jun gu Kang,2 Seung Hee Yang,2 Dong Ki Kim,2,1 Kwon Wook Joo,2,1 Yon Su Kim,2,1,2 Internal Medicine, Seoul National Univ Hospital; 2Kidney Research Inst, Seoul National Univ College of Medicine.

Background: The remnant kidney model has been well established in the rodents, whereas it has not been fully understood in higher and bigger animals. Canine remnant kidney model is important for better medical applications. We aimed to establish 1/16 canine remnant kidney model. Methods: Remnant kidney model was induced in beagle dogs by a two-step subtotal nephrectomy. First, left kidney was exposed by flank incision. Among a total of eight branches of left renal arteries, seven-eightths of left renal arteries were ligated. Ischemia induction was confirmed by visual identification of topical cyanosis. After 1 week, right kidney was removed and consequently 1/16 remnant kidney model was completed. A total of 20-weeks of subtotal nephrectomy, we sacrificed the animals and their renal histopathologic changes were examined.

Results: During 20 weeks, CKD dogs (n=12) and sham-operated dogs (n=2) were monitored. Blood pressure of CKD dogs had been maintained highly at 2 weeks. In spite of anti-hypertensive medication, 3 CKD dogs died from uremia and hypertension. After surgery, body weights were declined in both CKD and sham-operated dogs in first 2 weeks. Sham-operated dogs had recovered their body weight within 3 weeks, however, CKD dogs had recovered slowly until 3-months after surgery. Blood urea nitrogen, serum creatinine and proteinuria amount were significantly higher than those of sham-operated dogs during overall period. Renal function decline were accentuated during first 3 weeks after subtotal nephrectomy and last 2 weeks before sacrifice. Intra-renal infiltration of inflammatory cells, atrophy of renal tubular cells, and renal fibrosis were prominent in CKD dog than in sham.

Conclusions: We successfully established 1/16 remnant kidney model by renal artery ligation in beagle dogs.

TH-PO261
Molecular Score of Acute Kidney Injury Identifies Discarded Kidneys That Are Potentially Transplantable Konrad S. Famulski,1 Silke V. Niederhaus,2 Jeff Reece,1 Jonathan Bromberg,3 Philip F. Halloran,1 1Univ of Alberta, Edmonton, AB, Canada; 2Univ of Maryland, Baltimore, MD.

Background: Many kidneys from older deceased donors are discarded due to uncertainty based on conventional features (clinical or histology). We previously showed that the molecular AKI score in implantation biopsies (Bx) predicts future graft function better than histology. Now we hypothesize that AKI scores in kidneys accepted for transplantation will be similar to some discarded kidneys when decision to transplant is based on conventional features. Methods: Pre-implantation Bx from accepted and discarded kidneys were obtained from brain dead >90 years donors. Decision to discard was based on MAPI scores of wedge Bx in 20/28 discards. Molecular AKI scores and global gene expression were analyzed by microarrays.

Results: The molecular AKI scores in all kidneys were compared by principal component analysis (PCA).
of apoptosis is activated during CS/REW. We hypothesized that increased mitochondrial injury during CS/REW in mouse RTECs would result in release of mitochondrial AIF, thus activating caspase independent apoptosis. Furthermore, we hypothesized that squirrel RTECs would be protected from apoptosis and not release AIF during CS/REW.

**Methods:** Squirrel and mouse RTECs were subjected to cold storage (CS) in UW solution followed by rewarming (REW) in normal media as previously described (Jain, S. Transpl Int, 2015). Apoptosis was quantified by TUNEL assay. AIF was examined in mitochondrial and cytosolic fractions.

**Results:** Mouse RTECs exposed to CS/REW had significantly increased apoptosis vs. squirrel RTECs. Furthermore, mouse RTECs subjected to CS/REW had significantly increased mitochondrial AIF translocation to the cytosolic fraction vs. squirrel RTECs.

<table>
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<tr>
<th>Squirrel RTECs</th>
<th>Mouse RTECs</th>
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<td>Cont</td>
<td>CS/REW</td>
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<tr>
<td>TUNEL +ve cells</td>
<td>0.25±0.2</td>
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<tr>
<td>AIF</td>
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n = 3, * p<0.05 vs squirrel RTECs

**Conclusions:** The data provide evidence of mitochondrial disruption in mouse RTECs during CS/REW, resulting in caspase independent apoptosis mediated by AIF. One potential reason for the remarkable ability of hibernators to survive prolonged CS/REW far in excess tolerable by nonhibernators is mitochondrial preservation that prevents release of AIF. Understanding caspase independent pathways during CS/REW may lead to improved organ preservation, and novel therapies for DGF.

**Funding:** Other NIH Support - R03 DK96151-01 to Alkesh Jain

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**TH-PO264**

**Phenotype of Renal Tubular Cell Death During Delayed Graft Function**

Swati Jain, Robert J. Plenter, Danica Galesic Ljubanovic, Chelsea M. Ruller, Trevor L. Nydam, Alkesh Jain. Renal, Univ of Colorado, Aurora, CO.

**Background:** Delayed graft function (DGF) independently predicts reduced 5 yr kidney transplant survival. Treatments of DGF are lacking. Cold ischemia (CI) is a significant risk factor for DGF but the mechanism by which CI leads to DGF is unknown. The aim of this study was to determine the effects of CI on donor kidneys alone versus CI followed by warm reperfusion after kidney transplant (CI+Txp). We hypothesized that CI alone would produce a different injury phenotype to CI+Txp.

**Methods:** Male C57BL/6 mice aged 8-12 weeks, were subjected to mouse kidney transplant. Donor kidneys were subjected to 3 hours CI in UW solution, and processed immediately or subjected to syngeneic mouse kidney transplant. Renal function was assessed by serum creatinine (SCr). Renal tubular cell (RTC) apoptosis and necrosis were quantified by an independent nephropathologist. TLR4, RIP3, cleaved BID, cleaved caspase-8 (CC8) and cleaved caspase-3 (CC3) were examined by immunoblot.

**Results:** CI+Txp resulted in a significantly increased SCr (1.9±0.15) vs. transplant without CI (0.3±0.05). CI alone resulted in increased RTC apoptosis and CC3 but did not result in necrosis. In contrast, CI+Txp led to: (1) increased CC8, cleaved BID, Bax and CC3, and increased RTC apoptosis and also increased programmed necrosis; (2) increased RTC necrosis that was associated with increased RIP3 and TLR4.

**Conclusions:** CI results in RTC apoptosis alone without necrosis. In contrast CI+Txp results in a distinct injury phenotype of RTC apoptosis, and also programmed necrosis that is associated with: (1) increased RIP3 and TLR4; (2) CC8 activation of BID, which may further promote bax activation and thus programmed necrosis. Understanding the phenotype of injury following prolonged CI and kidney transplant may lead to novel therapies for DGF.

**Funding:** Other NIH Support - R03 DK96151-01 to Alkesh Jain

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**TH-PO263**

**Apoptosis During Extreme Cold Ischemia and Rewarming Involves a Caspase Independent Pathway**

Swati Jain, Charles L. Edelstein, Alkesh Jain. Renal, Univ of Colorado, Aurora, CO.

**Background:** Cold ischemia (CI) followed by warm reperfusion (REW) during hibernation is a natural model we have used to understand delayed graft function (DGF). We have shown that hibernating ground squirrel kidneys and tubular cells (RTEC) survive CS for several days in torpor followed by REW in Arousal without RTEC apoptosis. In contrast mouse & human kidneys demonstrate significant tubular apoptosis after CS/REW. We have previously shown that apoptosis during CS/REW in mouse RTECs is mediated in part by a caspase dependent pathway. Here we explore whether a caspase independent pathway

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

**Underline represents presenting author.**

149A
TH-PO265

Abstract Withdrawn

TH-PO266

Swine Leukocyte Antigens and Orthotopic Kidney Transplantation in Yorkshire Piglets and Yucatan Miniature Swine

Todd D. Merchel, Victor Monterroso, Daniel Moralero, Andrea Saucedo, Daniel Kleven, Chak-Sum Ho, N. Stanley Nahman, Surgery, Georgia Regents Univ; Laboratory Animal Sciences, Georgia Regents Univ; Pathology, Georgia Regents Univ; Gift of Life Michigan, Ann Arbor, MI; Medicine, Georgia Regents Univ.

Background: PCR with sequence-specific primers (PCR-SSP) is a rapid and inexpensive approach to low-resolution (Lr) swine leukocyte antigen (SLA) genotyping. PCR-SSP may be used in Yorkshire pigs (Yorks), cheaper than expensive Yucatan miniature swine (YMS), for kidney transplantation (KT). We performed dual exchange allogeneic KT (DEAK) in both Yorks and YMS, and correlated outcome with SLAs.

Methods: Orthotopic DEAK (30 kg sows) was performed in 2 YMS (Pig #9, SLA haplotype Lr-4/5.4, blood type A; and Pig #10, SLA Lr-4/5.5, A) and 2 Yorks (Pig #7, SLA Lr-6.12/22.15b, non-A; and Pig #8, SLA Lr-4.4/40.12, A). Species couples were operated simultaneously. For YMS Pig #9, the left kidney (LK9) was resected, ex vivo perfused on ice, and stored in an ice bath. LK10 was then removed, perfused and stored while LK9 was transplanted into #10. Then LK10 was transplanted into #9. Both R kidneys were removed. The same procedure was performed in Yorks. No immunosuppression was used; animals were sacrificed on POD 2-10.

Results: Mean pre-op creatinine (Cr) was 1.05 mg/dl. For YMS, Pig #10 rejected LK9 and died on POD-6 (Cr 19.6). Pig #9 accepted LK10 with Cr 2.4 at sac on POD-9. For Yorks, Pig #7 showed hyperacute rejection (RJX) of LK8 (POD-2, Cr 4.4). Both KT organs were well perfused at sac. For YMS, one SLA haplotype mismatch (Lr-6.7) led to RJX of LK7 by Pig #10, whereas complete SLA match in the other direction allowed graft acceptance of LK10 by Pig #9; both animals were blood type A. For Yorks, hyperacute RJX occurred in Pig #7 due to blood type incompatibility. Vascular RJX in Pig #8 resulted from a two class I haplotype-one class II haplotype mismatch.

Conclusions: Orthotopic DEAK and SLA typing with PCR-SSP are equally effective in Yorks and YMS, allowing for predictable patterns of RJX/acceptance. YMS may offer blood type incompatibility. Vascular RJX in Pig #8 resulted from a two class I haplotype-one class II haplotype mismatch. All KT organs were well perfused at sac.

TH-PO267

Development of Experimental Model of Renal Thrombotic Microangiopathy in Rat Allogeneic Bone Marrow Transplantation

Takafumi Kanemitsu, Go Kanzaki, Yuusuke Okabayashi, Michiko Aoki, Kiyotaka Nagahama, Akira Shimizu. Dept of Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.

Background: Renal thrombictic microangiopathy (TMA) after clinical hematopoetic stem cell transplantation (HSCT) is a well-recognized complication that carries a high risk of death. In TMA after HSCT, total body irradiation, use of immunosuppressants for prophylaxis against graft versus host disease (GVHD), viral infection, and GVHD have been proposed as risk factors. However, so far, experimental model of renal TMA after HSCT has been reported. Methods: In order to develop the experimental rat model of rat renal TMA after allogeneic BMT, we performed BMT from Lewis (RT1l) bone marrow cells (6×10¹⁰ cells) to DA (RT1a) rats after 10G irradiation without immunosuppression. We examined the clinical and pathological characteristics of several organs, including the skin, liver, gut and kidney during 9 months after BMT.

Results: In syngeneic BMT and non-BMT control rats, acute or chronic GVHD and renal TMA did not develop by 9 months. In DA rats after Lewis BM cell transplantation without immunosuppression, renal TMA in the kidney developed in 3 out of 6 rats 9 months after BMT with GVHD in the skin, gut, and liver. Renal dysfunction including the increased levels of the serum creatinine (0.33 to 0.1mg/dL) and urinary protein (0.4±0.1 g/day) developed at 9 months with skin rash, alopecia, decreased body weight, and liver dysfunction (AST: 231 mg/dL, ALT: 112 mg/dL, LDH: 987 mg/dL). Renal pathology showed collapsed and sclerotic glomeruli with endothelial cell injuries in all animals. Renal TMA findings were characterized by the glomeruli with mesangialiposis, duplication of the GBM, and fibrin thrombus formation. Exudative lesions in small arteries were also seen. These renal findings were quite similar findings as renal TMA after HSCT in humans.

Conclusions: In 50% of animals, renal TMA associated with GVHD developed with renal dysfunction after Lewis to DA rat allogeneic BMT. Further studies are needed to assess the mechanism of renal TMA after BMT.

TH-PO268

Beneficial Effect of Exendin-4 on Autophagy Dysfunction During Tacrolimus-Induced Pancreatic Islet Injury

Sun Woo Lim, Long Jin, Jin Jin, Chul Woo Yang. Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea.

Background: Autophagy is a cellular degradation-recycling system for aggregated proteins and damaged organelles. Previously, we reported that chronic calcineurin inhibitors (CNIs)-induced nephropathy was characterized by excessive autophagosome formation and decreased autophagic degradation rate. We suggested that lysosomal dysfunction may associate in the process of autophagic degradation. In this study, we evaluated the autophagic function in CNI-induced pancreatic beta cell injury, and combined treatment of exendin-4 (Exd), anti-diabetic agent has therapeutic effect by improving CNI-induced lysosomal dysfunction.

Methods: Rats were treated with tacrolimus (TAC, 1.5 mg/kg, s.c.) and Exd, (1 ug/kg, i.p.) for 4 weeks. The effects of Exd on TAC-induced pancreatic beta cell dysfunction were examined using IGTG, Section O, and HOMA-IR index and islet size. Using an INS-1 cells, we examined the effect of Exd on TAC-induced lysosomal dysfunctions such as pH increase, reduced cathespin B activity and LAMP-2A. Autophagosome formation and autophagic protein aggregates were confirmed by the expression of LC3-II and p62, respectively. Oxidative stress was measured by the concentration of 8-OHdG, MnSOD, catalse, and H2DCF-DA. The influence on apoptosis was examined by TUNEL assay, Annexin V, and active caspase-3.

Results: Four weeks of TAC treatment increased blood glucose levels and HOMA-IR index and decreased serum insulin level and islet size. But co treatment with Exd attenuated TAC-induced pancreatic beta cell dysfunction and islet size. Exd treatment improved TAC-induced pH increase, cathespin B activity and LAMP-2A expression in INS-1 cells. These were accompanied by restored expression of LC3-II and p62 which are markers for autophagic degradation rate. The markers for oxidative stress and apoptosis were also recovered by cotreatment of Exd.

Conclusions: The results of our in vivo and in vitro studies demonstrate that Exd has an effective anti-diabetic agent that exerted antioxidative and antiapoptotic effects via restoring TAC-induced autophagic dysfunction.

Funding: Government Support - Non-U.S.

TH-PO269

Klotho Deficiency Is Associated with Chronic Tacrolimus-Induced Oxidative Injury

Jin Jin, Myung Gyu Jung, Byung ha Chung, Chul Woo Yang. Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea.

Background: We previously demonstrated that experimental animal model of chronic calcineurin inhibitors (CNIs)-induced nephropathy showed down regulated Klotho in renal tissues. We suggested that Klotho deficiency is highly associated with prolonged treatment of CNI-induced oxidative injury and resultant apoptosis and renal dysfunction. To determine whether Klotho deficiency is closely associated with CNI-induced renal injury via oxidative stress, Klotho heterozygote mice were compared with wild type control.

Methods: Mice of wild type (+/+) and Klotho heterozygote (Kl/+ ) were daily treated TAC (0.25, 0.5, 1 mg/kg, s.c.) for 4 weeks under the 0.01% sodium diet. The effects of various dose of TAC and Klotho deficiency on renal function, fibrosis, and apoptosis. The expression of Klotho was measured in renal tissue and serum. Oxidative stress was evaluated with measuring 8-OHdG and MnSOD. Using a HK-2 cells, we examined the protective effect of recombinant Klotho under TAC treatment by measuring oxygen consumption rate (OCR), ATP production, amount of ROS, mitochondrial membrane potential (MMP), and apoptosis.

Results: Four weeks of TAC treatment induced renal dysfunction, renal fibrosis, and apoptosis in a dose-dependently in +/- mice. These changes were aggravated in Kl/+ mice receiving TAC. Reduced Klotho level in urine, serum, and renal tissue was accompanied increased renal injury by TAC treatment. Moreover, 8-OHdG was increased in +/- mice treated with TAC, and Kl/+ mice showed further increased 8-OHdG. The expression of MnSOD was reversely responded. Based on the in vivo results, in vitro test using HK-2 cells also performed by treatment of recombinant Klotho and/or TAC. Klotho treatment improved the mitochondrial function such as OCR, ATP production, MMP as well as ROS production and apoptosis.

Conclusions: The results of our in vivo and in vitro studies demonstrate that Klotho has a renoprotective role against TAC-induced renal dysfunction and cellular injury by reducing oxidative stress. These results suggest that Klotho has therapeutic potential in CNI-induced nephrotoxicity.

Funding: Government Support - Non-U.S.

TH-PO270

Discrepant Effect of Metformin on Hyperglycemia in Rats with Tacrolimus- or Sirolimus-Induced Diabetes Mellitus

Jian Jin, Long Jin, Ji Hyun Yu, Sun Woo Lim, Byung ha Chung, Chul Woo Yang. Transplant Research Center & Div of Nephrology, Dept of Internal Medicine, Seoul, St Mary’s Hospital, The Catholic Univ of Korea, Seoul, Korea.

Background: Metformin is the first choice used drug in the treatment of diabetes mellitus. However, the effect of metformin on immunosuppressant-induced hyperglycemia is controversial. In this work, we aimed to investigate the effects of metformin in tacrolimus- or sirolimus-induced diabetes mellitus.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Six groups of Sprague-Dawley rats were studied: animals received tacrolimus (1.25 mg/kg injected i.v. once), sirolimus (0.5 mg/kg) or vehicle (0.9% saline) twice daily. Body weight, water intake, and urine volume were measured before sacrifice. The effect of metformin on tacrolimus or sirolimus-induced hyperglycemia was evaluated by assessing intraperitoneal glucose tolerance test (IPGGT), insulin, and serum insulin level. For further analysis, isolated isolated renal tubular epithelial cells were treated with tacrolimus (30 ng/ml) or sirolimus (90 ng/ml) and metformin (165 ng/ml) for 12 h, then glucose-stimulated insulin secretion (GSIS) was performed.

Results: After four weeks, tacrolimus or sirolimus-treated animals showed decreased body weight and increased water intake and urine volume compared with vehicle group. Treatment with tacrolimus or sirolimus caused elevated blood glucose level and reduced serum insulin level. Islet size by measuring insulin-positive area was significantly decreased in tacrolimus or sirolimus-treated group. Combined treatment of metformin did not improve tacrolimus-induced blood glucose level. On the other hand, metformin recovered these value compared with the sirolimus alone. In vitro study of GSIS, combined treatment with metformin and tacrolimus showed a reduction in insulin secretion ability compared with tacrolimus alone. But, sirolimus and metformin-treated group showed higher level of insulin secretion than sirolimus alone.

Conclusions: In this study, we found that metformin confers to the insulin secretion capacity during sirolimus treatment, but not in tacrolimus. Therefore, use of metformin should be considered in transplant recipients receiving tacrolimus.

Funding: Government Support - Non-U.S.

TH-PO272

Background: Current immunosuppressive therapies are limited by non-specificity and toxicity. Lactic acid is a carbonylic acid present as L- and D- optical isomers. In mammals including humans, lactate is present almost entirely as L-lactate. L-lactate can accumulate in the contexts of ischemia and/or Warburg metabolism, and suppress T cell function.

Methods: We hypothesized that since D-lactate is more slowly eliminated than L-lactate, it may have immune modulatory effects similar to L-lactate that may be exploited for therapeutic immunosuppression, and tested both optical isomers in vitro and in vivo.

Results: We observed that while both D- and L-lactate (5-40 mM) markedly impaired murine and human CD4+ and CD8+ T cell proliferation in vitro, D-lactate had stronger effects than L-lactate. Neither D- nor L-lactate affected cell viability and apoptosis (7AAD, annexin V), and IL-2 and IFN-γ cytokine production by CD4 and CD8 T cells were unaffected. However, adding 20 mM D-lactate to CD4+CD25-Foxp3- T-effector cells (Teff) under polarizing conditions increased T Foxp3+ Treg formation. Our data indicated that use of specific, defined metabolites may have important therapeutic value as novel immunosuppressive agents.

Funding: Other NIH Support - NIAID

TH-PO273

Background: At transplantation (TX) into a CKD recipient, the donor’s endothelium is exposed to uremic and oxidative stress that may negatively influence graft function and structure. We hypothesized that in CKD milieu, graft endothelial damage is determined by uremic toxicity and exposure to uremic and oxidative stress. We also investigated whether healthy environment halts progressive endothelial loss in expanded criteria donor (ECD) graft.

Methods: Male inbred Lewis rats were used as donors and recipients. CKD developed in 24 rats (n=6 per group) by bilateral ablation of 2/3 of kidney mass. Control rats (n=24) were age-matched. Orthotopic TX was performed: healthy kidney to healthy rat (HD-HR); CKD kidney to healthy rat (CD-HR); healthy kidney to CKD rat (HD-CD); CKD kidney to CKD rat (CD-CD). Right donor kidney served as reference left (graft) kidney in TX. Donor kidney function was monitored for 10-14 days after TX. At wk 6, we evaluated graft function and morphology, and systemic oxidative (TBARS) and vascular damage (aorta calcification).

Results: Graft function (malink & PAH clearance) at wk 6 after TX confirmed improved allograft function after a short or long period of exposure to CKD milieu (2D-HR, 6D-HR, HD-CD, HD-CD). However, adding 20 mM D-lactate to CD4+CD25-Foxp3- T-effector cells (Teff) under polarizing conditions increased T Foxp3+ Treg formation. Next, IL-17 and TNF-α significantly induced the secretion of IL-6 and IL-8 from HPRTEpiC, however, addition of 1,25(OH)2D3 suppressed Th17 proliferation. Third, we investigated the protective action of 1,25(OH)2D3 on T cell proliferation and de-novo Foxp3+ Treg formation was increased in D-lactate treated Treg cells even at high concentration. In contrast, addition of 1,25(OH)2D3 did not suppress Th2 and regulatory T cells in a concentration-dependent manner, but did not suppress Th17 cell proliferation. In contrast, addition of 1,25(OH)2D3 significantly suppressed Th17 proliferation. Next, IL-17 and TNF-α significantly induced the secretion of IL-6 and IL-8 from HPRTEpiC, however, addition of 1,25(OH)2D3 significantly reduces the secretion of these cytokines.

Conclusions: This study suggests that addition of 1,25(OH)2D3 to Tc is beneficial by suppression of Th17 alloimmune responses and hence it could be proposed as therapeutic strategy to improve allograft outcome.

TH-PO274

Background: The molecular mechanisms underlying transplant allograft vasculopathy and chronic rejection are not fully elucidated. Glycosaminoglycans (GAGs) modulate inflammatory cell responses and Heparan sulfate (HS) is the predominant GAG in the endothelial glyocalyx. Binding to GAGs plays an important role in the function of chemokines. The role of donor allograft GAGs in renal transplant rejection is not well defined. In these studies, we investigated the effects of selective HS deficiency and interference with HS-chemokine interaction on renal allograft rejection in the mouse.

Methods: Donor renal allografts from mice with conditional deletion of the N-deacetylase-N-sulfotransferase-1 gene (Ndst1) in endothelial and myeloid/lymphoid precursors leading to HS deficiency were examined. M-T7, a viral-derived secreted N-deacetylase-N-sulfotransferase-1 gene (Ndst1) in endothelial and myeloid/lymphoid precursors leading to HS deficiency were examined. M-T7, a viral-derived secreted

Results: Using 733 biopsy samples (239 AR episodes) from 6 expression datasets as reference kidneys after TX in a CKD donor (all P<0.05). However, despite similar ischemia-reperfusion, TI and GS did not worsen in ECD grafts and TX of ECD grafts in healthy recipients did preserve glomerular and interstitial endothelium.

Conclusions: The role of donor allograft GAGs in renal transplant rejection is not well defined. In these studies, we investigated the effects of selective HS deficiency and interference with HS-chemokine interaction on renal allograft rejection in the mouse.

TH-PO275
Identification of Key Meta-Signatures Associated with Acute Rejection Post Kidney Transplant Weiwei Zhang, Zhengyi Yi, Karen Lok yee Keung, Li Li, Madhav C. Menon, Barbara T. Murphy. 1 Renal Div, Medicine, Icahn School of Medicine at Mount Sinai; Dept of Genetics and Genomics, Icahn School of Medicine at Mount Sinai.

Background: Acute rejection (AR) is a major contributor to chronic allograft dysfunction and graft failure. Kidney biopsy results are based on subjective interpretation. A number of methods which can analyze kidney biopsies has been performed by several independent studies in recent years, but the AR-associated signatures identified from these studies vary.

Methods: Meta-analysis and Bayesian network analysis were performed on 6 kidney biopsy expression datasets to identify key meta-signatures associated with acute rejection and the key drivers were validated in independent expression datasets of kidney transplant and kidney diseases.

Results: Using 733 biopsy samples (239 AR episodes) from 6 expression datasets as donor biopsy dataset, we identified 882 meta genes with differential expression in AR patients at FDR<0.05. Gene Ontology enrichment analysis indicated that genes involved in immune response, T/B cell activation and proliferation, antigen processing and presentation,

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protein kinase cascade and NFκB signaling pathways were upregulated, while genes involved in cellular stress were downregulated. The expression data of metastasis genes was used to build a meta-expression network from which functional submodules were identified. 14 key driver genes were subsequently derived from these network submodules that had differential connectivity in AR compared to noAR patients. The differential modules and key drivers all themselves significantly correlated with HLA antibody and graft survival. Finally, the differential expression of key drivers was validated in independent expression datasets from kidney transplants (N=839) as well as other kidney diseases (IgAn, Diabetic nephropathy and Lupus nephritis).

Conclusions: We identified a set of AR-associated key drivers that may play a common and pivotal role for driving the inflammatory responses in acute rejection in kidney transplantation as well as other kidney diseases, which will help the better understanding of molecular mechanism of acute rejection post transplant and therefore improve the early diagnosis/treatment of acute rejection to prevent renal failure.

Funding: NIDDK Support

TH-PO276

SNPs of Solute Carrier Family Genes Associated with Acute Renal Allograft Rejection in Korean Population By静香 Kim, Yeong Hoon Kim, S Meong ho Lee,1 Sunwoo Kang.1 1Dept of Nephrology, Inje Univ, Busan Paik Hospital, Busan, Korea; 2Dept of Nephrology, College of Medicine, Kyung Hee Univ, Seoul, Korea.

Background: Solute carrier family has been reported to be associated with various kinds of renal diseases. Thus, we hypothesized that single nucleotide polymorphisms (SNPs) of the solute carrier family genes might have association with acute rejection of kidney transplantation (KT) in Korean population. This study sought to investigate whether polymorphisms of some solute carrier family genes are involved in the development of acute renal allograft rejection.

Methods: We firstly selected 349 solute carrier family genes in NCBI gene database and searched the nonsynonymous SNPs on coding region in each genes. Finally we selected 420 nonsynonymous SNPs. The genotypes of these SNPs were performed using AxiomTM genome-wide human assay. SNPStats and SPSS 18.0 were used for the analysis of genetic data. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value.

Results: A total of 49 renal allograft recipients transplanted in Pusan Paik hospital. Acute rejection developed in 49 patients among them. Among 420 SNPs of 349 family carrier gene, three genes, rs5036 in SLC4A1, rs11643718 in SLC12A3, and rs1047099 in SLC2A4(1) only showed significant association with acute rejection (p<0.05).

Conclusions: These results suggest that these significant SNPs (rs5036 in SLC4A1, rs11643718 in SLC12A3, and rs1047099 in SLC2A4) may be associated with the susceptibility to the acute rejection in the KT patients of Korean population.

Funding: Clinical Revenue Support

TH-PO277

The Expression and Role of Human Cytomegalovirus-Induced Viral Chemokine Receptor US28 in Smooth Muscle Cells of Renal Allografts Wouter Lollinga,1 Raymond H. De Wit,2 Gwenda F. Vasse,1 Afsar Rahbar,1 Amelie Riezboes-brilman,1 Cecilia Süderberg-naaær,1 Willem Van Son, Kobus Van Son,1,2 Antoinette van der Meer,1 J. Smit,2 Jacob van den Born,1 NIDDK Support, 1Nephrology, UMC Groningen, Groningen, Netherlands; 2Medical Chemistry, VU, Amsterdam, Netherlands; 3Medicine, Karolinska Inst, Stockholm, Sweden; 4Medical Microbiology, UMC Groningen, Groningen, Netherlands.

Background: Renal transplantation is the preferred treatment for end-stage renal disease. Human cytomegalovirus (HCMV) infection is associated with decreased renal graft function and survival. HCMV expresses US28, a chemokine receptor that enables HCMV to escape immune surveillance and affect microenvironment in the graft. Our aim was to localize the expression of US28 in renal biopsies and determine its effect on viral dissemination in vitro.

Methods: US28 and immediate early antigen (IEA) expression was semi-quantitatively scored in recipient renal transplant biopsies (n=49) from HCMV-seropositive donors using immunohistochemistry. Expression in glomeruli, endothelium, smooth muscle cells, epithelium and inflammatory infiltrates was analyzed. Primary vascular smooth muscle cells were infected with MOI 0.01 with HCMV WT and US28-deficient HCMV (US28) carrying a GFP-tag, to follow viral dissemination in vitro.

Results: IEA was uniformly distributed over the renal compartments. US28 was expressed during active infection and latency. It was expressed in all compartments, but prevalent (Krukal-Wallis; P<0.001) in vascular smooth muscle (42% cells positive) and tubular epithelial cells (30%). It was also expressed in the neointima. Smooth muscle cells were permissive to HCMV and underwent lytic infection in vitro, but dissemination was delayed for US28-deficient HCMV.

Conclusions: In short, HCMV-induced US28 is expressed in smooth muscle cells of renal allografts. US28 expression here suggests a role in vascular disease following viral infection, especially given its presence in the neointima. Absence of US28 decreased HCMV dissemination in smooth muscle cells in vitro, yielding it an interesting target for intervention. The observation that HCMV may interfere with vascular function through the expression of chemokine receptor US28 is an intriguing finding worth further exploring.

TH-PO278


Background: Connective tissue growth factor (CTGF), a member of the CCN gene family, is an extracellular matrix (ECM)-associated heparin-binding protein involved in matrix production. CTGF has been shown to contribute to progression of fibro-proliferative diseases including fibrosis by modulating of proliferation, migration, and adhesion of fibroblasts. CTGF has also been shown to play a role in ECM remodeling in normal physiological processes including embryogenesis, implantation, and wound healing. However recent new insights into the pathogenesis of fibrosing kidney diseases lead us to re-evaluate CTGF in this context at a cellular level. We therefore generated a mouse model to study the tissue specific, conditional over-expression of CTGF using homologous recombination.

Methods: We generated mice conditionally over expressing CTGF in pericytes only. We cloned domains of CTGF and the WNT inhibitor DKK1 and tested their function on primary pericyte cultures.

Results: Overexpression of CTGF in pericytes has no impact on nephrogenesis or adult homeostasis but amplifies fibrogenic and inflammatory responses to kidney disease. CTGF domain IV activates Wnt/b-catenin signaling in pericytes, which is inhibited by recombinant DKK1. CTGF Dom IV rapidly phosphorylates the co-receptor of WNT/b-catenin signaling - LRP6. DKK1- blocks CTGF domain IV mediated fibrotic responses in culture including fibroctic gene activation, pericyte morphology changes and migration in JNK MAP kinase dependent, WNT partially dependent pathway. CTGF Dom-I also activates pericyte migration which is also inhibited by DKK-1, JNK inhibition or Wnt ligand secretion.

Conclusions: CTGF over expression restricted to kidney stroma in vivo is sufficient to amplify cell activation and myofibroblast transition. Multiple domains of CTGF drive fibrogenic responses in pericytes across acute rejection in vivo and JNK signaling pathways.

Funding: Pharmaceutical Company Support - Biogen

TH-PO279

Sphingosine Kinase 2 Mediates Kidney Fibrosis Through Epigenetic Change Tsuwoshi Inoue,1 Amandeep Bajwa,1 Heather M. Perry,1 Liping Huang,1 Hong Ye,1 Youichiro Wada,2 Diana L. Rosin,1 Mark D. Okusa,1 1Univ of Virginia; 2The Univ of Tokyo.

Background: In numerous forms of organ injury, interstitial fibrosis is a final common pathway. Despite recent epidemiological studies, therapies to focus on fibrosis and to delay progressive renal failure are limited. We recently found that sphingosine kinase 2 deficient-mice (SphK2KO) develop less fibrosis after folic acid (FA)-or ischemia-reperfusion-induced kidney injury. Sphingosine 1-phosphate (SIP) is produced by two sphingosine kinase isosforms (SphK1 and SphK2). SIP is involved in diverse functions, but the role of SIP produced by SphK2 is gathering attention as treatments focused on epigenetics have been identified. SphK2KO mice are primarily located in the nucleus, SphK1 is cytoplasmic. Sip production is regulated by SphK2 inhibits histone deacetylase (HDAC) and change in histone acetylation status, which can lead to an altered target gene expression. The aim of this study is to elucidate new mechanisms of kidney fibrosis through epigenetic changes.

Methods: Transcriptome analysis and ChIP-seq of H3K9ac and H3K7ac using primary renal cells or cell lines from WT, SphK1KO and SphK2K0 mice were applied to find new target genes that regulate fibrosis through histone acetylation.

Results: Microarray analysis identified 135 down-regulated (<=1/4) genes and 245 up-regulated (>4) genes in SphK2 KO compared to SphK1 KO mice. ChIP-seq (QuEST) revealed that 258 genes have H3K9ac and 589 genes have H3K9ac only in SphK1KO and not in SphK2KO. The combination of microarray and ChIP-seq analysis yielded 21 candidate genes. To determine the in vivo relevance of gene expression was evaluated using an in vivo fibrosis model (FA model and unilateral IR). We further applied SphK2 knock down to WT fibroblasts and overexpression to fibroblasts from SphK2KO to determine if the selected genes are regulated by SphK2. Based on these strategies, candidate genes were identified that are regulated by SphK2 through the change of histone acetylation.

Conclusions: The combination of microarray and ChIP-seq of H3K9ac and H3K7ac identified 21 candidate genes. A more detailed investigation is needed, but some genes regulated by SphK2 appear to modulate kidney fibrosis through epigenetic changes.

TH-PO280

MCP-1 Directly Induces Renal Tubulointerstitial Fibrosis Independently of Monocytes/Macrophages Induration Minjae Wu, Hye-Young Kang, Mi Jung Lee, Shin-Wook Kang. Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Previous studies have demonstrated the importance of monocyte chemotactrant protein-1 (MCP-1) and its receptor, C-C chemokine receptor 2 (CCR2), in the pathogenesis of tubulointerstitial fibrosis via the recruitment and activation of monocytes/macrophages. However, recent in vitro evidence has suggested that MCP-1 may act directly on renal cells via CCR2. Therefore, the results of a number of former studies showing the impacts of MCP-1/CCR2 blockade on renal injury may be partly attributed to a direct inhibitory effect of MCP-1 on renal cells, but this has not been clarified in vivo to date.

Methods: Monocyte/macrophage-deficient mice were induced by either liposome-clodronate or diphtheria toxin. These mice were treated with MCP-1-expressing lentivirus (LV) and/or R5102895, a specific inhibitor of CCR2. NRK-52E cells were treated with
recombinant MCP-1 with or without RS102895, or CCR2 siRNA. The mRNA and protein expression of fibromodulin and type 1 collagen in cultured NRK-52E cells and the whole kidney were evaluated by Western blot and real-time PCR.

**Results:** Fibromodulin and type 1 collagen expressions were increased in NRK-52E cells exposed to MCP-1, which was then significantly abrogated by co-administration with RS102895 or CCR2 siRNA. LV-MCP-1 transfection in mice (n=6) resulted in increased expression of macrophages, fibromodulin, and type 1 collagen mRNA and protein expression in the kidney. However, LV-MCP-1 transfection in monocyte/macrophage-deficient mice (n=6) resulted in increases in fibromodulin, fibronectin, and type 1 collagen mRNA and protein expression in the kidney. The degree of fibrosis and inflammatory cell infiltration in histopathological findings, total collagen content in kidney tissues and the expression of fibrotic markers in immunoblot analysis, which were reversed in the obstructed kidneys of fimasartan-treated mice.

**Background:** Interstitial fibrosis is a final pathological process in the progression of chronic kidney disease, whereas tubulointerstitial fibrosis has not been elucidated. In the present study, we investigated the role of Wnt4 on renal tubulointerstitial fibrosis via p38 mitogen-activated protein kinase (MAPK) pathway.

**Methods:** The MCP-1/CCR2 system is directly involved in MCP-1-induced renal fibrosis. The blockade of the MCP-1/CCR2 system can be a promising approach to treat various kidney diseases such as diabetic nephropathy, of which MCP-1-induced renal fibrosis is involved in the pathogenesis.

**TH-PO281**

T-Type Calcium Channel Blocker Attenuates Unilateral Ureteral Obstruction-Induced Renal Interstitial Fibrosis via Activation of the Nrf2 Antioxidant Pathway

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**Background:** Besides the effect on high blood pressure, T-type calcium channel blocker has been reported to exert a renoprotective effect in experimental models with renal fibrosis. However, the exact mechanism of T-type calcium channel blocker on tubulointerstitial fibrosis has not been elucidated. In the present study, we investigated whether the renoprotective effect of T-type calcium channel blocker is associated with modulation of the signaling of oxidative stress-induced renal fibrosis.

**Methods:** Treatment with a nontoxic dose of efonidipine, a T-type calcium channel blocker, or nifedipine, another T-type channel blocker, was initiated one day before unilateral ureteral obstruction (UUO) in C57BL/6 mice, and was continued until 3 and 7 days after UUO. Markers of renal fibrosis, inflammation, apoptosis and oxidative stress were evaluated.

**Results:** In the obstructed kidneys of UUO mice, treatment with efonidipine significantly attenuated interstitial fibrosis, collagen deposition and inflammation increased by UUO creation compared with treatment with nifedipine. Efonidipine significantly increased the expression of antioxidant enzymes such as HO-1, NQO1, catalase and SOD1. Increased apoptotic cell death and decreased Bcl-2 expression in the obstructed kidneys were also significantly ameliorated by treatment with efonidipine. The expression of the histone acetyltransferase p300/CBP-associated factor, which is known as a regulator of inflammatory molecules, was significantly inhibited by efonidipine. These beneficial effects of efonidipine were attributed to the increased nuclear expression of Nrf2 on UUO day 3 and the increased expressions of both total and nuclear Nrf2 with elevated Keap1 on UUO day 7, suggesting that efonidipine would promote activation of Nrf2 differently depending time course after UUO. Nifedipine had little effect on antioxidant enzymes, anti-apoptosis and Nrf2 signaling.

**Conclusions:** These results suggest that T-type calcium channel blocker exerts beneficial effects in renal interstitial fibrosis by activating Nrf2 and subsequent antioxidant enzymes.

**TH-PO282**

Fimasartan, the Novel Angiotensin Receptor Antagonist, Protects against Renal Inflammation and Fibrosis in Mice with Unilateral Ureteral Obstruction: A Possible Role of Nrf2

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**Background:** A newly developed angiotensin II receptor blocker, fimasartan, has effective blood pressure lowering effect via blocking renin-angiotensin system. Renal interstitial fibrosis is a final pathological process in the progression of chronic kidney disease, which is believed to be due to oxidative injury. Transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) is known to regulate cellular oxidative stress and induce antioxidant enzymes. This study investigated the role of Nrf2 in fimasartan-mediated antioxidant effects in mice with renal fibrosis induced by unilateral ureteral obstruction (UUO).

**Methods:** Fimasartan was administered intraperitoneally (3mg/kg/day) from the day of UUO surgery in C57BL/6 mice and was continued for 7 days after operation.

**Results:** UUO-operated mice revealed renal inflammation and fibrosis as evidenced by the degree of fibrosis and inflammatory cell infiltration in histopathological findings, total collagen content in kidney tissues and the expression of fibrotic markers in immunoblot analysis, which were reversed in the obstructed kidneys of fimasartan-treated mice. Fimasartan treatment upregulated renal expression of Nrf2 and its downstream signaling molecule Keap1, such as NQO1, HO-1, Nos 1, 2 and 4, GSTm2 and GSTt3 in both protein and mRNA levels. Furthermore, fimasartan increased the expression of antioxidant enzymes including CuSOD, MnSOD and catalase. Significantly less apoptosis in TUNEL staining, decreased pro-apoptotic protein, along with increased anti-apoptotic protein were observed in fimasartan-treated mice.

**Conclusions:** In conclusion, these results demonstrate that fimasartan has beneficial effects on renal oxidative stress, inflammation and fibrosis, which may be via upregulation of Nrf2 signaling, subsequently the induction of antioxidant pathways.
Methods: As in vivo and in vitro model of renal fibrosis, Sprague-Dawley rats were subjected to unilateral ureteral obstruction (UUO) for 1 or 7 days. Fibroblast-like rat proximal tubule cells (NRK-49F) were treated with transforming growth factor β (TGF-β) for 0, 1, 3, or 5 days. To access the involvement of its peroxidase activity in TGF-β-induced renal fibrosis, wild type Pdx5 (WT) and double mutant Pdx5 (DM), converted two active site cysteines at Cys 48 and Cys 152 residue to serine, were transiently expressed in NRK-49F cells.

Results: The protein expression of Pdx5 was reduced in UUO kidneys. Upregulation of fibrotic markers, such as fibronectin, vimentin, and alpha-smooth muscle actin (α-SMA), was delayed for 10 and 20 days in time point of higher Prdx5 expression in TGF-β-treated NRK-49F cells. The overexpression of wild type Pdx5 by transient transfection in NRK-49F cells attenuated the TGF-β-induced upregulation of fibronectin and α-SMA. On the other hand, the transfection of the double mutant Pdx5 did not prevent the activation of fibrotic markers. Overexpression of Pdx5 also suppressed the TGF-β-induced upregulation of Stat3 phosphorylation, while phosphorylation of Smad2/3 was unchanged.

Conclusions: Pdx5 protects TGF-β-induced renal fibrosis in NRK-49F cells by modulating Stat3 activation in a peroxidase activity dependent manner.

TH-PO286
Fucoidan Reduces Pressure-Induced Fibrotic Responses in Renal Tubular Cells Through Down-Regulating β-Catenin
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Background: Fucoidan is a kind of natural fucose-enriched sulfated polysaccharides found mainly in various species of brown algae and brown seaweed. In recent years, many studies show fucoidan reduces hypoxia nephropathy, and also inhibits liver fibrosis. However, the influence of fucoidan on renal fibrosis is not clear yet.

Methods: Rat renal tubular cells (NRK-52E) are applied in this study. We study the influence of low-molecular-weight fucoidan (50 Da) on renal fibrosis in a pressure-stressed cell model. Sixty mmHg of pressure will be applied on NRK-52E cells for different periods to induce EMT. The expression of EMT markers and β-catenin will be monitored by Western blotting.

Results: NRK-52E cells were subjected to 60 mmHg of pressure for the indicated periods. Cellular E-cadherin, TGF-β, CTGF, fibronectin, α-SMA and Snail were detected by Western blotting. We found sixty mmHg of pressure induces EMT markers expression in NRK-52E cells. Fucoidan (0.1 – 1 mg/ml) reduced pressure-induced α-SMA and fibronectin in NRK-52E cells. Fucoidan reduced pressure-induced CD44 and β-catenin, which may be a critical mechanism of anti-fibrosis effect of fucoidan. NRK-52E cells were pretreated with fucoidan for 30 min and then treated with TGF-β for 24 h. We found fucoidan could reduce TGF-β-induced α-SMA and fibronectin in NRK-52E cells.

Conclusions: In summary, fucoidan at adequate doses inhibits pressure-induced fibrotic responses in rat renal tubular cells. The investigation of the protective effect of fucoidan against renal fibrosis may provide a new therapeutic agent for CKD patients.

Funding: Government Support - Non-U.S.

TH-PO287
Indoxyl Sulfate Exacerbates Oxidative Stress and Impairs NF-κB/NR2 Levels in RAW Macrophages
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Background: Indoxyl sulfate (IS), a uremic toxin produced by intestinal bacteria, is accumulated in Chronic Kidney Disease (CKD) patients and exhibits potent inflammatory effects. However, no informed scientific evidence has evaluated the effects of this toxin on nuclear factor-κB (NF-κB) and nuclear factor-kb (NFkb) expression, which regulate the expression of many detoxifying enzymes and the transcription of pro-inflammatory cytokines genes, respectively, in CKD. Thus the aim of the study was to evaluate the influence of IS in NR2, NF-κB and malondialdehyde (MDA) levels in RAW macrophage cells.

Methods: Mouse RAW 264.7 macrophage cells were incubated overnight with IS (250, 500, 1000 or 4000nM) according to the recommendations of the European Uremic Toxicity Work Group. Nucleus and cytoplasm were separated using a specific Kit. Quantitative Real-Time PCR analysis and Western Blotting were performed to evaluate the NF2 and NFκB levels. MDA levels were measured by High Performance Liquid Chromatography with visible detection.

Results: In macrophages culture NR2 nuclear translocation and NF-κB protein were not activated by IS, however, NF-κB mRNA expression was stimulated by IS at the concentration of 1000 nM, 4 fold higher than detected in CKD patients i.e.

Figure 1. IS up-regulates NF-κB mRNA expression in RAW macrophages

Figure 2. IS exacerbates lipid peroxidation in RAW macrophage

MAA levels were increased by IS in the cells (Figure 2).

Conclusions: IS exacerbates oxidative stress and could activate NF-κB mRNA expression especially for the highest concentrations in RAW macrophages culture.

TH-PO288
Association of Intraglomerular Cytokine Environment with Distinctive Infiltrating Myeloid Cell Populations in Lupus Nephritis
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Background: Glomerular infiltrating myeloid cells are important in mediating intraglomerular tissue damage, cellular dysfunction, and functional obliteration in lupus nephritis.

Methods: A spontaneous chronic lupus model using NZM2328 mice and an anti-GBM-induced GN model were used to assess glomerular cytokine environment and myeloid cell infiltration in SLE by confocal microscopy. Glomeruli were isolated by magnetic bead trapping and single cell suspensions were analyzed by flow cytometry.

Results: In NZM2328 mice with severe proteinuria, increased CD11b+ dendritic cell (DC), CD103+ CDC, and MHCII+ macrophages were found infiltrating the kidney interstitium. However, glomerular infiltrating cells in these sick mice consisted mostly of MHC-II1+ M2-like macrophages but not MHCII+ cells. Microarray analysis of FACS-purified mesangial cells followed by confocal microscopy analysis of cytokine staining showed that mesangial cells mainly produced IL-6, M-CSF, stem cell factor, KC, and MP2. Immunofluorescence also showed that endothelial cells produced IP-10 whereas podocytes produced IL-1b. These cytokines likely determine the differences in cellular distribution between the interstitium and glomerulus and mediate GN. Anti-GBM-induced GN showed disproportionately high glomerular infiltration of PMN and Ly6C+ macrophages compared to NZM2328 mice with chronic GN, which suggest significant differences in pathogenesis between the 2 SLE models.

Conclusions: The secretion of selected cytokine and chemokines by glomerular parenchymal cells support a pathway for mediating the infiltration of Ly6C+ monocytes and PMN by CXCRC2 and CXCR4 chemokines and the development of monocytose into CD11b+MHC-low macrophages. These infiltrating cells are likely to interact with other cells to cause the pathological conditions in GN.

Funding: Other NIH Support - NIAID

TH-PO289
Mono-Sodium Urate (MSU) Activates PKR and NLRP3 Inflammasome in Human Renal Proximal Tubular Cells (HRPTCs)

Background: Protein kinase R (PKR) is triggered by double stranded RNA (dsRNA) which directly interacts with NLRP3 and activates NLRP3 inflammasomes. Inflammasome is a multiprotein complex consists of caspase-1, ASC, and NLRPs proteins. Inflammasome activation and maturation augments secretion of proinflammatory cytokines interleukin (IL)-1β and IL-18. High serum uric acid levels have also been reported to promote both acute and chronic tubulointerstitial disease. However, the role of
PKR in MSU mediated tubular cell inflammasome complex has not been investigated. We hypothesized that MSU triggers PKR pathway to activate NLRP3 inflammasomes in tubulointerstitial fibrosis.

Methods: Human renal proximal tubular cells (HRPTCs) were incubated with MSU (100 μg/ml) for either 24 or 48 hours and assayed for pyroptosis by a morphologic assay (through staining with H3342 and propidium iodide). True PKR was further studied in the presence or absence of caspase-1 inhibitor and then assayed for pyroptosis. To establish a causal relationship between NLRP3-mediated induction of K-efflux and inflammasome formation, HRPTCs were treated with MSU with/without glyburide.

Results: MSU exposure enhanced tubular cell pyroptosis. MSU-induced transcription of NLRP3, caspase-1, and IL-1β. MSU exposure augmented protein expression of PKR, NLRP3, IL-1β and caspase-1. MSU-induced pyroptosis was attenuated by caspase-1 inhibitor. Glyburide treatment showed down-regulation of NLRP3, caspase-1 and IL-1β expressions in MSU treated HRPTCs.

Conclusions: MSU activates PKR which leads to NLRP3 inflammasome activation and pyroptosis in HRPTCs.

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

Underline represents presenting author.
Tamm-Horsfall Protein (Uromodulin) Regulates IL-23 Expression in S3 Segments of Renal Proximal Tubule Brush Border Composition

Background: The Na-H Exchanger Regulator Factor Inosorn 1 (NHERF1), a multifunctional scaffolding protein, is required for regulated forward trafficking and brush border membrane (BBM) anchoring of the type II sodium phosphate cotransporter, Npt2a. We have shown that OK cells, a model of proximal tubule, lacking NHERF1 (OKH) have decreased BBM expression of Npt2a, SGLT1, ezrin, GGTase and Munc18. OKH cells also show a 50% decrease in total RNA levels and a near absence of Npt2a mRNA. We hypothesize that NHERF1 plays a defining role in BBM protein expression.

Methods: To test this hypothesis, we performed proteomic analysis of BBM proteins from WT and NHERF1 deficient (KO) mice and measured mRNA expression of selected transport proteins from WT and OKH cells.

Results: We identified 148 proteins whose expression was downregulated at least two-fold and 78 proteins whose expression was upregulated at least three-fold in KO mouse BBM. 14 proteins were absent in KO. Integrity Pathway Analysis demonstrated that 113 of the downregulated proteins were involved in cellular organization, assembly, function, or maintenance, specifically, microvilli and actin cytoskeleton structure (Shroom4, Fascin), protein trafficking (CLIC1 and 4), signaling (taperin, FGFR2), and repair. Immunohistochemistry of KO kidneys and scanning electron microscopy of OKH cells show no obvious defects in cell structure/polarity. The mRNA levels of Npt2a, SGLT1 and NHE3 in OKH were less than 50% of WT but promoter activity of SGLT1 was similar.

Conclusions: We conclude that the presence of NHERF1 defines renal BBM protein expression through post-transcriptional, trafficking, and anchoring mechanisms.

Funding: Other NIH Support - NIA, Veterans Administration Support, Clinical Revenue Support

Cell Signaling/Oxidative Stress

Tamm-Horsfall Protein (Uromodulin) Regulates IL-23 Expression in S3 Segments of Renal Proximal Tubule Brush Border Composition

Radtima Micunovic, Shehnaz Khan, Frank Witzmann, Tarek M. El-Achkar. Indiana Univ School of medicine.

Background: We recently showed that Tamm-Horsfall protein regulates granulopoiesis by inhibiting the expression of IL-23 in S3 segments and the resultant activation of the IL-23/IL-17 axis. The molecular mechanism of this observation is unclear.

Methods: We performed laser micro-dissection (LMD) of S3 segments from THP-/‐ and THP+/‐ kidneys sections followed by 2 Dimensional – Differential Gel Electrophoresis (2D-DIGE) to identify pathways that are modulated by THP in vivo. We also used an unbiased, label free proteomics approach to understand the signaling of THP on human proximal HK-2 cells. Additional experimental methodology is described in Results.

Results: Bioinformatics analysis of differentially expressed proteins in S3 segments dissected from THP-/‐ compared to THP+/‐ kidneys revealed that the free radical scavenging network had the highest score of clustering, suggesting that THP regulates redox balance in S3 segments. Using in vivo reporter dyes and by measuring enzymatic markers of oxidative stress (OS), we found increased OS in S3 segments from THP-/‐ compared to THP+/‐ kidneys. Label-free proteomic analysis of HK-2 cells revealed that incubation of these cells with THP inhibited multiple pathways that converge on Rac-1 signaling. Since Rac-1 signaling is essential to the activation of NADPH oxidase (NOX), a major source of reactive oxygen species in cells, we verified that THP-/‐ mice had increased expression of Rac-1 and Nox-2 but not Nox-4. Treatment of HK-2 cells with THP directly decreased IL-23 expression. In addition, oxidative insult using H2O2, but not LPS, stimulated IL-23 mRNA expression in these cells, suggesting that oxidative stress but not classical endotxin signaling, is needed for IL-23 induction in epithelial cells.

Conclusions: Taken together, our data support that THP inhibits Rac-1/NOX-2 oxidative stress in S3 segments, which in turn regulates the production of IL-23 and activation of the IL-23/IL-17 axis. These findings significantly enhance our understanding of how THP shapes the function and reactivity of S3 segments, which could have both renal and systemic implications, through the regulation of granulopoiesis.

Funding: Veterans Administration Support

Cell Signaling/Oxidative Stress

Hyaluronan Mediated Motility Receptor Regulates Cell Motility in Glomerular Endothelial Cells in Response to Shear Stress

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Background: Laminar shear stress (SS) is an important determinant of vascular health. The glyocalyx is a carbohydrate-rich layer that covers the endothelial cell surface. Glyocalyx translates shear forces into intracellular signals. Hyaluronan (HA) motility mediated receptor (HMMR) promotes cell motility and invasion through interactions with HA on the cell surface in non-renal cells.

Methods: Human conditionally immortalized glomerular endothelial cells (GEnC) were exposed to LSS (10 dyn/cm2) using an orbital rotator for 0, 24, 48 and 72h. Effects on expression of glyocalyx-related genes were analysed using a custom designed focused Taqman qPCR array. HMMR and CD44 (another hyaluronan receptor) and production of HA by radiolabelling were also assessed. Motility assays (scratch assay, 2D chemotaxis and Electric Cell-Substrate Impedance Sensing) were performed on GEnC and siRNA HMMR knockdown GEnC with and without HA fragments. HMMR expression was assessed on freshly isolated and cultured glomeruli.

Results: There was a significant increase in versican expression, peaking at 24h. Thrombomodulin expression significantly increased and reached a plateau within 24h. CD44 expression peaked at 72h of LSS. There was a dramatic decline in HMMR expression by 24h of LSS (10-fold decrease p<0.0001) and levels remained suppressed over 72h. Furthermore, HMMR recovery to nearly pre-LSS level after a period without LSS for 24h. LSS increased release of HA into culture medium. What is more, HA fragments increased cell motility where LSS for 24h reduced it. HA fragments did not increase cell motility on siRNA HMMR knockdown GEnC. HMMR expression was increased in isolated glomeruli after 24h in culture.

Conclusions: HMMR is exquisitely shear-sensitive in vivo and ex vivo and acts as a marker for LSS exposure in endothelial cells. Chronic LSS reduces cell motility. Our data suggest this is due to HMMR expression changes and that HMMR is likely to play important roles in glomerular physiology and disease.

Funding: Government Support - Non-U.S.
Methods: Immunogold and co-IP were performed to examine co-localization and interaction of TRPC6 and β-Catenin. Cell surface biotinylation and high-throughput analysis were used for quantitative analysis of cell surface levels of TRPC6. Calcium imaging was performed to measure calcium influx mediated by TRPC6. Glomerular isolation, biotinylation and podocyte enrichment were performed to determine podocyte membrane TRPC6 expression in vivo.

Results: Co-localization of TRPC6 and podocyto was observed in podocyte foot processes by immunogold double labeling in mouse kidney. Interaction of the two proteins was observed by co-IP in cultured podocytes and mouse glomeruli. TRPC6 levels on cell surface increased in podocytes and decreased in synpo expressing podocytes. Consistent with the changes in expression levels, calcium influx mediated by TRPC6 was enhanced in synpo knockdown podocytes and reduced in synpo expressing podocytes.

Mechanistically, we found both actin and microtubule cytoskeletons were involved in regulation of membrane TRPC6 expression affected by synpo. Membrane TRPC6 expression in podocytes was elevated upon LPS treatment and was restored by cyclosporine A (CsA) in WT mice. Functionally, CsA treatment significantly reduced LPS proteinuria in WT mice (71%) and to a lesser extent in TRPC6-/- mice (45%).

Conclusions: Synaptoptin limits expression of TRPC6 on podocyte plasma membrane. CsA, a drug that stabilizes synpo, is shown to lower podocyte surface TRPC6 levels upon LPS treatment. The partial benefit of CsA in reducing LPS proteinuria in TRPC6-/- mice suggests that CsA protects podocytes partially by lowering cell surface expression of TRPC6 through stabilization of synpo.

Funding: NIDDK Support

TH-P0300

APOL1 Risk Variants Enhance Podocyte Oxidative Stress Xiuxian Lan, Hongxu Wu, Yingchao Wei, Malhotra, Karl Leong, Merchant, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: APOL1 variants have been implicated for increased prevalence and acceleration of the rate of progression of kidney diseases amongst African Americans. Since oxidative stress has been demonstrated to play a role for loss of podocytes in both experimental animal and human kidney disease models, we hypothesized that APOL1 variants could be inducing podocyte injury through augmentation of oxidative stress.

Methods: Human podocytes (HPs) stably expressing Vector, APOL1G0, APOL1G1, or APOL1G2 were used. Pseudo type HIV or empty vector (control) virus was transduced into Vector/HPs, G0/HPs, G1/HPs, and G2/HPs. After 48 h, cells were loaded with DCFDA and ROS generation was assayed every 10 min for 60 min by a fluorometer. Three sets of experiments were carried out in triplicate. Protein blots of HPs expressing Vector, APOL1G0, APOL1G1 and APOL1G2 were probed for cellular markers for oxidant stress and associated down stream signaling (phospho-p53, phospho-Fox0A3, p27, BAD, RIP3, MnSOD, and catalase). To evaluate the status of apoptotic pathway, protein blots of HPs expressing Vector, APOL1G0, APOL1G1, and APOL1G2 were probed for caspase-3 and then re-probed for actin. To determine the role the activation of Ang II type 1 (AT1R) and II (AT2R), protein blots of HPs expressing APOL1 variants and vectors were probed for AT1R and AT2R.

Results: Both HPG1 and HP G2 displayed increased ROS generation when compared to Vect/HPs and G0/HPs, G1/HPs, and G2/HPs displayed higher expression of pro-oxidant molecules, including RIP3, p27, BAD, phospho-Fox0A3, phospho-p53, phospho-HP1 and HP/ G2 also enhanced expression of cleaved caspase-3 when compared with vector/HPs and G0/ HPs. However, both G1/HPs and G2/HPs displayed lower expression of MnSOD and catalase. Both G1/HPs and G2/HPs displayed higher ROS generation and enhanced expression of pro-oxidant molecules in HIV milieu when compared to vector/HPs and G0/HPs.

Conclusions: These results indicate that APOL1 variants can have potential to augment oxidative stress in podocytes and this effect is further exacerbated in HIV milieu.

TH-P0301

The SMAD2/3 Ratio Is Controlled By PLC in Podocytes Carl J. May,1,2,3 Gavin Iain Welsh,1,2,3 Moin Saleem1,2,3,4 1Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom; 2Children’s Renal Unit, Bristol Children’s Hospital, Bristol, United Kingdom.

Background: Podocytes are thought to be the target cell in nephritic syndrome pathogenesis. Mutations in PLCE1 which encodes a lipid signalling enzyme, have been reported in congenital nephrotic syndrome in Europeans. However, the effects of mutant β-Catenin in the mature podocyte are not clear.

Methods: A conditionally immortalised human podocyte cell line was established from a patient, with a SNP at nucleotide 321 of PLCE1 that leads to a stop codon. This led to the loss of expression of β-Catenin unable to bind to α-Catenin or TCF. To examine the impact of β-Catenin acting in only one of its subcellular localization, we expressed β-Catenin either in the membrane or in the nucleus. Knockdown of endogenous β-Catenin was conducted by morpholino injection and co-expression of the mutants by injection of mRNA. After that the integrity of the glomerular filtration barrier was analyzed.

Results: Our analysis revealed that β-Catenin tethered to the membrane only seems to be able to partially retain the glomerular filtration barrier, whereas nuclear β-Catenin alone cannot abrogate the impact of the β-Catenin knockdown and leads to loss of high molecular weight proteins from the glomerular filtration barrier. β-Catenin missing the function of binding TCF have a normal glomerular filtration function, while the expression of β-Catenin unable to bind to β-Catenin leads to proteinuria.

Conclusions: These results suggest that the cell-cell adhesion function of β-Catenin is of greater importance for the maintenance of the glomerular filtration barrier than its role as a transcription factor.

Funding: Government Support - Non-U.S.

TH-P0304

Vitamin D (VD) Upregulates Nephrin in HIV-Induced Dedifferentiated Podocytes Through Down Regulation of SNAIL Nirupa Chandell, Rivka Lederman, Ashwani Malhotra, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY.

Background: HIV infection of kidney cells plays a key role in the development of HIV-associated nephropathy (HIVAN). We recently observed that HIV-induced dedifferentiations of podocytes regulated through SNAIL. We hypothesize that VD has potential to prevent

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the Nephrin downregulation through modulation of SNAIL expression. VD may be required for podocyte differentiation to finally achieve normalization of slit diaphragm proteins (Nephric and WT-1) and nephrin, accompanied by upregulation of mesenchymal marker desmin both in vitro and in vivo. Furthermore, AOPPs worsen proteinuria, aggravated glomerulosclerosis and renal fibrotic lesions. Concomitantly, SDF-1α/CXCR4 signaling was remarkably induced in podocytes by AOPPs. Administration of AMD3100, a specific inhibitor of CXCR4, reduced proteinuria, ameliorated podocyte dysfunction and renal fibrotic lesions triggered by AOPPs. These findings suggest that chemokine receptor CXCR4 may play a crucial role in mediating oxidative stress-induced podocyte injury, proteinuria and renal fibrotic lesions.

Funding: Government Support - Non-U.S.

TH-PO307
PKCα Is Identified as a Novel Binding Partner of β-catenin in Podocytes Xueqiao Yu,1 Beina Teng,1 Michelle Duong,1 Mario Schiffer,1 Medical School Hannover.

Background: PKCα, one conventional isoform of PKC, is a binding partner of β-catenin. However, a link between PKCα, a novel isoform, and β-catenin remains unclear. PKCα regulates the cytoskeleton by phosphorylating RGCAP1, a protein involved in the regulation of β-catenin in the cell-cell adhesion complex. So, we investigated the association between PKCα and β-catenin.

Methods: Staining was performed on murine kidney sections and podocytes to examine the β-catenin expression. Time courses were performed in murine wild type and PKCα−/− podocytes. 7 promising phospho-motifs in β-catenin were selected and site-specific mutations were produced. The interaction between the β-catenin mutants and PKCα were verified by immunoprecipitation. The mutants were overexpressed in murine podocytes using adenovirus. Zebrafish larvae were injected with mutant β-catenin RNA. Results: During the development of mice β-catenin showed increasing expression level in the glomeruli. However, the upregulation of β-catenin in wild type mice was much higher than those of PKCα−/− mice. When in wild type podocytes, β-catenin showed a translocation from the perinuclear areas to the nuclei during differentiation, the distribution of β-catenin switched the reverse way in PKCα−/− podocytes from the nuclei to the perinuclear areas. During the time course, the expression of active β-catenin was increased and total β-catenin decreased in the wild type podocytes under the stimulation of PMA. However, in the PKCα−/− podocytes, both active β-catenin and total β-catenin displayed decreased expression level. 3 of 7 mutant β-catenin exhibited decreased interaction with PKCα in immunoprecipitation, indicating these phospho-motifs as important binding sites. Overexpression of these 3 mutants in wild type podocytes, showed no changes in the time course. These 3 mutant β-catenin were unable to rescue the β-catenin knockdown zebrafish.

Conclusions: It is the first time to indicate that PKCα binds β-catenin directly and they are involved in the process of glomerular disease and podocyte differentiation. 3 phospho-motifs in β-catenin are proved as binding sites for PKCα.

TH-PO308
Reactive Lipids Affect Podocyte Homeostasis Through the Redox Sensitive RhoA-Slit Diaphragm Protein-Akt Axis Kristian Studlag, Claudia Kruger, Oxidative Stress and Disease Lab, Pennington Biomedical Research Center, Baton Rouge, LA.

Background: Podocyte loss is a characteristic early feature of obesity and diabetes related glomerular disease. Despite much attention on reactive lipids in diabetic kidney disease, surprisingly little is really known regarding their biological role in podocytes.

Results: Here we developed a quantitative lipid radical generating system using the donor AAPH, and conditionally immortalized podocytes to test the effects of reactive lipids on podocyte homeostasis. Overexpression of these 3 mutants in wild type podocytes, showed no changes in the time course. These 3 mutant β-catenin were unable to rescue the β-catenin knockdown zebrafish.

Conclusions: It is the first time to indicate that PKCα binds β-catenin directly and they are involved in the process of glomerular disease and podocyte differentiation. 3 phospho-motifs in β-catenin are proved as binding sites for PKCα.

TH-PO306
CXC4 Plays a Crucial Role in Mediating Oxidative Stress-Induced Podocyte Injury Hongyan Mo,1 Xue Hong,1 Lili Zhou,1 Youhua Liu,1 TH-PO306

methods: In a mouse model of adriamycin nephropathy (ADR), CXC4 RNA and protein expression, as well as oxidative stress was examined. AOPPs, advanced oxidation protein products, were utilized to trigger oxidative stress, and their effects on podocyte dysfunction and CXC4 expression were assessed. AMD3100, a specific inhibitor of CXC4, was used to block CXC4 action both in vitro and in vivo. Results: CXC4 expression was significantly induced in podocytes as early as 3 days after injection of ADR, and levels of CXC4 mRNA receiving TNFα and TNFβ and TGFβ2 and TGFβ3 received the most significant oxidative stress in podocyte, as detected by MDA assay of kidney homogenate, NBT/NTB staining in podocyte, and induction of NOX2, a major subunit of NADPH oxidase. Similar results were obtained when we stained for CXC4 in human kidney biopsies from patients with proteinemic kidney diseases including IgAN, crescent, and FSGS. Using immortal podocytes, and cell lines of podocyte injury induced by ADR or AOPPs, we found that AOPPs induced significant loss of podocyte marker WT-1, nephrin and podocalyxin, accompanied by upregulation of mesenchymal marker desmin both in vitro and in vivo. Furthermore, AOPPs worsen proteinuria, aggravated glomerulosclerosis and renal fibrotic lesions. Concomitantly, SDF-1α/CXCR4 signaling was remarkably induced in podocytes by AOPPs. Administration of AMD3100, a specific inhibitor of CXCR4, reduced proteinuria, ameliorated podocyte dysfunction and renal fibrotic lesions triggered by AOPPs. These findings suggest that chemokine receptor CXCR4 may play a crucial role in mediating oxidative stress-induced podocyte injury, proteinuria and renal fibrotic lesions.

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TH-PO309

The Redox Sensitive Glycogen Synthase Kinase (GSK) 3β Suppresses the Self-Protective Antioxidant Response in Podocytes upon Oxidative Glomerular Injury

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Background: GSK has been recently implicated in the pathogenesis of kidney diseases, including proteinuric glomerulopathy. However, prior studies were less conclusive because they relied solely on chemical inhibition of GSK3, which produce poor discrimination between the isoforms of GSK3 from potential off target activities. This study aimed to examine the effect of podocyte specific ablation of GSK3β on glomerular pathophysiology.

Methods: GSK3β was selectively knocked out (KO) in mature glomerular podocytes in adult mice by employing the tetracycline-inducible Cre-loxP site specific gene targeting system. KO mice and control littermates were subjected to intraperitoneal protein overload followed by examination of proteinuria and glomerular histology.

Results: In murine podocytes, the ββ twitch phenotype of the redox sensitive GSK3 was found to be predominantly expressed in glomeruli and distributed intensely in podocytes. Podocyte specific ablation of GSK3β resulted in a phenotype no different from control littermates with normal kidney function. Electron microscopy demonstrated more glycogen accumulation in podocytes but otherwise normal glomerular ultrastructures in KO mice. Upon oxidative glomerular injury induced by protein overload, KO mice excreted significantly less albuminuria and had much attenuated podocyteopathy, characterized by glomerulosclerosis, the loss of podocyte specific marker synaptopodin and β-III tubulin expression of podocyte injury marker desmin, as shown by fluorescent immunohistochemistry staining and by immunoblot analysis of isolated glomeruli. The antiproteinuric and glomerular protective effect observed in KO mice was concomitant with diminished accumulation of reactive oxygen species and attenuated oxidative injuries in glomeruli, which was likely secondary to a reinforced Nrf2 antioxidant response in glomerular podocytes.

Conclusions: Collectively, our data suggests that GSK3β is dispensable for glomerular function and histology under normal circumstances but may serve as a therapeutic target for protecting from glomerular oxidative injuries.

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

TH-PO310

Vitamin D Receptor (VDR) Inversely Modulates Renin Angiotensin System (RAS) Through MDM2 and p53 in Kidney Cells

Hong Xu, Weng Shabir, Haque, Xiaolian Lan, Ashwani Malhotra, Pravin C. Singh.
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Background: Vitamin D has been reported to be a negative regulator of renin transcription. However, this concept is not able to provide a logical explanation for activation of the RAS in VDR knockout (KO) mice. We hypothesized that VDR inversely modulates the RAS through regulation of MDM2 and p53 expression. Since MDM2 is a negative regulator of p53 (MDM2 induces transcriptional repression and proapoptotic degradation), VDR would also negatively regulate p53 via MDM2. p53 is known to activate the transcription of angiotensinogen (Agt) and AT1R. On that account we further hypothesize that vitamin D down regulates the RAS through upregulation of VDR/MDM2 and down regulation of p53.

Methods: Protein blots of control and VDRKO mice were probed for MDM2. The protein blots of control and siRNA-VDR/HP and p53/HPTCs and cells (HPTC) were silenced for VDR. Protein blots of control and VDRKO mice were probed for MDM2. The same blots were reprobed for p53, angiotensinogen (Agt), renin, AT1R, and actin. RNAs were extracted from renal tissues of control and VDRKO mice. cDNAs were synthesized with specific primers for MDM2, p53, Agt, and renin. Human podocytes (HP) and tubular cells (CT) were silenced for VDR. Protein blots of control and silenced VDR/HP and siRNA/HPTC were probed for MDM2, p53 Agt, and AT1R. To evaluate the role p53, cells were transfected with either p53 plasmid or siRNA/p53. To evaluate relationships amongst VDR, MDM2, and p53, protein blot of VDR agnostic treated p53/HP and p53/HPTCS and siRNA/p53/HP and HPTCs were evaluated for MDM2 and p53 expression.

Results: Renal tissues of VDRKO mice displayed attenuated protein and mRNA expression of MDM2 but enhanced expression of p53, Agt, renin, and AT1R. Both podocytes and tubular cells lacking VDR also displayed attenuated expression of MDM2 but enhanced expression of p53. Agt, renin, and AT1R. HPS and HPTCs displaying enhanced expression of p53 also displayed down regulation of VDR but activation of RAS; on the other hand, HPS and HPTCs silenced for p53 displayed upregulation of VDR but down regulation of RAS. VDR agonist enhanced expression of VDR and MDM2 but down regulated expression of p53 and the RAS.

Conclusions: VDR determines the status of the RAS through modulation of MDM2 and p53 expression in kidney cells.

TH-PO311

The Role of CD133 Molecule in Renal Papillary Cells and Its Possible Involvement in Wnt Signaling and Cellular Senescence Prevention

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Background: The nature of cells involved in homeostasis/repair of adult human kidney is unclear. In human tissue, using the AC133 antibody, recognizing a stem cell-specific glycoprotein-dependent epitope of promin (CD133), CD133+ cells with phenotypic and functional characteristics of mesenchymal stem cells were detected in all nephron segments as scattered distinct cells with a dedifferentiated phenotype that survive and proliferate after damage. However, the role of the CD133 in the progenitor phenotype and its possible modulation is unknown. In the present study, we aim to evaluate the role of the CD133 in the maintenance of cellular stem-like phenotype and its involvement in cellular senescence.

Methods: CD133+ progenitor cells were isolated from the inner medullary of human kidney biopsies. We generated CD133 knock-down (kd) cell lines by infecting them with lentiviruses carrying GFP-shRNA plasmids. Cytotoxicity was evaluated by BrdU uptake or MTT assay. Sphereoid formation was evaluated by sphere counting and MTT assay after 48h of hypoxia. The senescence was evaluated by β-galactocysteine expression and telomere length measurement by real time PCR. The activity of the Wnt pathway was investigated using a Wnt-reporter luciferase reporter.

Results: Preliminary data showed CD133 kd cells downregulated the stem-related gene Oct4A and acquired the differentiation marker AQPI. The activity of Wnt pathway seemed to be reduced in CD133 silenced cells both in basal culture conditions as well as after oxidative stress. As shown by a Wnt-reporter assay. Functionally, CD133 kd cells did not modify their response to cisplatin, cyclosporine or hydrogen peroxide, suggesting that CD133 may not be involved in resistance to damage. At variance, in CD133 kd cells the sphere formation was slightly reduced, both in number and size. Interestingly CD133 kd cells showed an increased expression of β-galactocysteine, a marker of senescence, compared to CD133+ cells, along with a telomere lengthening.

Conclusions: Our preliminary data suggest that CD133 may be involved in the maintenance of a stem-like phenotype in renal cells along with a delay of senescence.

Funding: Government Support – Non-U.S.

TH-PO312

The Effect of Wnt5a/Cα2+ Pathway on High-Glucose Induced Fibrosis of Human Peritoneal Mesothelial Cells

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Background: Fibrosis is the main reason of ultrafiltration failure. Human Peritoneal Mesothelial Cells (HPMC) expresses Wnt5a, which induces noncanonical wnt signaling pathway. Here we investigate the possible role of the Wnt5a/Cα2+ pathway in fibrosis of HPMC in vivo.

Methods: Wnt5a mRNA was detected by RT-PCR. The expression of connective tissue growth factor (CTGF) was detected by ELISA.

Results: Western blot showed the expression of Wnt5a in HPMC was elevated in HG groups, which depended on concentration and action time. Wnt5a mRNA expression in HPMC was high in early stage, and increased in 24h. According to the results of Western blot and immunofluorescence in HPMC, Wnt5a expression was elevated in HG group, and the expression was increased with the increase of concentration and action time.

Conclusions: The canonical Wnt5a/Cα2+ signaling pathway may be activated and necessary for the fibrosis of HPMC.

Funding: None.

TH-PO313

The Serine Protease Hepsin Mediates Urinary Secretion and Polymerisation of Zona Pellucida Domain Protein Uromodulin

Qingyu Wu, Ling Han, Celine Schaeffer, Sara Santambrogio, Eric Otling, Romain Perrier, Marcel Bokhove, Angela Bachi, Edith Hummler, Olivier Devuyts, Qingyu Wu, Luca Jovine, Luca Rampoldi. 1 San Raffaele Scientific Inst, Milan, Italy; 2 Karolinska Inst, Stockholm, Sweden; 3 Univ of Zurich, Zurich, Switzerland; 4 Univ of Laosanne, Lausanne, Switzerland; 5 FIRC Inst of Molecular Oncology, Milan, Italy; 6 Lerner Research Inst, Cleveland.

Background: Uromodulin is the most abundant protein in the urine. Genetic and functional evidence demonstrated that this protein, exclusively produced by renal epithelial cells, plays key roles in kidney function and disease. Uromodulin mainly exerts its function as an extracellular filamentous matrix whose assembly depends on a conserved, specific proline-rich region, leading to cell-cell adhesion, cell-matrix adhesion and formation of the zona pellucida (ZP) polymertisation domain. In this work we aimed to understand the nature of such cleavage.

Methods: We used a comprehensive approach, ranging from biochemistry, molecular and cell biology in cells stably expressing uromodulin and in urine and kidney samples of relevant knock-out mice.

Results: Starting from the observation that uromodulin is uniquely cleaved at the urinary site and assembled into polymeric filaments in MDCK cells we demonstrate that physiological cleavage of uromodulin depends on a serine protease, and that this enzyme is likely membrane bound. Differential expression analysis in different cell models identified two candidate enzymes, hepsin and prostatin. Both interact with uromodulin, and could induce its specific cleavage in transfected cells and in vitro. Through gene silencing in

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MDCK cells and extensive analysis of urinary uromodulin processing in vivo in hepsin and prostatin knock-out mice, we demonstrate that hepsin is the enzyme responsible for the physiological cleavage releasing urinary uromodulin.

Conclusions: Our findings define a key aspect of the biology of uromodulin that could pave the way for future studies on the regulation of its secretion. Given the similar function of the physiological cleavage in the secretion of uromodulin and the conservation of cleavage site in ZP domain proteins, our results are likely relevant for other members of this protein family.

Funding: Private Foundation Support

TH-PO314 The Effective Favorable Effect of Adipor on Renal Diabetic Nephropathy through Improvement of Endothelial Dysfunction in db/db Mice Yasemi Kim, Ji Hee Lim, Min Young Kim, Hyung Wook Kim, Cheol Whee Park. Dept of Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: Adiponectin is one of the numerous adipocyte-derived adipokines that interplays with others to exert the milieu of metabolic syndrome. It binds to adiponectin receptors (AdipoR), AdipoR1 and AdipoR2 and exhibits anti-diabetic effects via activation of AMPK and PPAR-α. Orally active synthetic small molecule Adipor agonist, AdiporOn binds to both AdipoR and ameliorates obesity-related disease. Therefore, we investigated the possible role of AdipoRos in renal physiology in the view of prevention and development of diabetic nephropathy in diabetic mouse model.

Methods: Male db/db mice were fed a diet containing AdipoRos (30 mg/kg/day) for 4 weeks from 17 to 20 weeks of age. Serum, urine and renal tissue were obtained to analyze for changes in metabolic parameters, molecular levels and renal structure.

Results: AdipoRos treatment showed decreased amount of albuminuria with no significant changes in the levels of serum adiponectin, glucose and creatinine and it seems to be weight neutral. Increased expressions of AdipoR1 in the renal cortex and consistent up-regulations of phosphorylated AMPK and PPAR-α level were associated with AdipoRos treatment. AdipoRos treatment showed favorable effects on diabetes-induced GBM thickening, foot process widening and slit diaphragm space narrowing and further decreased glomerular matrix expansions and inflammation.

Conclusions: Increased expressions of renal AdipoR1, not AdipoR2, indicates that renal injury may cause a compensatory up-regulation of relevant receptors in kidneys to mitigate further renal injury. AdipoRos may control oxidative stress in glomerulus through AMPK and PPAR-α activated pathways and further contribute to prevent deterioration of renal function. The protective role of AdipoRos against the development of albuminuria seems to occur through a direct action on podocytes independently of systemic effects of adiponectin. Its reduction of oxidative stress provides protection against albuminuria and podocyte damage thereby ameliorating endothelial dysfunction in diabetic nephropathy.

Funding: NIHDKK Support, Private Foundation Support

TH-PO315 Diabetes-Induced Impairments in Slit-Robo Signaling Augment Glomerular Angiogenesis Darren A. Yaun, Stephen G. Szeto,1 Mingliang Lu,1 Lauren Yuk-sum Chan,1 Krystale A. De freitas,1 Lisa Robinson,1 Ahmad Mohammad Omar Sidiqi.2 St. Michael’s Hospital Keenan Research Centre for Biomedical Science, Toronto, ON, Canada; 1Faculty of Medicine, Univ of Toronto, Toronto, ON, Canada; 2The Hospital for Sick Children, Toronto, ON, Canada.

Background: Diabetic nephropathy is characterized by glomerular endothelial cell (GEC) injury. One of the earliest manifestations of this injury is glomerular angiogenesis, a process that classically is thought of as being driven by increased glomerular VEGF production. Slit2 is a regulator of angiogenic function, exerting either pro- or anti-angiogenic effects through its Robo1 and Robo4 receptors, respectively. We have shown previously that glomerular endothelial Robo4 expression is downregulated by high glucose exposure, whereas Robo1 expression is unchanged. Objectives: To determine whether high glucose-induced alterations in Robo1 and Robo4 expression regulate VEGF-induced angiogenesis in the diabetic kidney.

Methods: GEC responsiveness to VEGF in angiogenesis assays was examined in both normal glucose (NG) and high glucose (HG) conditions, and following Robo1 knockdown. Using Robo4 knockout (KO) mice, the effect of Robo4 deficiency on diabetic glomerular angiogenesis was also analyzed using fluorescence microscopy (FMA) and PECAM-1 immunohistochemistry.

Results: As compared to GEC grown in NG medium, GEC grown in HG medium expressed lower levels of the anti-angiogenic Robo4 receptor, but not the pro-angiogenic Robo1 receptor, and exhibited greater VEGF responsiveness. Loss of Robo eliminated VEGF-induced GEC network formation and migration in both normal and high glucose conditions. In contrast, Robo4 deficiency was associated with enhanced PECAM-1 density and glomerular capillary length in Robo4 KO mice (compared to their WT littermates) after 4 weeks of STZ-induced diabetes.

Conclusions: Our observations suggest that diabetic glomerular angiogenesis is driven not only by increased VEGF production, but also by enhanced glomerular endothelial VEGF responsiveness. Our data also suggest that this increased responsiveness is promoted by a shift in glomerular endothelial slit2-Robo signalling, favouring more pro-angiogenic Robo1, and less anti-angiogenic Robo4 activity.

Funding: Government Support - Non U.S.

TH-PO316 Dynamic Regulation of Endothelial Specific Molecule 1 in Diabetic Mouse Kidney Xiaoxiao Zheng,1 Fariborz Sorouh,2 Sanchita Bhattacharya,3 Mohammad F. Kiani,1 Vivek Bhalla.1 1Div of Nephrology, School of Medicine, Stanford Univ, Stanford, CA; 2Dept of Mechanical Engineering, College of Engineering, Temple Univ, Philadelphia, PA; 3Dept of Pediatrics, School of Medicine, UC San Francisco, San Francisco, CA.

Background: Performing glomerular gene expression profiling in diabetic mouse models revealed differential susceptibility to nephropathy (DN), we identify endothelial specific molecule 1 (Esmin-1), as a novel candidate gene in the development of DN.

Methods: We studied Esmin-1 function using a bioinspired microfluidic assay (BMFA) and Esmin-1 expression by qPCR and ELISA in diabetic and non-diabetic mice.

Results: Esmin-1 is up-regulated in diabetic kidneys. Exposure to LFA-1-ICAM-1 interactions, mimicking the leukocyte: endothelial cell interface, and leukocyte infiltration into glomeruli is a known risk factor for DN. In a BMFA, pre-treatment of leukocytes with Esmin-1 inhibits rolling and transmigration in a dose-dependent manner. Consistent with the diminution of leukocyte infiltration, 4 weeks after induction of diabetes, Esmin-1 mRNA is markedly attenuated in glomeruli from DN susceptible, DBA/2J, mice relative (fold: 0.085 ± 0.012, p<0.05). Secretion of Esmin-1 is also lower from glomeruli of DN-susceptible mice (132.6 ± 41.6 vs. 226.4 ± 79.3 pg/mg creatinine, p<0.05), despite no increase in urine albumin and a ~50% decrease in circulating Esmin-1 in diabetic mice. Further in vitro studies in cultured glomeruli show that hyperglycemia significantly increases Esmin-1 mRNA and protein and suggest that urine Esmin-1 reflects increased production by glomeruli.

Conclusions: These results demonstrate that diabetes induces Esmin-1 in glomeruli, and this induction is attenuated in DN susceptible mice. These data suggest that increased production of glomerular Esmin-1 would be sufficient to attenuate leukocyte infiltration and improvement of ED in DN. Furthermore, we propose urine Esmin-1 as a non-invasive candidate biomarker for resistance to DN.

Funding: NIDDK Support, Private Foundation Support


Background: A small GTP-binding protein, Rho, and its effector, Rho-kinase, have several pathological functions. We previously demonstrated that in obesity adipocyte cellular hypertrophy activates Rho/Rho-kinase signaling through mechanical stretch, leading to inflammatory changes and fibroblast signaling, that not only contributes to obesity-induced kidney damage (O J Obesity, 2012). We examined whether Rho/Rho kinase was activated in enlarged PT that were supposed to be under the mechanical stress and contributed to the pathophysiology of obesity-induced diabetic kidney damage.

Methods: We created mice that overexpressed dominant negative RhoA genes specifically in PT under the control of promoter of sodium-phosphate co-transporter (PT-DN-RhoA) TG. PT-DN-RhoA TG mice (DN) and their wild-type littermates (WT) were fed high fat diet (HFD) or low fat diet (LFD) for 12 weeks and compared in phenotypes.

Results: WT on HFD not only developed obesity but also manifested histological changes, including the enlargement in PT as well as in glomeruli, vacuolation of PT, the infiltration of inflammatory cells and the overexpression of stress fibers, which paralleled the increase in urinary albumin and GFR of tubular injury markers. Enhanced Rho kinase activity was noted particularly in PT. Inflammatory cytokines were subsequently overexpressed in WT on HFD as compared with those in WT on LFD. In DN, the activation of Rho kinase was attenuated in PT region leading to the decrease in the size, vacuolation and stress fiber formation in PT cell, the decrease in inflammatory cells infiltration and cytokine expressions, and the reduction in albuminuria and PT impairment.

Conclusions: Excess fat intake causes obesity-induced renal injury, which are mediated by an Rho/Rho-kinase activation in PT and inflammatory process. It is surmised that hypertrophic process in PT during obesity formation affects Rho/Rho-kinase activation presumably through mechanical stress. This process subsequently induces inflammation and accelerates the histological changes of PT. The intervention of Rho/Rho-kinase may constitute a novel strategy blocking the progression of obesity-induced renal damages.

Funding: Private Foundation Support

TH-PO318 SUL121: A Novel Compound Preserving Endothelial Function and Inhibiting Progression of Kidney Damage in Type 2 Diabetes Mellitus in Mice Leo E. Deelman, Sebastiania Lambooy, Arash Bidadkosh, Hendrik Buikema, Robert H. Henning. Clinical Pharmacy and Pharmacology, Univ Medical Center Groningen, Univ of Groningen, Groningen, Netherlands.

Background: Diabetic nephropathy is a common complication of Type 2 Diabetes mellitus (T2DM), a chronic metabolic disorder with increasing incidence worldwide. To stop the progression of diabetic kidney disease, new strategies are urgently needed. Endothelial dysfunction (ED) and reactive oxygen species (ROS) are important targets for novel therapies to stop diabetic nephropathy. To improve ED and inhibit ROS, we recently developed the compound SUL121, a putative hydrogen sulfide (H2S) inducer and inhibitor of ROS.

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Methods: To test the therapeutic effects of SUL121 in diabetic and normal mice, db/db and lean control mice were subcutaneously injected with osmotic mini pumps delivering SUL121 or vehicle from age 10 to 18 weeks. Mice were placed in metabolic cages every two weeks until termination at which time endothelial mediated relaxation in aortic rings was assessed. ROS status and H2S levels were measured in plasma, and renal expression of H2S producing enzymes was determined.

Results: While treatment with SUL121 did not alter the glycomic state in db/db, it prevented albuminuria and diabetic kidney damage, as evidenced by an inhibition of the progression of albumin excretion rate, lower albumin creatinine ratio, decreased focal glomerulosclerosis, worse score and normalization of kidney weight. In addition, SUL121 normalized systemic ROS formation, increased renal expression of the H2S producing enzymes, cystathionine gamma lyase and cystathionine beta synthase (CSE and CBS), and prevented the development of endothelial dysfunction in db/db. SUL121 treatment in lean control mice demonstrated no observable side-effects, indicating that SUL121 is well tolerated.

Conclusions: Thus, SUL121 represents a novel compound inhibiting the progression of experimental diabetic kidney disease via a mechanism that inhibits both oxidative stress and preserves vasorelaxation.

Funding: Pharmaceutical Company Support - This study was partially financed by Sulfateq B.V., a company that owns patents on SUL121, and produces and markets similar compounds., Government Support - Non-U.S.

TH-PO319
Coagulation Factor Xa and Protease-Activated Receptor 2 as Novel Targets for Treating Diabetic Nephropathy
Yuuji Oe, Emiko Sato, Hiroshi Sato, Sadayoshi Ito, Nobuyuki Takahashi.  
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Background: Role of hypercoagulability in pathogenesis of diabetic nephropathy (DN) remains elusive. We have recently demonstrated that elevated coagulation factor III (tissue factor) exacerbates DN (J Thromb Haemost 2010, PNAS 2011). Tissue factor activates factor X (FXa), which in turn stimulates protease-activated receptor 2 (PAR2). PAR2 causes inflammation and fibrosis. Accordingly, we hypothesized that activation of FXa-PAR2 signaling exacerbates DN.

Methods: To test this hypothesis, we used diabetic mice with reduced expression of endothelial NO synthase (NOS3) as a model of DN. We first tested whether inhibiting FXa ameliorates DN by administering an oral FXa inhibitor Edoxaban (50 mg/kg/day) for 3 months in diabetic mice lacking nNOS (Ins2+/−; Nos3−/−). We next tested whether lack of PAR2 ameliorates DN using diabetic mice lacking PAR2 (F2rl1−/−; Nos3−/−). Finally, the effects of FXa or PAR2 agonist (SLIGKV) on human endothelial cells (EA-hy926) and conditionally immortalized murine podocytes were evaluated.

Results: Renal expression of FXa and PAR2 was up-regulated in DN, together with elevation of FXa activity in the urine. Edoxaban and lack of PAR2 both reduced renal expression of inflammatory and profibrotic genes, and ameliorated diabetic glomerulosclerosis and urinary albumin excretion. FXa or a PAR2 agonist (SLIGKV) increased IL-8 secretion and gene expression of MCP1 and PAI1 in human endothelial cells. These treatments also increased Meps1 mRNA level in murine podocytes.

Conclusions: We conclude that FXa - PAR2 signaling exacerbates DN possibly through up-regulating inflammatory response. FXa - PAR2 signaling is a promising target for treating or preventing DN.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO320
Herniation of the Mesangium Together with Sprouting of Blood Vessels Out of the Glomerular Entrance Is a Frequent Feature of Diabetic Nephropathy
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Background: In contrast to diabetic retinopathy, where neovascularizations have a central pathogenetic impact, in diabetic nephropathy (DN) angio-proliferative processes are generally not considered as a major factor underlying disease progression. The studies by Osterby and Nyberg (J Diab Compl 1987, 1:122) and Min and Yamanaka (Virchows Arch A 1993, 423:201) have shown neovascularizations in DN but have found little evidence of tissue herniation.

Methods: Re-evaluation of biopsies of DN (archive: Dep. of Molecular Pathology, German Cancer Research Center, Heidelberg) has revealed that the proliferation of newly formed blood vessels out of the glomerular entrance into the surroundings of the glomerulus is a frequent feature in DN.

Results: In a total of 437 biopsies (so far evaluated) 60.2% contained aberrant vessels at the vascular pole or in periglomerular position. 13% of these cases were associated with diffuse mesangial sclerosis (DMS), 35% with transitional stages from DMS to nodular glomerulosclerosis (NGS) and 52% with nodular sclerosis (NS). The cause of these lesions based on extensive studies of the glomerular entrance accompanied by herniation of the expanded mesangium with displacement of the extraglomerular mesangium and the macula densa. The aberrant vessels spread into glomerular surroundings, preferentially along the outer aspect of Bowman’s capsules, leading to invasion of peritubular capillaries. These vessels mostly have the structure of small arterioles. Frequently, almost regularly, accumulations of exudative material are encountered beneath the endothelium or within the layer of smooth muscle cells.

Conclusions: It is suggested that the exposure of mesangial areas to environmental stimuli results in the formation of neovascularizations. The development of these lesions from glomerular entrance to the aberrant vessel. The encroachment of these processes along the transition to the tubule likely contributes to the tubulo-interstitial disease.

TH-PO321
Exploiting Angiopoietin-Tie Signaling for Treatment of Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in the US, and is characterized by microvascular dysfunction. The Angiopoietin-Tie signaling pathway plays a key role in endothelial health and survival. The endothelial Tie2 receptor tyrosine kinase becomes activated upon binding its endogenous ligand Angiopoietin1 (ANGPT1). This activity elicits a cascade of intracellular signaling events, leading to junctional reinforcement and vasculo-protection. VE-PTP is a Tie2 selective phosphatase, which negatively modulates Tie2 signaling intensity. Here we tested whether augmentation of Tie2 signaling by VE-PTP inhibition protects against DN.

Methods: To test the therapeutic potential of Tie2 activation, we treated Ins2+/− DBA/2J mice with a VE-PTP inhibitor (AKB-9785, Aerio) or vehicle control (n=8 in each group). In parallel, cell-based analyses were performed to elucidate ANGPT-Tie signaling events. The role of VE-PTP on the phosphorylation status of Tie2 expressed in HEK293 cells was determined by LC-tandem mass spectrometry (LC-MS/MS).

Results: 17-week treatment of AKB-9785 improved the general status of Ins2+/− mice (body weight change from baseline; vehicle +15%, AKB-9785 +35%, P<0.01). Further, AKB-9785 preserved mFR of Ins2+/− mice (vehicle 560 ml/min, AKB-9785 945 ml/min with 6-week daily treatment, P<0.007). LC-MS/MS identified 13 phospho-tyrosine residues in Tie2; all sites were dephosphorylated by VE-PTP co-expression. Treatment with either recombiant Angpt1 or AKB-9785 rapidly induced Tie2 phosphorylation, suggesting Tie2 can be activated in a lig-and-independent fashion. Administration of AKB-9785 to Angpt1 KO mice confirmed ligand-independent Tie2 activation occurs in vivo.

Conclusions: Our data suggest that the small molecule inhibitor, AKB-9785 is a potent activator of Tie2 phosphorylation, has positive effects in a preclinical rodent model of Type 1 diabetes and is an attractive therapeutic candidate for DN.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute (NHLBI)

TH-PO322
Berberine Ameliorate High Glucose and Advanced Glycation End Products Induced Glomerular Endothelial Cell Permeability
Nanmei Liu, Jinmin Hospital of Shanghai.

Background: Glomerular endothelial cells (GECs) are important part of the glomerular filtration barrier. The dysfunction of glomerular endothelial cells (GECs) could be a characteristic of early stage diabetic nephropathy (DN). Accumulating evidence indicate that advanced glycation end products (AGEs) play a pivotal role in the progressive of glomerulosclerosis or thickening of the glomerular basement membrane in DN. Berberine, a xanthone from some Chinese herbs such as Coptis chinensis (Huanglian), Hydrastis canadensis, was reported as an extracts from some Chinese plant medicine such as Huanglian Letasiova S(Rhizoma coptidis); Huangbai (cortex phellodendri), Gold Seal ( hydrastis canadensis), was reported to reduce albuminuria in rats with diabetes. This study was to investigate the changes of monolayer permeability in GEnCs caused by high concentration glucose and AGEs, and the effects of Berbine.

Results: This study was to investigate the changes of monolayer permeability in GEnCs caused by high concentration glucose and AGEs, and the effects of Berbine.

Methods: Methods: To test the therapeutic potential of Tie2 activation, we treated Ins2+/− DBA/2J mice with a VE-PTP inhibitor (AKB-9785, Aerio) or vehicle control (n=8 in each group). In parallel, cell-based analyses were performed to elucidate ANGPT-Tie signaling events. The role of VE-PTP on the phosphorylation status of Tie2 expressed in HEK293 cells was determined by LC-tandem mass spectrometry (LC-MS/MS).

Results: 17-week treatment of AKB-9785 improved the general status of Ins2+/− mice (body weight change from baseline; vehicle +15%, AKB-9785 +35%, P<0.01). Further, AKB-9785 preserved mFR of Ins2+/− mice (vehicle 560 ml/min, AKB-9785 945 ml/min with 6-week daily treatment, P<0.007). LC-MS/MS identified 13 phospho-tyrosine residues in Tie2; all sites were dephosphorylated by VE-PTP co-expression. Treatment with either recombiant Angpt1 or AKB-9785 rapidly induced Tie2 phosphorylation, suggesting Tie2 can be activated in a lig-and-independent fashion. Administration of AKB-9785 to Angpt1 KO mice confirmed ligand-independent Tie2 activation occurs in vivo.

Conclusions: Our data suggest that the small molecule inhibitor, AKB-9785 is a potent activator of Tie2 phosphorylation, has positive effects in a preclinical rodent model of Type 1 diabetes and is an attractive therapeutic candidate for DN.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute (NHLBI)
Arginase Inhibition: A New Treatment for Preventing Progression of Established Diabetic Nephropathy

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Background: Our previous publication showed that inhibition of arginase prevents the development of diabetic nephropathy (DN). However, identification of targets that retard the progression of established DN—which is more clinically relevant—is lacking. Therefore, we tested the hypothesis that arginase inhibition would prevent the progression of established DN. Effects of arginase inhibition were compared to treatment with the ACE inhibitor captopril, a current standard of care in DN.

Methods: Experiments were conducted in Ins2Δβ2 mice treated with the arginase inhibitor S-(2-boronoethyl)-L-cysteine (BEC) or captopril starting at 6 wk of age or 12 wk (early treatment) or at 12 wk of age for 6 wk (late treatment).

Results: Early and late treatment with BEC resulted in protection from DN as indicated by reduced albuminuria, histological changes, kidney macrophage infiltration, urinary TBARS, and restored nephrin expression, kidney nitrate/nitrite, kidney eNOS phosphorylation, and renal medullary blood flow compared with vehicle-treated Ins2Δβ2 mice at 18 wk of age. Interestingly, early treatment with captopril reduced albuminuria, histological changes, and kidney macrophage infiltration without affecting the other parameters, but late treatment with captopril was ineffective.

Conclusions: These findings highlight the importance of arginase inhibition as a new potential therapeutic intervention in both early and late stages of diabetic renal injury.

Funding: NIH Support

TH-PO324

Transgenic TGF-β1 Receptor Type II (TbRII) Overexpression in Podocytes Promotes STZ-Induced Diabetic Nephropathy in Rats

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Background: Glomerular TGF-β1 is increased early in the course of diabetic nephropathy. The podocytes are sources and targets of TGF-β1. This study addresses the hypothesis that increased TGF-β1 in diabetic rats stimulates the development of diabetic nephropathy via selective signalling in podocytes.

Methods: Transgenic rats carrying the TgTrβRII driven by the podocin promoter were generated. Increased TbRII expression was verified by Northern blotting, in-situ hybridization and Western blotting. Glomerular expression profiling was performed by real time RT-PCR. Western blotting and immunohistochemistry. Podocyte density was determined by counting WT-1 stained podocytes per glomerular area, which was determined morphometrically in 200 glomeruli per rat. At 2 months of age rats received STZ (40 mg/kg i.v.) or saline, respectively. Body weight and kidney function were evaluated by urinary albumin excretion in the 24-h urine and by creatinine clearance at monthly intervals.

Results: TGR expressed the transgenic receptor specifically in podocytes. Glomerular TbRII protein levels were almost twice that of WT. At 5 months of age 40 % of TGR exhibited moderately increased albumin excretion up to 2.2 mg/24hr vs. 0.11 mg/24hr in TgTR-PO324

TH-PO325

Comparison of Glomerular and Podocyte mRNA Profiles in eNOS–/– Diabetic Mice Induced by Streptozotocin

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Background: Gene expression profiles have never been reported in primary podocytes isolated from the diabetic kidney. Here, we compared mRNA profiles in both isolated glomeruli and sorted podocytes between diabetic and control mice.

Methods: IRG mice carrying a two-color fluorescent reporter gene were first crossed into eNOS–/– mice and then with podocin-rtTA and TetON-Cre mice allowing us to permanently label podocytes. Then, mice were injected with either streptozotocin (STZ- eNOS–/– mice) or saline (WT-eNOS–/– mice). Glomeruli were isolated at 14 days after STZ injection. RNA was sequenced in both isolated glomeruli and sorted podocytes from STZ-eNOS–/– and WT-eNOS–/– mice.

Results: Consistent with the previous reports, expression of podocyte-specific markers in isolated glomeruli were down-regulated to the STZ-eNOS–/– mice compared to CL-eNOS–/– mice. However, these differences disappeared when mRNA levels were corrected for podocyte number/glomerulus. Interestingly, expression of these markers in sorted podocytes did not differ between diabetic and non-diabetic mice. These data suggest that reduced expression of podocyte markers in isolated glomeruli is likely secondary to reduced podocyte number/glomerulus, rather than loss of differentiation markers. Analysis of the differentially expressed genes (DEGs) between diabetic and non-diabetic mice revealed distinct pathways between glomeruli and podocytes. The up-regulated DEGs in isolated glomeruli were involved mostly in the regulation of mitochondrial function and oxidative stress pathway, while the up-regulated DEGs in sorted podocytes were heavily involved in the actin organization.

Conclusions: In conclusion, our data suggest that podocyte-specific gene expression in transcriptionome obtained from glomeruli may not represent those of podocytes in diabetic kidneys.

Funding: Other NIH Support - JCH is supported by NIH 1R01DK078897, NIH 1R01DK088541, and NIH P01-DK56492.

PYC is supported by NIH 1R01DK098126-01A1., Veterans Administration Support, Government Support - Non-U.S.

TH-PO326

SS-31, a Mitochondrial Therapeutic, Prevents High Fat Diet-Induced Podocyte Injury

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Background: High fat diet (HFD) leads to rapid onset of microalbuminuria and podocyte injury that precedes the onset of insulin resistance and hyperglycemia in mice. It was recently suggested that glomerular injury is triggered by palmitate-induced mitochondrial dysfunction in podocytes (Sun et al., Kidney Int, 2015). We investigated the protective effects of SS-31, a mitochondrial therapeutic, against HFD-induced podocyte injury.

Methods: 4-week-old C57BL/6 mice were fed normal diet (ND) or HFD for 28 weeks. 4 weeks later, HFD mice received streptozotocin (40 mg/kg, i.p., x 5). Body weight (BW), glucose blood (BG) and glucose tolerance tests (GTT) were determined after 8 and 24 weeks of HFD. SS-31 (2 mg/kg, sc) or saline was administered to HFD mice daily starting at 8 weeks. Kidneys were harvested at 28 weeks for histopathology.

Results: GTT was abnormal at 8 weeks despite no change in BW or BG. BW and BG were significantly increased at 28 weeks. Histological examination revealed mesangial expansion, thickening of the glomerular basement membrane, elevated collagen IV, and loss of podocyte markers (pocodin and synaptopodin). Electron microscopy revealed extensive vacuolization and swelling in podocytes, with swollen mitochondria, autophagic vacuoles, and loss of foot processes. TGFβ1, TNFα and MCP-1 were all significantly increased. Treatment with SS-31 significantly prevented HFD-induced pathological changes in the glomeruli without affecting BW, BG or GTT.

Funding: Private Foundation Support

TH-PO327

Tristetraprolin Overexpression Ameliorated Inflammation in db/db Mice and Mouse Podocytes

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Background: Tristetraprolin (TTP), also known as a posttranslational modulator of inflammation in high glucose-induced podocytes and in db/db mice kidneys.

Results: These results suggest that SS-31 can protect podocytes against HFD-induced mitochondrial toxicity without changing BW, insulin resistance or hyperglycemia. SS-31 (Bendavia™), currently in clinical trials for acute kidney injury, may be useful in the treatment of diabetic nephropathy.

Funding: Private Foundation Support

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

Underline represents presenting author.

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TH-PO328
CIN85 Deficiency Prevents Nephrin Endocytosis in Podocytes Under Diabetic Conditions
Beita Teng, Hermann G. Haller, Mario Schiffer. Medical School Hannover, Hannover, Germany.

Background: Podocytes are important for the maintenance of the glomerular filter in the kidney. Podocyte damage is associated with ultrastructural changes and decreased expression of components of the slit diaphragm in many glomerular diseases. Nephrin, a podocyte specific protein is crucial for the intact filtration barrier. Loss of nephrin has been observed in rodent models of experimental diabetes as well as in human diabetic kidney disease. CIN85, a homologue of CD2AP, was identified as a binding partner of nephrin and mediates the nephrin endocytosis via ubiquitination in podocytes.

Methods: Using STZ injection, we induced a type I diabetes in BLC57/N wild type and CIN85Dex2 mice to examine diabetes induced dysregulation of glomerular filtration barrier and alteration of extracellular matrix. We then generated immortalized cell lines of podocytes for the CIN85Dex2 and the CD2AP−/− to examine nephrin endocytosis in both cell types on the molecular level. To inquire the impact of CIN85 and CD2AP on filtration barrier integrity in zebrafish, we examined proteinuria in zebrafish injected with capped mRNAs.

Results: We can demonstrate that the loss of nephrin expression and onset of the proteinuria in diabetic mice is associated with an increased accumulation of ubiquitinated proteins and expression of CIN85 in podocytes. The CIN85Dex2 deficiency leads to preserved nephrin surface expression, reduced proteinuria and Collagen-IV deposition in glomeruli under diabetic conditions. High glucose levels induced an increased CIN85 expression in contrast to a significantly reduced expression of CD2AP and nephrin in both murine and human podocytes. Furthermore, by high glucose stimulation, the CD2AP−/− podocytes, which express more full-length CIN85, showed an increased nephrin endocytosis compared to the CIN85 knockout podocytes. In addition, injection of capped CIN85 mRNA induced a severe edema and proteinuria in zebrafish embryos which could be rescued by co-injection of CD2AP mRNA.

Conclusions: Our findings suggest that CIN85 is involved in the endocytosis of nephrin in podocytes under diabetic conditions promoting the development of glomerulosclerosis. Therefore CIN85 might be a novel treatment target to prevent diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO330
Insulin Signaling in Glomeruli and Podocytes from Insulin Resistant db/db DBA/2J Mice Mette Viberg Östergaard,1,2 Jesper Worm,1 Lisbeth N. Fink,1 Richard Coward,1 1Global Research, Novo Nordisk A/S, Maaaloev, Denmark; 2Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

Background: Impaired insulin signaling in the podocyte may contribute to the glomerular pathology in systemic insulin resistance and type 2 diabetes (T2D). We hypothesize that insulin signaling in the podocyte is altered early during development of insulin resistance and T2D due to alterations in insulin receptor (IR), IGFR-1 receptor (IGF-1R) or insulin/IGF-1 hybrid receptor (HR) expression levels.

Methods: The development of insulin resistance, T2D, albuminuria, and renal pathology was characterised in db/db DBA/2J mice and wild-type (wt) littermates from 1 week of age. Insulin-induced Akt homozygous (mT/mG) reporter strain enriched in the DBA/2J background is crossed with the db/db DBA/2J strain to enable isolation of insulin resistant GFP podocytes by FACs and characterisation of podocyte IR, IGF-1R and HR expression levels.

Results: The body weight was >50% higher in db/db vs. wt mice (P<0.001) from 8 weeks. From week 9, db/db males were hyperglycaemic with non-fasting blood glucose ranging from 23.4-30.7 mEq/l (wt range 6.3-7.7 mEq/l; P<0.05). Insulin tolerance tests showed development of whole-body insulin resistance by 8 weeks in males and female db/db vs. wt mice (P<0.05). The urinary albumin-to-creatinine ratio was elevated in db/db vs. wt mice from 7-12 weeks of ages (range of means 2451-5957 vs. 75-479 µg/mg; P<0.01). GFP podocytes were successfully isolated from glomerular single cell suspensions from db/db GFP−/− and wt mice and their purity validated by qPCR analysis of Npyh2, Pecam1, and Pdgfrb.

Conclusions: The db/db mouse in the DBA/2J background show early signs of systemic insulin resistance and glomerular disease. Isolating podocytes from this model will allow us to further clarify the roles of IR, IGF-1R and HR in podocytes during the development of insulin resistance and diabetic nephropathy.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

TH-PO331
PKC-α Triggers EGFR Ubiquitination, Endocytosis and MAPK/ERK Activation in Podocytes with High Glucose Stimuluation Hua Su, Yanhong Wei, Chun Zhang. Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

Background: PKCα and EGFR are both involved in diabetic kidney disease, however the association between these two proteins during high glucose induced podocyte injury is unclear.

Methods: Diabetes was induced in SD rats by a single intra-peritoneal injection of STZ at a dose of 55 mg/kg body weight in sodium citrate buffer. 14 days later the rats were sacrificed and the cortex of kidney was removed and subjected to plasma membrane isolation and lipid raft fraction. In vitro study human podocyte cell line was employed, and after differentiation it was treated with high glucose or osmotic control for 24 h. The membranous protein expression and endocytosis were assessed by biotinylation and MesNa treatment experiments It showed that the ubiquitination and activation E1 enzyme respectively.

Results: By plasma membrane isolation and lipid raft separation we identified that in diabetic rat the abundance of PKCα in membranous fraction and lipid raft domain was elevated, whereas EGFR level was reduced in abovementioned compartments. Consistently, in high glucose treated podocyte the membranous EGFR was downregulated accompanying with the increased membranous PKCα expression which was examined by biotinylation and plasma membrane isolation. Furthermore by immunoprecipitation, biotinylation and MesNa treatment experiments it showed that the ubiquitination and endocytosis of EGFR were enhanced in podocyte under high glucose stimulation which accompanied with MAPK/ERK signaling activation and the injury of podocyte which was proved by the reorganization of F-actin fibers and increased desmin level. However above processes could be ameliorated by either PKCα or ubiquitin activating E1 enzyme inhibitor.

Conclusions: Our observations demonstrate that in high glucose treated podocyte PKCα mediates EGFR ubiquitination, endocytosis from cell plasma membrane and eventually leads to the activation of MAPK/ERK signaling pathway which partially attributes to podocyte injury in diabetic kidney disease.

Funding: Government Support - Non-U.S.

TH-PO332
Activation of Protein Kinase C-β in the Podocyte by Diabetes-Associated Inflammatory Mediators Brad Dieter,1 Rick L. Meck,2 Robert J. Anderberg,1 Sheryl K. Cooney,1 Katherine R. Tuttle,1 1Providence Health Care, Spokane, WA; 2School of Medicine, Univ of Washington, Seattle, WA.

Background: Activation of protein kinase C-β (PKC-β) is a key signal transduction mediator strongly implicated in development and progression of diabetic kidney disease (DKD). However, the potential role of PKC-β in podocyte mechanisms of DKD has not been previously studied. The aim of this study was to determine whether advanced glycation end-products (AGE) or serum amyloid A (SAA), inflammatory mediators in DKD, activate PKC-β and downstream consequences of inflammation and apoptosis in podocytes.

Methods: Podocytes were exposed to AGE (300 mg/ml) or exogenous SAA (10 mg/ml) for 1 hour. PKC-β activity was measured as the phosphorylated form and by membrane

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fraction (Western blot). Immunostaining with confocal microscopy was used for PKC-β localization. PKC-β was inhibited by LY379196 (100 nm) in podocytes exposed to AGE and SAA. PKC-β deficiency did not alter blood pressure. In addition, PKC-β expression was confirmed by mRNA microarray. PKC-β deficiency increased diabetic kidney damage in diabetic mice. TH-PO335

Myo-Inositol Oxigenase (MIOX) Contributes to Renal Tubular Damage via Endoplasmic Reticulum (ER) Stress and a Hyaluronic Acid (HA) Production

The role of MIOX in the progression of diabetic nephropathy remains to be explored. We previously indicated its increased expression in diabetic nephropathy and its transcriptional regulation by high glucose, hormonal, and oxidative stress. Both ER stress and a macrophage accumulation are contributing factors for progression of the renal tubular injury. In this study, we examined the role of MIOX for the ER stress and chemokine induction. Methods: MIOX knockout mice were fed with high fat diet (HFD) or treated with tunicamycin (Tm). We crossed MIOX transgenic mice with PEPCk Cre mice for generating mice with predominant tubular expression of MIOX. HK2 cells were subjected to Tm treatment and transfected with MIOX siRNA. ER stress was gauged by examining the expression of C/EBP homologous protein (CHOP), XBP1 and GRP94 (transcriptional factor), GRP78 and GRP94 (ER molecular chaperones) in kidney tissues or HK2 cells. Results: XBP1, CHOP, GRP78 and GRP94 increased in mice receiving HFD or Tm treatment. These expressions decreased in the MIOX KO mice compared with wild type mice. While, the expressions of GRP78, ADD1 and PKR in kidneys increased in MIOX transgenic mice. Also, tubular injury observed following Tm treatment was alleviated in MIOX KO mice but worsened in MIOX transgenic mice. MIOX expression increased with Tm treatment in a dose-dependent (0.3 - 10 mg/mL) and time-dependent (0.5 - 24 hr) manner in HK2 cells. The serum levels of the above proteins increased following Tm treatment in HK-2 cells. Simultaneously, Tm treatment increased HA synthesis in HK2 cells. The transection of MIOX siRNA decreased the expression of XBP1, MCP1, IL6 and hyaluronan synthase 2 (HAS2) under the Tm treatment. Overexpression of MIOX contributed increased PKR (1.6-fold, p=0.002), CHOP (1.8-fold, p=0.001) and GRP94, as well as induction of MCP1, IL6 and HAS2. Conclusions: These findings indicate that MIOX contributes to ER stress and HA syntheses and chemokine induction induction may contribute to macrophage accumulation. Funding: NIDDK Support

TH-PO336

Mitochondrial-Targeted MitoQ Attenuated Renal Tubular Damage in Diabetic Nephropathy by Regulation of Mitochondrial Quality and Modulating Mitophagy

In this study, we examined the role of MIOX for the ER stress and chemokine induction. Methods: The expressions of CHOP, XBP1 and GRP94 increased in mice receiving HFD or Tm treatment. These expressions decreased in the MIOX KO mice compared with wild type mice. While, the expressions of GRP78, ADD1 and PKR in kidneys increased in MIOX transgenic mice. Also, tubular injury observed following Tm treatment was alleviated in MIOX KO mice but worsened in MIOX transgenic mice. MIOX expression increased with Tm treatment in a dose-dependent (0.3 - 10 mg/mL) and time-dependent (0.5 - 24 hr) manner in HK2 cells. The serum levels of the above proteins increased following Tm treatment in HK-2 cells. Simultaneously, Tm treatment increased HA synthesis in HK2 cells. The transection of MIOX siRNA decreased the expression of XBP1, MCP1, IL6 and hyaluronan synthase 2 (HAS2) under the Tm treatment. Overexpression of MIOX contributed increased PKR (1.6-fold, p=0.002), CHOP (1.8-fold, p=0.001) and GRP94, as well as induction of MCP1, IL6 and HAS2. Conclusions: These findings indicate that MIOX contributes to ER stress and HA syntheses and chemokine induction induction may contribute to macrophage accumulation. Funding: NIDDK Support

TH-PO334

Podocyte SIRT1 Deficiency Contributes to Albuminuria and Renal Fibrosis in Diabetic Kidney Damage in Mice

Yi Hun, Chuanming Hua. Department of Nephrology, Huashan Hospital, Shanghai, China.

Background: SIRT1 has been shown to play an important role in stress response, metabolic disorder and aging process, and is suggested to be involved in the pathogenesis of diabetic kidney disease. The study examines whether and how SIRT1 deficiency is involved in diabetic renal injury.

Methods: High fat diet plus 5-day-low-dose STZ was used to model type 2 diabetes. Urinary albumin excretion, kidney histology and extracellular matrix protein accumulation were assessed in SIR1 KO, WT and SIRT1 deficient mice. Blood pressure was determined by tail-cuff method. Endothelium selective SIRT1 knockout was generated by crossing floxed SIRT1 mice with SLC Cre, and recombination was induced by tamoxifen. Podocyte selective SIRT1 knockout were generated by crossing floxed SIRT1 mice with PodocinCre. Deletion of SIRT1 in endothelium and podocytes was confirmed by immunohistochemistry.

Results: In diabetic kidney, SIRT1 expression was significantly reduced. Urinary albumin excretion of diabetic SIRT1 heterozygote was markedly increased by 4 fold compared with littermates. Renal histology showed mesangial expansion. Sirius red staining revealed more fibrosis and qPCR higher expression of PAI-1, aSMA, Col 18a1, Loxl2 gene, in diabetic SIRT1 knockout than wild type. Loping one allele of SIRT1 did not alter blood pressure in diabetic mice, suggesting that the diabetic kidney damage in the SIRT1 deficient mice is not caused by blood pressure change. To further examine the mechanism by which SIRT1 deficiency increased diabetic damage, endothelium and podocyte SIRT1 was selectively deleted respectively. Following STZ challenge, podocyte SIRT1 deficient mice showed higher albuminuria and developed diabetic kidney damage, compared with wild type. Podocyte SIRT1 deficiency did not alter blood pressure. In contrast, endothelium SIRT1 deletion did not cause significant change in albuminuria and kidney damage in diabetic mice.

Conclusions: SIRT1 deficiency, especially in podocyte is responsible for the development of albuminuria and renal fibrosis. The mechanism by which podocyte SIRT1 protects the kidney from diabetic kidney damage remains to be explored. Funding: Government Support - Non-U.S.
Methods: C57Bl/6 male mice were randomized to a low fat diet (LFD - 10% of total calories from fat) or a high-fat diet (HFD - 60% of total calories from fat) and treated with L-NIL, a specific iNOS inhibitor (0.1% in drinking water) for 16 weeks.

Results: Mice fed a HFD exhibited a significant increase in body weight, fasting blood glucose, plasma levels of NEFA, triglyceride and insulin. iNOS inhibition with L-NIL decreased these changes, and mice fed a HFD. Interestingly, the significant increase in albuminuria and mesangial matrix expansion was not ameliorated with L-NIL while there was a significant amelioration in glucosuria and proteinuria, suggesting that iNOS inhibition is more suitable for tubular function than glomerular function. Moreover, the urinary sodium excretion, a stable product of sodium reabsorption, significantly declined in mice fed a HFD, was reduced with L-NIL treatment. Inflammation, as attested by macrophage infiltration and enhanced MCP-1 level, was also prevented in L-NIL in the adipose tissue.

Conclusions: These results suggest that inhibition of iNOS leads to beneficial effects in kidney and adipose tissue in mice fed a HFD. This study opens new areas of investigation on the involvement of iNOS in obesity-induced organ injury.

Funding: Government Support - Non-U.S.

TH-PO338

The Impact of Diabetes on Total Glomerular Number and Size in Kidney Estimated by Synchrotron Radiation Micro-CT In SPRing-8 Yumi Takiyama,1 Toshihiro Sera,2 Masanori Nakamura,2 Ryoiro Beshso,1 Kentaro Uesugi,1 Naoto Yagi,2 Masakazu Haneda.1 1Dept of Medicine, Asahikawa Medical Univ, Hokkaido, Japan; 2Dept of Mechanical Engineering, Kyushu Univ, Fukuoka, Japan; 3Graduate School of Science and Engineering, Saitama Univ, Saitama, Japan; 4Research & Utilization Div, Japan Synchrotron Radiation Research Inst, Hyogo, Japan.

Background: To investigate the impact of diabetes on the number and volume of glomeruli in the whole kidney, we explored CT imaging of male type 2 diabetic db/db mice and of non-diabetic db/+ mice at 22 week of age using synchrotron radiation.

Methods: Perfused kidneys with contrast medium were removed and visualized using the synchrotron radiation micro-CT in SPRing-8. X-ray image was detected on the fluorescent screen lens coupling sCMOS camera detector with 15.5μm in the pixel size. A segmentation algorithm was conducted to identify and count all glomeruli within the whole kidney, using image analyzing Amira software.

Results: Db/db mice had larger glomerular volume and more glomerular number in right kidney than left kidney. Intriguingly, diabetes abolished this laterality in db/m mice. Especially, the cortical glomerular size was remarkably increased. On the other hand, diabetes failed to affect the total glomerular number in kidneys. The mean glomerular volume was strongly correlated with fasting blood glucose, kidney volume, urinary volume and glomerular number in all mice, and urinary volume was a significant independent determinant of the mean glomerular volume, whereas the mean glomerular volume was associated with glomerular number.

Conclusions: Our study, for the first time, showed the impact of diabetes on total glomerular number and glomerular volume of the whole kidney by developing new imaging analyzing system, providing the possibility of glomerular hypertrophy in subjects before diabetes onset.

TH-PO339

NADPH Oxidase-Nox5 Plays a Deleterious Role in Diabetic Nephropathy Jay Chandra Jha,1 Stephen P. Gray,2 Claudine Banal,1 Harald H. Schmidt,2 Mark E. Cooper,1 Rhian Touy,2 Chris R. Kennedy,2 Karin Jandeleit-Dahm.1 1Diabetes Complications Div, Baker IDI Heart and Diabetes Inst, Melbourne, Australia; 2Dept of Pharmacology, Maastricht Univ, Maastricht, Netherlands; 3Best of Cardiovascular and Medical Sciences, Univ of Glasgow; Glasgow, United Kingdom; 4Dept of Medicine, Ottawa Hospital Research Inst, Ottawa, Canada.

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease. It has been indicated that recently discovered NADPH oxidase, Nox5 could play a role in diabetes, but is present in humans but not in mice. Thus, there is a paucity of information about Nox5 in animal models of DN. We examined the role of Nox5 in a model of human inducible Nox5 transgenic mice expressing Nox5 selectively in either endothelial cells (VEcadNox5+) or vascular smooth muscle cells (SM22Nox5+) in the setting of diabetes.

Methods: VECadNox5+ or SM22Nox5+ mice were rendered diabetic via streptozotocin injections. At week 10 urine samples were collected for the assessment of albuminuria. Animals were culled and kidneys were removed for the assessment of structural damage as well as gene and protein expression of markers of inflammation and fibrosis.

Results: Both VECadNox5+ and SM22Nox5+ mice demonstrated a further increase in albuminuria (eg:24hrs) compared to their respective Nox5 deficient mice in the presence of diabetes (control & diabetic VECadNox5: 209±33 & 4139±714; control & diabetic SM22Nox5: 1848±23 & 5888±771). A higher mean arterial pressure and systolic blood pressure were also observed in db/db in comparison with db/+ mice. Animals also demonstrated diastolic function deterioration.

Conclusions: Our findings of an additional increase in albuminuria and glomerulosclerosis as well as increased expression of pro-fibrotic and pro-inflammatory markers in Nox5 transgenic diabetic mice suggest a deleterious effect of Nox5 in the context of diabetic nephropathy and emphasize its role as a target for new renoprotective agents.

Funding: Government Support - Non-U.S.

TH-PO340

Resveratrol Exhibits Protective Effects on Early-Stage Diabetic Nephropathy by Restoring Mitochondrial Function of Renal Tubular Cells Hao Ding, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Diabetic nephropathy (DN) is a progressive and irreversible renal disease. Mitochondrion plays an important role in the pathogenesis of DN. Resveratrol (RSV), a naturally occurring sirtuin-1 (SIRT1) activator, has been shown to promote mitochondrial function. The aim of the present study is to investigate the renoprotective effects of RSV and delineate its underlying mechanism in early-stage DN.

Methods: Diabetes was induced by streptozotocin (STZ) injection in male CD-1 mice. Two weeks after the onset of DM, the DM mice were further divided into three subgroups concomitantly treated with placebo, RSV 50mg/kg or RSV 100mg/kg for 28 consecutive days. At the end of RSV treatment course, the mice were sacrificed. Primary kidney proximal tubular cells (PTCs) were cultured in high glucose with indicated concentrations of RSV.

Results: In diabetic mice, RSV treatment postponed the progression of DN, as demonstrated by ameliorating the increases of urine albumin excretion, mean arterial pressure level, plasma blood glucose level and plasma triglyceride level. Meanwhile, the increases of plasma creatinine level, plasma BUN level, glomerular diameter, mesangial accumulation and renal fibrosis in diabetic mice were also reduced by RSV treatment. Moreover, orally administration of RSV partly restored the distribution and expression of nephrin, WT1 and podocin. We demonstrated that hyperglycemia increased mitochondrial mass and mitochondrial DNA content, upregulated miRNA and protein expression of oxidative phosphorylation enzyme complexes in early-stage DN but led to mitochondrial dysfunction both in vitro and in vivo RSV acted as a phosphodiesterase 4B inhibitor and SIRT1 activator, attenuated high glucose-induced mitochondrial network fragmentation and impaired oxidative phosphorylation capacity both in vitro and in vivo. Furthermore, it was shown that the protective role of RSV on early-stage DN was probably through AMPK-ACC pathway.

Conclusions: These findings suggested that RSV exhibited a strong ability to inhibit high-glucose-induced PTCs damage and may serve as a promising new therapeutic approach for treating early-stage DN.

Funding: Government Support - Non-U.S.

TH-PO341


Background: Endothelial dysfunction represents a predominant early feature of diabetes and makes diabetic patients prone to renal complications. Recent evidence has indicated possible role of xanthine oxidase ( XO) in the pathogenesis of vascular dysfunction associated with diabetes. However, it is not clear whether XO activity is involved in pathogenesis of diabetic nephropathy (DN). We investigated the contribution of XO activation on the progression of mouse DN by selective XO inhibitors, Topiroxostat (Top) and Fexubosat (Feb).

Methods: Male Ins2Akita heterozygote (Akita; 10 weeks old) mice were used. Wild-type (WT) mice were used for control. Akita mice were treated with Top (3mg/kg/day), Feb (1mg/kg/day) or Vehicle (Vehi) for 4weeks. Serum uric acid and urinary albumin excretion (UAE) were measured. Glomerular pathological changes were also examined by light microscope and electron microscope. Glomerular permeability was assessed using 2 photon microscopy and fluorescent labeling albumin.

Results: Serum uric acid levels showed no significant difference between all groups. Akita+Top or Akita+Feb groups showed significant reduction of UAE in comparison with Akita+Vehi group. Mesangial expansion, glomerular collagen IV deposition, and glomerular endothelial injury (examined by lectin stain and transmission electron microscope) were ameliorated in Akita+Top or Akita+Feb group compared with Akita+Vehi group. Furthermore, glomerular permeability was deteriorated in Akita+Vehi group compared with WT group. These changes were ameliorated with addition of Top or Feb.

Conclusions: XO inhibitors preserved glomerular endothelial function and improved deteriorated glomerular permeability, indicating that XO activation is involved in pathogenesis of DN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Effect of Mitochondria-Targeted Ubiquinone Q in Tubular Oxidative Injury of Diabetic Nephropathy Modulated by Mitochondrial ROS/NLRP3/IL-1β Biological Axis

Xiaoxuan Xu,1 Li Xiao,1 Chun Hu,2 Yachun Han,1 Yasuphal S. Kanwar,3 Fuyou Liu,2 Lin Sun.2

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Background: To understand the underlying mechanism by MitoQ attenuate the progression of DN.

Methods: 18 patients with DN or primary minimal changes disease were enrolled. Renal pathological changes were observed. MitoQ was intraperitoneally injected to the db/db mice for 4 weeks and 8 weeks. The injury of kidney and concentrations of XOR activity of kidney in NLRP3, IL-1β, Caspase-1, FN, Collagen I and mitochondrial translocation of NLRP3 were observed.

Results: The expression of NLRP3, IL-1β, IL-18 increased in kidney of DN patients, which were positively associated with the renal pathological change, oxidative injury in db/db mice. MitoQ ameliorated proteinuria, renal damage, mitochondrial dysfunction, oxidative stress, and apoptosis in the kidney of db/db mice, which was accompanied with decreased NLRP3/IL-1β biological axis related protein and Caspase-1, FN, Coll-1. MitoQ also decreased the expression of NLRP3, IL-1β, Caspase-1, FN, Coll-1 and attenuated mROS and apoptosis in HK-2 cells. It also recovered MMP and decreased mitochondrial translocation of NLRP3 induced by high glucose. These effect was blocking partially in transfient with lentiviral vectors expressing NLRP3 plasmid, while this effect was abolished by treated with NLRP3 siRNA.

Conclusions: This data indicated that MitoQ ameliorate injury of renal tubular of DN through mROS/NLRP3/IL-1β axis.

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TH-P3042

Role of DUSP4 in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease and is characterized by de novo and pre-existing glomerular abnormalities. Podocyte death plays a role in the progression of DN. We have found that chronic blockade of MMPs with a broad spectrum inhibitor, XL784, reduced renal injury in type 2 diabetic nephropathy rats. However, the precise mechanisms leading to the sustained activation of p38 MAPK remain unresolved. DUSP4, a dual specificity phosphatase, is known to bind directly to p38 MAPK and inhibit its activity in several models of diabetes.

Methods: Type 1 diabetic (DM) mice with deletion of DUSP4 (DM-DUSP4KO) was generated and studied during 7 months to evaluate renal function and pathology. Glomerular filtration rate (GFR) and 24h albumin excretion levels were measured in DM mice with or without deletion of DUSP4. Activation of p38 MAPK and expression levels of DUSP4 in podocytes exposed to high glucose (HG) for 96 hours were evaluated by PCR and immunoblot.

Results: The mRNA expression of DUSP4 is reduced by 50% in the renal cortex of DM mice. Although elevated GFR in DM mice was similar in DM-DUSP4KO (0.34 vs 0.35 mL/min), albumin excretion was further exacerbated by 3.4 fold in DM-DUSP4KO compared to DM mice. In vitro, immunoblot analysis showed that HG level exposure reduced the expression of DUSP4 by 40%, which correlated with an increase of p38 MAPK phosphorylation by 70% in podocytes.

Conclusions: Our results suggest that decrease of DUSP4 expression in podocytes and renal cortex of diabetic mice contributes to podocyte dysfunction in diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-P3043

Telomerase Deficiency-Dependent Senescence Promotes Diabetic Nephropathy (DN) Progression

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Background: Diabetes is a common disease in the elderly, and a link with telomere shortening has been reported, although whether it is Diabetes is a common disease in the elderly, and a link with telomere shortening has been reported, although whether it is a cause or a consequence of the disease has not been determined. Both telomerase reverse transcriptase (TelT) and telomerase RNA (TelRc) are essential to maintain telomere length.

Methods: To investigate the role of telomerase in DN, we measured telomerase expression in kidneys from mice with streptozotocin (STZ)-induced (type I) and db/db (type II) diabetic (DM) mice. We also studied expression of DUSP4 and p38 MAPK KO mice with TelT or TelRc deletion. In vitro studies were performed in primary cultured glomerular endothelial cells (GEhCs).

Results: Renal telomerase expression decreased in both type I and type II diabetic nephropathy mice with age-matched controls. 26 weeks after STZ injection, TelT and TelRc KO mice had more albuminuria than WT, and EM indicated increased GBM thickness, although mesangial expansion was similar. β-galactosidase, a marker of cell senescence, was mildly elevated in non-diabetic TelRc and TelRc KO mice. Diabetes accelerated senescence, especially in TelRc KO mice. We also showed that p38 MAPK KO mice induced diabetes and gain in endothelial cells. GEhCs from TelT deletion proliferated much slower than WT in normal glucose medium (glucose 5.5 mM). After incubation for 96 hours in high glucose (30 mM) medium, GEhCs exhibited cellular senescence, with a marked increase in cells with TelRc deletion. There was minimal senescence with incubation with the mammalian nutrient control.

Conclusions: These results indicate that telomerase deficiency promotes DN progression and accelerates glomerular endothelial senescence, implicating a role for the telomere shortening of aging as a predisposing factor for development of DN.

Funding: NIDDK Support, Veterans Administration Support

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TH-P3044

Knockout of Matrix Metalloproteinase 2 Attenuates the Progression of Renal Disease in Streptozotocin-Induced Diabetic Dahl Salt Sensitive Rats

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Background: We have found that chronic blockade of MMPs with a broad spectrum inhibitor, XL784, reduced renal injury in type 2 diabetic nephropathy rats. However, the isoforms involved in the development of diabetic nephropathy are unclear.

Methods: The present study examined the role of MMP2 in the development of diabetic nephropathy using a MMP2 knockout (KO) rat in the Dahl salt sensitive (SS) genetic background that we created. Nine week old SS and MMP2 KO rats (n=10) were treated with intravenous injection of STZ (50 mg/kg) to induce diabetes with an insulin implant (2 U/day) to maintain blood glucose around 400 mg/dL. Blood pressure and proteinuria were followed for 12 weeks. Age-matched SS rats (n=5) were studied to serve as a non-diabetic control for the assessment of renal hemodynamics and injury.

Results: Blood glucose levels of STZ rats increased from 242±38 mg/dL to 47.1±2.7, 15.0±2.6 and 19.7±2.3 mmHg in SS-STZ rats, respectively. Proteinuria increased from 45.4±3 mm/day in SS-STZ rats versus 94.8±4 mg/day in MMP2 KO-STZ rats. The renal expression of MMP2 increased from 45.4±3 mm/day in SS-STZ rats but it was absent in MMP2 KO-STZ rats. The kidneys of SS-STZ rats developed more severe glomerulosclerosis, mesangial expansion, and renal fibrosis than MMP2 KO-STZ rats. Glomerular filtration rate (GFR) in SS-STZ rats fell by 33% in comparison to time control SS rats, but GFR only fell by 12% in MMP2 KO rats. Moreover, proteinuria also decreased in MMP2 KO rats.

Conclusions: These data indicate that activation of MMP2 may contribute to the development of diabetes induced renal injury and suggest that a MMP2 selective inhibitor may be useful to prevent the progression of renal disease in diabetic patients.

TH-P3045

Inhibition of Enhanced Xanthine Oxidoreductase Activity Prevents the Progression of Diabetic Nephropathy by Attenuating Oxidative Stress

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Background: Telomere shortening of aging as a predisposing factor for development of DN.

Methods: 18 patients with DN or primary minimal changes disease were enrolled. Renal pathological changes were observed. MitoQ was intraperitoneally injected to the db/db mice for 4 weeks and 8 weeks. The injury of kidney and concentrations of XOR activity of kidney in NLRP3, IL-1β, Caspase-1, FN, Collagen I and mitochondrial translocation of NLRP3 were observed.

Results: The expression of NLRP3, IL-1β, IL-18 increased in kidney of DN patients, which were positively associated with the renal pathological change, oxidative injury in db/db mice. MitoQ ameliorated proteinuria, renal damage, mitochondrial dysfunction, oxidative stress, and apoptosis in the kidney of db/db mice, which was accompanied with decreased NLRP3/IL-1β biological axis related protein and Caspase-1, FN, Coll-1. MitoQ also decreased the expression of NLRP3, IL-1β, Caspase-1, FN, Coll-1 and attenuated mROS and apoptosis in HK-2 cells. It also recovered MMP and decreased mitochondrial translocation of NLRP3 induced by high glucose. These effect was blocking partially in transfient with lentiviral vectors expressing NLRP3 plasmid, while this effect was abolished by treated with NLRP3 siRNA.

Conclusions: This data indicated that MitoQ ameliorate injury of renal tubular of DN through mROS/NLRP3/IL-1β axis.

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Interaction of the EGF Receptor and the Hippo Pathway in Diabetic Nephropathy
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Background: Activation of both EGFR and the Hippo signaling pathway can control cell proliferation, apoptosis and differentiation, and their dysregulation may contribute to tumorigenesis. Previous studies have shown that activation of EGFR signaling in renal epithelial cells can exacerbate diabetic kidney disease. YAP, a transcription factor that is regulated by the Hippo signaling pathway, which is a kinase cascade in which Mst1/2 kinases and Sav1 form a complex to phosphorylate and activate Lats1/2, which phosphorylate and inhibit the downstream effector, YAP. Methods: We first investigate that low type 1 diabetes in proximal tubule EGFR deletion mice (EGFRe−/−) and their wild type littermates (WT) by daily low dose streptozotocin injections for 5 consecutive days. A subset of wild type diabetic mice were administrated the EGFR kinase inhibitor, Erlotinib. Cell signaling studies were performed in a proximal tubule epithelial-like cell line (LLC-PK1).

Results: STZ injection induced similar levels of hyperglycemia in EGFRe−/− mice. Both total and phosphorylated YAP (at Ser127) increased in diabetic WT mice, primarily in proximal tubule cells, and these increases were inhibited in EGFRe−/− mice or by administration of Erlotinib. Further studies demonstrated that EGFR-PI3K-Akt signaling pathway activation mediated YAP gene expression, YAP nuclear translocation and signaling pathway activation with the TEAD transcription complex, which led to up-regulation of expression of TEAD-dependent genes, CTGF and AREG (amphiregulin). In a proximal renal tubule cell line, either pharmacologic or genetic inhibition of EGFR or Akt blunted YAP expression in response to high glucose treatment. In addition, knocking down YAP expression by specific siRNA inhibited cell proliferation in response to high glucose or exogenous EGFR.

Conclusions: This is the first study to demonstrate that the Hippo pathway downstream effector YAP activation is a mediator of EGFR-mediated renal epithelial injury in diabetes.

Funding: NIDDK Support, Veterans Administration Support

TH-PO348
Role of Histone Modification in 12-Lipoxygenase Related P21 Gene Regulation in Diabetic Nephropathy
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Background: Glomerular hypertrophy is characterized pathological changes of diabetic nephropathy, which is associated with p21 protein overexpression under diabetic condition. It has been demonstrated epigenetic histone modifications like acetylation (Ac) and methylation (Me) are involved in gene transcriptional regulation. We have certified 12-lipoxygenase (12-LO) and its metabolic product 12(S)-HETE can activate p21 expression, but the mechanism details are still unclear.

Methods: Mesangial cells (MC) from Rat were used for this study. Chromatin immunoprecipitation assay, QRT-PCR and Luciferase assay were used to detect transcriptional activity, enrichment of H3K Ac as well as Me in the promoter (P1) and transcribe (T) region induced by 12(S)-HETE; transcribe was used to overexpression of p300 to see changes of 12(S)-HETE related p21 regulation as well as epigenetic modifications.

Results: 12(S)-HETE enhanced p21 transcriptional activity and mRNA expression; in the promoter regions of p1, P2 and T1 transcribe region, 12(S)-HETE induced significant H3K9Ac as well as H3K4Me1 epigenetic modifications, but no changes were seen in T2 region; on the contrary, 12(S)-HETE treatment prevented H3K9Me3 at p21 promoter obviously, suggest complex Me involved in 12(S)-HETE associated p21 regulation; furthermore, overexpression of p300 obviously enhanced basal as well as 12(S)-HETE associated p21 transcriptional regulation in MC. At same time, 12(S)-HETE treatment also induced histone acetyltransferase p300 occupancy at p21 promoter, reduced demethylase LSD1 nuclear expression and occupancy at p21 promoter.

Conclusions: 12(S)-HETE can induce p300 occupancy at p21 promoter, reduced LSD1 nuclear expression and occupancy at p21 promoter, therefore enhanced H3K9Ac as well as H3K4Me1 at p21 promoter and transcribe regions, decreased H3K9Me3 at p21 promoter, increased p21 expression.

Funding: Government Support - Non-U.S.

TH-PO349
E-Box CpG Hypomethylation of NN in Producing Enzyme Nampit in Proximal Tubules Enables a Constant Supply of NN from Tubules to Glomeruli, which is Disrupted in Diabetic Nephropathy
Mihoko Murakoa, Kazuhiro Hasegawa, Shu Wakinoko, Hiroshi Takeda. Keio Univ.

Background: Nicotinamide mononucleotide (NN) producing enzyme nicotinamide phosphoribosyltransferase (Nampit) cooperates with a longevity gene, Sir2, to exert the stress resistance. We previously reported that high expression levels of Nampit lead to NN production in the proximal tubules (PTs), which contributes to the sufficient supply of NN to glomeruli (Nat Med 2013). Downregulation of Nampit and NN in PTs in diabetic nephropathy is linked to glomerular damage. However, the underlying molecular mechanisms by which Nampit is regulated remain unknown. Here, we investigated how Nampit expression is consistently retained at high levels in PTs under normal conditions and decreased in DN.

Methods: Expression levels of Sir1, TGF-β, and Nampit were measured in PTs of mice with DN. A promoter analysis was performed, and luciferase reporter and gel

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Conclusions: These data support the hypothesis that sustained NMDA receptor expression and/or activation contribute to the progression of diabetic nephropathy, and suggest that targeting these receptors might be a useful therapeutic strategy.

Funding: Private Foundation Support

TH-P0352
Role of the N-Type Calcium Channel in a Mouse Model of Diabetic Nephropathy Shoko Ohno,1 Hideki Yokoi,1 Kiyoshi Morio,2 Masato Kasahara,3 Takashige Kuwabara,1,4 Moin Saleem,5 Kazuwa Nakao,2 Motoko Yanagita,1 Masashi Mukoyama,1,4 1Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 3Inst for Advancement of Clinical and Translational Science, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 4Dept of Nephrology, Graduate School of Medical Sciences, Kamamoto Univ, Kamamoto, Japan; 5Academic Renal Unit, Univ of Bristol, Bristol Children’s Hospital, Bristol, United Kingdom.

Background: Recent clinical studies have shown that an L-N-type calcium channel blocker clinidine reduces urinary protein in hypertensive patients with proteinuria. In the present study, to explore the functional role of N-type calcium channel (Ca2.2) in diabetic nephropathy, we investigated renal injury in Ca2.2-deficient diabetic db/db mice. Methods: We employed mice lacking the N-type calcium channel 1α subunit gene (Ca2.2-/-) to generate db/db (diabetic), Ca2.2-/- double mutant mice. Because the genetic background plays an important role in developing diabetic nephropathy, in this study, we backcrossed Ca2.2-/- knockout mouse on the C57BL/6J background to those on the C57BLKS background. Results: Ca2.2-/- was localized in glomeruli, including podocytes, and vascular walls. Diabetic Ca2.2-/- mice showed lower BP than diabetic WT mice by ~20 mmHg, and exhibited ~50% reduction in urinary catecholamines. Compared with diabetic WT mice, both diabetic Ca2.2-/- and Ca2.2-/- mice revealed a significant reduction by (~70%) in UAE. The increase in mesangial matrix and downregulation of nephrin in diabetic WT mice were alleviated in diabetic Ca.2.2-/- mice. There was an improvement in glycerol control in diabetic Ca2.2-/- mice but not in diabetic Ca2.2-/- mice. Furthermore, db/db mice receiving clinidine showed a significant reduction in UAE. In vitro, depolarization-dependent calcium entry was abolished by o-conotoxin, a Ca2.2-specific inhibitor. The reduction of nephrin expression by TGF-β was abolished with Ȧ-conotoxin and cilnidipine in podocytes. Conclusions: Ca2.2-/- exerts renoprotective effects against the progression of diabetic nephropathy.

D-Carnosine Prevents Diabetic Nephropathy in db/db Mice Giuseppe Pugliese, Carla Iacobini, Stefano Menini. Dept of Clinical and Molecular Medicine, La Sapienza Univ, Rome, Italy.

Background: The endogenous dipeptide L-carnosine was shown to act as a quencher of reactive carbonyl precursors of advanced glycation end products (AGEs). However, in human, it is rapidly inactivated by carnosinase. This study was aimed at evaluating the efficacy of the carnosinase-resistant compound D-carnosine (DC) in preventing diabetic nephropathy in db/db mice. Methods: Adults male db/db mice and the corresponding db/m mice in controls were treated with a DC derivative (60 mg/kg body weight in the drinking water) or vehicle for 14 weeks. Glomerular sclerosis index (GSI), mean glomerular area (mGA), fractional mesangial area (fMA), and mean glomerular volume (mGV) were assessed morphometrically. Serum AGEs and isoprostane-8-epi-PGF2α were measured by Transmission Electron Microscopy as foot process width (FPW) was measured. Results: AST-120-administered SHR/ND rats showed significantly lower levels of urinary protein excretion, urinary albumin excretion, and the FPW as compared with SHR/ND rats. The renal histological damage, the number of ED-1 positive cells and KIM-1 positive area were reduced by the administration of AST-120. AST-120-administered KK-A' mice also showed lower levels of urinary protein and albumin excretion. Conclusions: These results indicate that the administration of AST-120 at an early stage of diabetic nephropathy has a protective effect on the disease progression.

TH-P0353
Blockade of KCa3.1 Attenuates Diabetic Nephropathy Through Induction of Autophagy Chunling Huang, Xinxing Chen, Carol O. Pollock. Renal Lab, Kolling Inst of Medical Research, Univ of Sydney, Sydney, New South Wales, Australia.

Background: Autophagy is emerging as an important pathway in many biological processes and diseases including diabetic nephropathy. It was reported that oxidative stress plays a critical role in diabetic nephropathy, and blockade of KCa3.1 ameliorates renal fibrotic responses in diabetic nephropathy through inhibition of the TGF-β1 pathway. The aim of the study is to identify the role of KCa3.1 on dysfunctional tubular autophagy in diabetic nephropathy. Methods: Human proximal tubular cells (HK2 cells) transfected with scramble siRNA or KCa3.1 siRNA were exposed to TGF-b1 for 48h. The formation of autophagosomes was examined using transmission electron microscopy (TEM). The autophagy marker LC3-II was measured by western blotting and immunofluorescence staining. The activation of oxidative stress was measured by nitrotyrosine using immunofluorescence staining. The signaling pathways of P38, Akt and mTOR were assessed with antibodies. In vivo, the expression of LC3-II and nitrotyrosine were examined by immunofluorescence or immunohistochemistry staining in kidneys from diabetic KCa3.1-/- and KCa3.1+/+ mice. Results: TEM results demonstrated that several autophagic vacuoles appeared in HK2 cells transfected with KCa3.1 siRNA. Western blotting and immunofluorescence staining results showed that TGF-b1 significantly increased LC3-II in scramble siRNA-transfected HK2 cells which was reduced in KCa3.1 siRNA transfected-HK2 cells. Blockade of KCa3.1 with transfected siRNA reversed TGF-b1 induced-activation of P38, Akt and mTOR signaling pathways. In vivo, diabetic induced upregulation of LC3-II and nitrotyrosine were dramatically attenuated in the kidneys of diabetic KCa3.1-/- mice compared to diabetic KCa3.1+/+ mice. Conclusions: Blockade of KCa3.1 attenuated diabetic nephropathy through induction of autophagy.

TH-P0356

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase IIb/III in metabolic syndrome associated with diabetes, displays antifibrotic activities via a novel mechanism of action. In a double-blind single ascending dose (400 to 2400 mg/day) in healthy volunteers, a significant safety and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in CKD patients with no SAEs observed at 800 mg for 10 consecutive days. In the present study, we examined whether PBI-4050 affected hyperglycemia, insulin resistance and the development of renal fibrosis as well as biomarkers in obese db/db mice.
Methods: db/db mice were uninephrectomized at week 6 and received vehicle (water) or PBI-4050 (100 or 200 mg/kg/day) by daily gastric gavage from 6 to 24 weeks of age.

Results: PBI-4050 treatment ameliorated the fasting hyperglycemia and abnormal glucose tolerance tests seen in vehicle-treated db/db mice. In addition, PBI-4050 led to higher serum insulin, C-peptide and GIP levels which correlates with the improvement of β-cells function observed by immunohistochemistry analysis. Kidney function was also improved by PBI-4050 treatment as shown by significant decrease in hyperfiltration, proteinuria and mesangial expansion lesions. Furthermore, expression of IL-6, Collagen I, MMP2 and Timp1 in kidney were downregulated by PBI-4050 treatment. Moreover, using a two-color cytokine microarray panel, serum IL-6 and IL-9 levels were significantly reduced in PBI-4050-treated mice.

Conclusions: These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production and β-cells function and survival, and prevents renal fibrosis in association with pro-fibrotic and fibrotic biomarkers.

TH-PO357

Kidney pSMAD2 in Type 1 and Type 2 Diabetic Nephropathy Patients

TH-PO358

Kidney pSMAD2 in Type 1 and Type 2 Diabetic Nephropathy Patients and in Mouse Models of Diabetic Nephropathy

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Background: Fibrosis is a hallmark of diabetic nephropathy (DN) leading to chronic kidney disease. However, we lack good animal models resembling kidney pathology of human DN. Here we present a new mouse model of type 2 diabetes.

Methods: Human (type 1-T1D and T2D) and murine (db/db and streptozotocin (STZ) treated mice) kidneys were stained for pSMAD2. Kidney transcriptional signature of 44 genes including TGFβ/BMP target-genes, BMP modulators, TGFβ superfamily ligands and EMT markers was evaluated in the mouse models.

Results: Nuclear as well as cytoplasmic pSMAD2 expression was increased in tubules of diabetic patients. T1D patients displayed elevated staining in proximal tubuli, whereas T2D patients showed elevated staining in distal tubuli. Increase in SMAD2 activation in distal tubules was also observed in STZ-treated mice, while db/db mice showed noSMAD2 activation. Genetic profiling showed increased expression of BMP antagonists and other genes (CTGF, Gremlin, KCP, USAG1) promoting increased TGFβ signaling in both models of DN.

Conclusions: Early experimental DN displays little fibrogenesis, but studying the nuclear pSMAD2 expression suggests that the TGFβ/activin A pathway is upregulated in diabetic DN models. The tubular compartment showed increased pSMAD2 activity in both mouse and man but expression pattern differed between T1D and T2D patients and translated poorly into the mouse models of DN tested in this study. Genetic profiling of murine tissue samples locates local nodes of BMP pathways suggesting damping of the renoprotective BMP7 pathway in both T1D and T2D models.

TH-PO359

Role of Liver X Receptors in Diabetic Nephropathy and Obesity Related Glomerulopathy

Morten Tonnesen,1 Kar Neng Lai,2 Joseph C K Leung,1,2 Sydney C.W. Tang.1 Dept of Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong; 2. Dept of Medicine and Therapeutics, and Li Ka Shing Inst of Health Sciences, The Chinese Univ of Hong Kong, Hong Kong.

Methods: pSMAD2 expression was increased in murine kidney tissue in association with pro-fibrotic and fibrotic biomarkers.

Conclusions: These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production and β-cells function and survival, and prevents renal fibrosis in association with pro-fibrotic and fibrotic biomarkers.

TH-PO360

Dual Activation of FXR and TGR5 by INT-767 Mediates Protection from Diabetic Nephropathy and Retinopathy


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Background: Multiple organ dysfunction in diabetes patients is a major contributor to mortality and morbidity. Early experimental DN displays little fibrogenesis, but studying the nuclear pSMAD2 expression suggests that the TGFβ/activin A pathway is upregulated in diabetic DN models. The tubular compartment showed increased pSMAD2 activity in both mouse and man but expression pattern differed between T1D and T2D patients and translated poorly into the mouse models of DN tested in this study. Genetic profiling of murine tissue samples locates local nodes of BMP pathways suggesting damping of the renoprotective BMP7 pathway in both T1D and T2D models.

TH-PO359

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TH-PO357

Kidnaptin Protects Against Diabetic Nephropathy in db/db Mice by Suppressing AGER–RAGE-Induced Oxidative Stress

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Background: Kidnaptin is a serine protease inhibitor that exerts anti-inflammatory, anti-apoptotic and anti-oxidative effects in regulating cellular dysfunction. As oxidative stress plays a crucial role in the pathogenesis of diabetic nephropathy, we aim to investigate the effect and mechanisms of kidnaptin gene transfer on diabetic renal injury in the db/db mouse model of type 2 diabetes.

Methods: Plasmid with kidnaptin gene was injected into the kidney of db/db mice using ultrasound-mediated microbubble-inducible gene transfer. The therapeutic potential of kidnaptin in diabetic kidney was evaluated by histopathology, renal function, oxidative and fibrotic pathways.

Results: Kidnaptin expression was induced in tubules of kidney after gene transfer compared with mice treated with empty plasmid. In db/db mice, kidnaptin overexpression reduced serum creatinine and BUN levels, ameliorated glomerulosclerosis and tubulointerstitial injury and attenuated renal fibrosis by inhibiting TGFβ1 signalling and the downstream plasminogen activator inhibitor-1 and type IV collagen expression. Furthermore, kidnaptin gene transfer significantly attenuated elevated oxidative stress in db/db mice as evidenced by suppressed levels of Nox4 and the oxidative marker (8-OHdG and 20-kDa carbonylation) in diabetic renal tissue. Finally, kidnaptin inhibited expression of RAGE in both diabetic kidney and AGE-stimulated cultured proximal tubular epithelial cells, reflecting an anti-oxidative mechanism via AGER/RAGE axis.

Conclusions: Our results suggest a renoprotective role of kidnaptin against progression of diabetic nephropathy via anti-oxidative properties. Kidnaptin reduced AGER–RAGE-induced Nox4 expression, leading to suppression of oxidative stress and TGFβ-β-mediated renal fibrosis.

Funding: Research Grants Council of Hong Kong (GRF grant number 7796/11M) and the National Basic Research Program of China 973 program no. 2012CB517600 (no 2012CB517600).

TH-PO358

Kidney pSMAD2 in Type 1 and Type 2 Diabetic Nephropathy Patients and in Mouse Models of Diabetic Nephropathy

Lise Thomsen,1,2 Troels Krarup Hansen,3 Morten Tonneсен,1 Emilie De Heer,4 Peter Dijks,4 Alexander Rosendahl.1 1. Diabetes Complications Biology and Pharmacology, Novo Nordisk A/S, Målev, Denmark; 2. Dept of Clinical Medicine – Dept of Endocrinology and Internal Medicine, Aarhus Univ Hospital, Aarhus, Dominican Republic; 3. Dept of Pathology, Leiden Univ Medical Center, Netherlands; 4. Dept of Molecular Cell Biology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Fibrosis is a hallmark of diabetic nephropathy (DN) leading to chronic kidney disease. However, we lack good animal models resembling kidney pathology of human DN. Here we present a new mouse model of type 2 diabetes.

Methods: Human (type 1-T1D and T2D) and murine (db/db and streptozotocin (STZ) treated mice) kidneys were stained for pSMAD2. Kidney transcriptional signature of 44 genes including TGFβ/BMP target-genes, BMP modulators, TGFβ superfamily ligands and EMT markers was evaluated in the mouse models.

Results: Nuclear as well as cytoplasmic pSMAD2 expression was increased in tubules of diabetic patients. T1D patients displayed elevated staining in proximal tubuli, whereas T2D patients showed elevated staining in distal tubuli. Increase in SMAD2 activation in distal tubules was also observed in STZ-treated mice, while db/db mice showed noSMAD2 activation. Genetic profiling showed increased expression of BMP antagonists and other genes (CTGF, Gremlin, KCP, USAG1) promoting increased TGFβ activity in both models of DN.

Conclusions: Early experimental DN displays little fibrogenesis, but studying the nuclear pSMAD2 expression suggests that the TGFβ/activin A pathway is upregulated in diabetic DN models. The tubular compartment showed increased pSMAD2 activity in both mouse and man but expression pattern differed between T1D and T2D patients and translated poorly into the mouse models of DN tested in this study. Genetic profiling of murine tissue samples locates local nodes of BMP pathways suggesting damping of the renoprotective BMP7 pathway in both T1D and T2D models.
**TH-P0361**

**High Fat Diet and BCL2-Modifying Factor (Bmf) Overexpression Together Promote Tubular Apoptosis in BMF-Transgenic Mice via Reactive Oxygen Species Generation**

Anindita Ghosh,1 Hasna Maachi,1 Shabana Abd,1 Yixuan Shi,1 Chao-Sheng Lo,1 Isabelle Chenier,1 Janos G. Plotkin,2,3 Yixuan Shi,1 Shao-Ling Zhang,1 John S.D. Chan.1,2,3,4,5 CRCHUM, Univ of Montreal, Montreal, QC, Canada; 1Pediatric Nephrology Unit, Mass Gen Hosp, Boston, MA.

**Background:** We previously reported that the pro-apoptotic gene Bmf is up-regulated in renal proximal tubular cells (RPTCs) of diabetic obese mice (db/db) compared to normal lean mice (db/m+). We investigated whether high-fat diet (HFD) regulates Bmf expression and RPTC apoptosis and studied its underlying molecular mechanism(s) in RPTCs.

**Methods:** Non-transgenic (non-Tg) mice, catalase-Tg (Cat-Tg) and Bmf-Tg mice overexpressing the respective rat Cat and human Bmf in RPTCs, respectively, were fed normal chow or HFD from 4 to 20 weeks of age. All animals were euthanized at 20 weeks. Blood glucose (BG), systolic blood pressure (SBP) and urinary albumin creatinine ratio (ACR) were monitored bi-weekly. Renal oxidative stress and ROS generation were quantified by dihydorothidiamine staining and lucigenin assay, respectively. RPTC apoptosis was evaluated by TUNEL assay, immunostaining for active caspase-3 and Bax expression. Pro-apoptotic protein and gene expression were assessed by Western blotting and quantitative-PCR. Rat RPTCs stably transfected with the plasmid pGL4.20 containing rat Bmf gene promoter were also studied.

**Results:** Non-Tg mice fed HFD had increases in BG, ACR, acetylated p53, renal oxidative stress and pro-apoptotic genes (Bax, Bmf) expression and RPTC apoptosis. Catalase overexpression prevented HFD-induced RPTC apoptosis and pro-apoptotic gene expression in Cat-Tg mice. In contrast, overexpression of Bmf gene in RPTCs with or without HFD aggravated RPTC apoptosis, pro-apoptotic genes expression and ACR. In vitro, high glucose and palmitate attenuated SIRT1 expression, enhanced acetylated p53 expression and stimulated Bmf gene transcription.

**Conclusions:** We conclude that HFD and Bmf may act in concert to induce ROS-mediated tubular apoptosis, suggesting an important role for Bmf in tubular atrophy in diabetes.

*Funding: Government Support - Non-U.S.*

**TH-P0362**

**Prevention of Diabetic Nephropathy and Other End Organ Damage by Stem Cell-Based Cure of Type 1 Diabetes Mellitus in Mice and Rats**

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**Background:** Endogenous insulin replacement by pancreas or islet transplants is currently the optimal treatment to achieve insulin independence and end organ protection in patients with T1D. However, the limited availability of cadaveric pancreas donors, and both the need for permanent anti-rejection therapy and repeated islet transplants continue to prevent the widespread use of these therapies. Auto- and allo-isolation of transplanted islet cells is currently tested with encapsulation technologies, several of which have failed early. Because β-Cells cannot be adequately expanded ex vivo, Embryonic or induced Pluripotent Stem Cells are evaluated instead. In our present studies, we succeeded in vitro and in vivo to achieve permanent engraftment and cell survival in diabetic mice.

**Results:** In WT B6;129 mice background and WT littersates were treated with streptozotocin (STZ) 125 mg/kg i.p. for 2 doses to induce type 1 diabetes (DM). Mice with persistent blood glucose levels > 300 mg/dL (n = 10-genotype) were sacrificed at 3 months. Endothelial and perivascular cells from WT and KO mice were cultured in 2% FBS and used at passages 1 and 2.

**Conclusions:** In WT B6;129 mice, ID1 levels were increased 15-fold and 3 months in response to STZ-induced DM with increased expression detected in glomerular capillary endothelial cells compared with normal mice. WT mice had no pathological changes despite severe hyperglycemia. In contrast, ID1 -/- mice developed mesangial expansion and matrix deposition, focal capillary aneurysms and glomerular arteriolar hypertrophy and increased proteinuria (n = 12/group, p = 0.05) KO mice showed a 5-fold increase in glomerular endothelial and tubular epithelial cell proliferation by Ki67 immunohistochemistry. These changes occurred despite no significant difference in average glucose between WT and KO mice. Comparison of primary co-cultures of WT and KO endothelial and perivascular cells demonstrated 10-fold decreased angiopoietin-1 expression by qPCR and decreased autophagy in response to TGFβ in KO cells. These results correlated with marked p62 accumulation in glomerular arteriolar in normal and diabetic KO mice.

**Conclusions:** Glomerular endothelial ID1 expression is increased with type 1 DM. KO mice develop diabetic nephropathy suggesting a protective effect of endothelial ID1. *Funding: Veterans Administration Support*

**TH-P0365**

**Heterogeneous Nuclear Ribonucleoprotein F Stimulates Sirtuin 1 (Sirt 1) Expression and Attenuates Renal Proximal Tubular Cell Damage in a Murine Model of Type 2 Diabetes**

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**Background:** We hypothesized that overexpression of the transcription factor heterogeneous nuclear ribonucleoprotein F (hnRNP F) can stimulate sirtuin 1 (SIRT1, a NAD-dependent deacetylase) expression and signaling in renal proximal tubular cells (RPTCs), subsequently attenuating RPTC apoptosis in a murine model of type 2 diabetes (db/db mice).

**Methods:** We made and studied db/db (BKS strain) transgenic (Tg) mice specifically overexpressing hnRNP F in their RPTCs. Blood glucose (BG), systolic blood pressure (SBP) and albuminuria were monitored bi-weekly in adult male non-diabetic db/m+ littermates, diabetic db/db and db/db hnRNP F-Tg mice from 10 weeks of age. Animals were sacrificed at week 20 and kidneys were prepared for histology and apoptosis studies. Renal oxidative stress and reactive oxygen species (ROS) generation were quantified by dihydorothidiamine staining and lucigenin assay, respectively. Renal proximal tubular (RPT) gene expression was evaluated by real-time quantitative-PCR (qPCR). Blotting revelation of RPTCs stably transfected with hnRNP F orhnRNP F or siRNA were also performed. Results: db/db mice developed higher BG, SBP, renal hypertrophy and albuminuria at week 20 as compared to db/m+ littermates; db/db hnRNP F-Tg mice did not have elevated SBP, renal hypertrophy or albuminuria. ROS generation, apoptosis, acetylated p53, Bax and active caspase-3 expression were significantly increased in RPT of db/db mice but not in db/db hnRNP F-Tg mice. In contrast, SIRT 1 and catalase expression were significantly decreased in RPT of db/db mice but not in db/db hnRNP F-Tg mice.

*Funding: Government Support - Non-U.S.*

**TH-P0364**

**Development of Diabetic Nephropathy in Streptozotocin-Treated ID1 Knockout Mice**

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**Background:** Cell injury induces expression of Id1, a BHLL transcription factor inhibitor that regulates cell cycle and differentiation. Id1 knockout results in increased tissue fibrosis in injury models. Since Id1 may have an important role in maintaining vascular stability during hyperglycemia and oxidative stress associated with diabetes, preliminary studies were undertaken to determine what dose to determine in vivo knockout would result in kidney pathology in a diabetic nephropathy resistant strain of mice.

**Methods:** Id1 -/- mice in a B6;129 background and WT littermates were treated with streptozotocin (STZ) 125 mg/kg i.p. for 2 doses to induce type 1 diabetes (DM). Mice with persistent blood glucose levels > 300 mg/dL (n = 10-genotype) were sacrificed at 3 months. Endothelial and perivascular cells from WT and KO mice were cultured in 2% FBS and used at passages 1 and 2.

**Results:** In WT B6;129 mice, ID1 levels were increased 15-fold and 3 months in response to STZ-induced DM with increased expression detected in glomerular capillary endothelial cells compared with normal mice. WT mice had no pathological changes despite severe hyperglycemia. In contrast, Id1 -/- mice developed mesangial expansion and matrix deposition, focal capillary aneurysms and glomerular arteriolar hypertrophy and increased proteinuria (n = 12/group, p = 0.05) KO mice showed a 5-fold increase in glomerular endothelial and tubular epithelial cell proliferation by Ki67 immunohistochemistry. These changes occurred despite no significant difference in average glucose between WT and KO mice. Comparison of primary co-cultures of WT and KO endothelial and perivascular cells demonstrated 10-fold decreased angiopoietin-1 expression by qPCR and decreased autophagy in response to TGFβ in KO cells. These results correlated with marked p62 accumulation in glomerular arteriolar in normal and diabetic KO mice.

**Conclusions:** Glomerular endothelial Id1 expression is increased with type 1 DM. KO mice develop diabetic nephropathy suggesting a protective effect of endothelial Id1. *Funding: Veterans Administration Support*
Finally, overexpression of hnRNP F stimulates SIRT1 protein, mRNA and gene promoter activity and reverses high glucose (35 mM D-glucose) and palmitate inhibition of SIRT1 expression in rat RPTCs in vitro.

Conclusions: Overexpression of hnRNP F attenuated RPTC apoptosis in type 2 diabetic mice via up-regulation of SIRT1 gene expression and signaling.

Funding: Government Support - Non-U.S.

TH-PO366
Lack of CD2AP Disrupts Glucose Transporter 4 Trafficking and Attenuates Glucose Uptake


Background: Recent data indicate that adapter protein CD2AP is downregulated in diabetic conditions via PI3K/Akt signaling in podocytes. In this study we investigated the role of CD2AP in insulin-dependent glucose transporter 4 (Glu4) trafficking and glucose uptake.

Methods: Glucose uptake was measured using tritium-labeled 2-deoxyglucose. CD2AP+/− and wildtype (WT) podocytes were transfected with HA-Glut4-GFP were utilized to quantify the amount of Glut4 on the plasma membrane and to study the trafficking of Glu4 by live cell imaging. Protein complexes were analyzed by coimmunoprecipitation and Duolink proximity ligation assay (PLA).

Results: The level of glucose uptake was 32% lower in CD2AP−/− podocytes compared to WT podocytes in the basal state. After insulin stimulation, glucose uptake in WT cells increased 19%, whereas CD2AP−/− podocytes failed to respond. Knockdown of CD2AP in L6 myoblasts with siRNA lowered glucose uptake by 20% in the basal state and blunted insulin-induced glucose uptake in line with this, insulin stimulation increased HA-Glut4-GFP on the plasma membrane by 50% in WT podocytes, whereas no difference was observed in cells lacking CD2AP. Live cell imaging revealed dynamic trafficking of HA-Glut4-GFP in response to insulin in WT cells, whereas in CD2AP−/− podocytes HA-Glut4-GFP formed insulin unresponsive clusters in the perinuclear region. Subcellular fractionation indicated that CD2AP−/− podocytes found in intracellular membrane fractions together with Glut4, IRIAP and sortilin, constituents of Glut4 storage vesicles (GSVs). Coimmunoprecipitation and PLA assays revealed that CD2AP forms a complex with GGA2, a clathrin adaptor which sorts Glut4 to GSVs. We further found that lack of CD2AP increases the interaction between GGA2 and clathrin. Insulin stimulation further increased GGA2-clathrin interaction and led to perinuclear accumulation of the complex in CD2AP−/− podocytes.

Conclusions: Our results indicate that CD2AP facilitates glucose uptake into podocytes and muscle cells. Interaction of CD2AP with GGA2 suggests a role for CD2AP in sorting of insulin responsive Glut4 to the plasma membrane in podocytes.

Funding: Private Foundation Support

TH-PO367
Tauroursodeoxycholic Acid (TUDCA) Ameliorates Both Tubulur and Glomerular Injury in Diabetic Nephropathy, Thus Providing an Added Value to ACE-Inhibition

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Background: Therapeutic inhibition of the Renin-Angiotensin Aldosterone System (RAAS) is firmly established in diabetic nephropathy (dNP). Despite efficient RAAS inhibition dNP frequently progresses to end-stage renal disease, necessitating the need of additional and mechanistically distinct therapeutic approaches. We have recently demonstrated that amplification of endoplasmic reticulum stress using TUDCA protects mice from dNP (Madhusudan et. al., Nat Commun 2015). To foster clinical evaluation of TUDCA, which is approved for other medical indications, we determined the efficacy of TUDCA in db/db mice in addition to ACE-inhibition (Enalapril).

Methods: 16 weeks old db/db mice with established albuminuria were randomly assigned to control (PBS), Enalapril (50mg/Kg, i.p. daily), or combined Enalapril and TUDCA treatment. Mice were analyzed after 6 weeks of treatment. Albuminuria, glomerular and tubular damage (PAS-staining, electron microscopy, malondialdehyde), and markers of ER-stress were measured.

Results: Both agents (Enalapril and TUDCA) resulted in a significant reduction of UACR, glomerular hypertrophy, and FMA (fractional mesangial area). The combined treatment was more efficient with regard to UACR reduction, but similarly protective against glomerular sclerosis. Unlike Enalapril, TUDCA conveyed additional tubular protection, which was associated with reduced ER-stress (e.g. nuclear ATF6) in the tubular compartment.

Conclusions: A combined therapy of TUDCA and Enalapril is more efficient than Enalapril alone in preventing the progression of dNP in db/db mice. These results should foster translational efforts evaluating TUDCA in patients with dNP.

Funding: Government Support - Non-U.S.

TH-PO368
Fatty Acid Binding Protein 3 Might Mediate Diabetic Nephropathy in Mouse Lacking eNOS Gene

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Background: Insulin deficiency leads to an increase in serum free fatty acid concentration. Diabetic glomerular nodules often contain lipid droplet, suggesting that abnormal fatty acid metabolism might contribute to the development of diabetic glomerular injury. However, its precise mechanism remains unclear. Fatty acid binding proteins (FABPs) are currently considered as key molecules for lipid metabolism.

Methods: Since diabetic eNOS knockout (KO) mouse is considered to be a good model for human diabetic nephropathy, we here investigated whether FABP could mediate glomerular and tubular injury in this model.

Results: First of all, oil red O staining demonstrated that lipid droplets were accumulated in the injured glomeruli in diabetic eNOSKO mice, suggesting that lipid abnormality was involved in the injured process. Microarray assay with isolated glomeruli revealed that among 10 isoforms in FABP family, FABP3 mRNA was most highly expressed in diabetic eNOSKO mice compared to non-diabetic eNOSKO mice. We found that FABP3 protein was predominantly located in the mesangial cells while glomerular injuries were associated with inflammatory processes, such as macrophage infiltration and MCP-1 induction in the diabetic eNOSKO mice. Overexpression of FABP3 resulted in a greater response to palmitate, a saturated FA, to induce MCP-1 in the rat mesangial cells. Furthermore, tubular FABP3 was likely exclusively translocated from cytoplasm to basolateral membrane in proximal tubular epithelial cells under diabetic condition. In turn, the heart, a major organ for FABP3 protein in normal condition, did not show any significant changes in its expression level under diabetic condition in either wild type or eNOSKO mice.

Conclusions: FABP3 likely mediates diabetic glomerular and tubular injury.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma

TH-PO369
Cinacalcet Ameliorates Diabetic Nephropathy Through Intracellular Ca++-Dependent Histone Deacetylases Dependent Effects In Db/db Mice In Vivo

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Background: In cardiovascular system, the Calcium-sensing receptor(CaSR) stimulates the production of NO in the endothelial cells. A decrement in NO bioavailability associated with AMPK inactivation and increased generation of reactive oxygen species are critical to the pathogenesis of diabetic vascular complications. Therefore, we evaluated the renoprotective effect of cinacalcet on gluctocotostasis through AMPK-protein kinase (AMPK)-eNOS-NO pathway in diabetic nephropathy in db/db mice and human glomerular endothelial cells (HGECs).

Methods: Male C57/BLKS db/db mice and db/m controls at 8 weeks of age were divided to receive either a regular diet or a diet containing cinacalcet (10 mg/kg; n=8, respectively). Mice were followed for 12 weeks and were evaluated for renal functions, pathologic phenotypes, and AMPK-eNOS-NO pathway.

Results: Cinacalcet ameliorated albuminuria in db/db mice without influencing the changes in blood glucose and Ca++ concentrations. The mesangial area expansion and inflammatory cell infiltration in the glomerulus were observed in db/db mice, which were all restored by cinacalcet treatment. Cinacalcet increased expression of CaSR, phosphorylation of CaMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α-a target of AMPK-NO pathway. An increase in the ratio of Bcl-2/Bax in renal cortex and decrease in urinary 8-hydroxy-deoxyguanosin and isoprostanes concentrations enhanced the expression of superoxide dismutase; SOD1 and SOD2. In cultured HGECs, cinacalcet decreased oxidative stress and apoptosis by increasing intracellular Ca++ and by stimulating phosphorylation of CaMKβ, LKB1 and AMPK, which were associated with an increase in the phosphorylation of eNOS-NO as well.

Conclusions: In conclusion, the results suggest that cinacalcet improves gluctocotostasis through an increase in intracellular Ca++ and subsequent activation of the CaMKβ-LKB1-AMPK signaling in the kidney, especially GECs, and may be a potential therapeutic modality for type 2 diabetic nephropathy.

TH-PO370
Ectopic Expression of TIMP-1 and LTBP-2 in Proximal Tubule-Specific Namp Deficient Mice Aggravates Bridging Fibrosis in Diabetic Nephropathy

Kazuhiro Hasegawa, Hirokazu Muraoka, Shu Wakinot, Hiroshi Ito. Keio Univ.

Background: Nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme for nicotinamide adenine dinucleotide (NAD) synthesis, and Sirt1, an NAD+-dependent histone deacetylase, exert protective effects in various tissues, leading to enhanced stress resistance and extended longevity. We previously reported that proximal tubule-specific (PT-Specific) Sirt1 transgenic mice are protected against diabetic nephropathy (DN), and that PT-conditionnal knockout (KO) aggravates DN (Nat Med 2013). However, the role of Nampt in DN remains unknown. In this study, we established PT-specific conditional Nampt-deficient mice to investigate the role of Nampt in DN initiation and progression.
Methods: We generated PT-specific, Namp-deficient mice by crossing Namp−/− mice breeding with H2-Kb+G-actin-Cre transgenic mice: WT (C57BL/10ScSnTg(Act-cre)252Imm) and KI (C57BL/10ScSnWiFi(Act-cre)252Imm) were injected with saline (Sal; control) or streptozotocin (STZ) to induce DN. The phenotypes of four groups of mice, WT+Sal, KI+Sal, WT+STZ, and KI+STZ, were analyzed at 8 and 24 weeks after treatment.

Results: At 24 weeks in WT+STZ mice, Namp expression was reduced in PTs in parallel to renal fibrosis progression. PMN, Masson trichome, and EVG staining revealed thickening of the tubular basement membrane and basement membrane of Bowman’s capsule. Peritubular and periglomerular fibrosis in the cortex and perivascular fibrosis surrounding interlobular arteries and veins in the medulla were clearly detected in KI+STZ mice. These fibroses were bridging fibrosis connecting the tubule and glomerulus. DNA microarray, real-time PCR, and immunoelectron microscopic findings clearly showed that expression of tubular tissue inhibitor of metalloproteinase 1 (TIMP-1) and latent transforming growth factor beta binding protein 2 (LTBP-2) was elevated in KI+STZ ecotopically in PTs. Such expression caused basement membrane thickening and fibrosis. All changes were further enhanced in KI+STZ mice.

Conclusions: Namp deficiency in PTs induces bridging fibrosis and overproduction of TIMP-1 and LTBP-2. Disruption of Namp in PTs causes the initiation and progression of DN-induced fibrosis through the novel mechanism of PT-perivascular periocular fibrotic interplay.

TH-PO371

The Presence of the Anti-Fibrotic MicroRNA Crosstalk in the Effect of N-Acetyl-Seryl-Aspartyl-Lysyl-Proline on Kidney Fibrosis in Diabetics Keizo Kanasaki,1,2 Swayan Prakash Srivastava,1 Shi Sen,1 Daisuke Koya,1,2 1Diabetology and Endocrinology, Kanazawa Medical University, Kanazawa, Japan; 2Div of Anticipatory Molecular Food Science and Technology, Kanazawa Medical University, Kanazoku, Ishikawa, Japan.

Background: N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is an endogenous peptide with anti-fibrotic activity. We have shown that restoration of fibroblast growth factor receptor 1 (FGFR1) and concomitant induction of microRNA (miR)-let-7s were involved in the anti-fibrotic action of AcSDKP. Endothelial-mesenchymal transition (EndMT) could be the important source of matrix producing mesenchymal cells in fibrotic kidney. Interferon (IFN)γ is a potential inhibitor of FGFR1; miR-29 targets IFNγ 3’UTR.

Methods: Streptozotocin-induced diabetic CD-1 mice were used for all animal experiments. Mice were sacrificed at 6 months after the induction of diabetes; either AcSDKP or PBS was given by osmotic mini-pump for 1 month from 5 months after diabetic induction. In vitro experiments were performed using Human Dermal Microvascular Endothelial Cells (HMVEC).

Results: In diabetic C57BL/6 mice with renal fibrosis, the prominent induction of IFNγ and EndMT; these alterations were all reversed by AcSDKP or STZ in urine, anti-fibrotic miRs, such as miR-29s and miR-let-7s, as well as endothelial transcription factor, was measured. VEGF expression and VEGF protein release was significantly altered in EC.

Conclusions: AcSDKP deficient mice exhibited suppressed levels of AcSDKP in urine, anti-fibrotic miRs, such as miR-29s and miR-let-7s, as well as the prominent induction of IFNγ and EndMT; these alternations were all reversed by AcSDKP treatment. Transfection studies in HMVEC revealed that miR-29s and miR-let-7s demonstrated crosstalk regulation against the mesenchymal cell activation program. Antigomirs for miR-29 induced IFNγ and suppressed both FGFR1 and miR-let-7s; neutralising antibody for IFNγ restored the levels of both FGFR1 and miR-let-7s.

Conclusions: The present study provides insight into the physiologically relevant anti-fibrotic actions of AcSDKP via anti-fibrotic miRs crosstalk mechanisms. IFNγ is the potential inhibitor of FGFR1; miR-29 targets IFNγ 3’UTR.

TH-PO372

Novel Drug-Inducible Megalin Knockout Mice Reveal Marked Increase of Both Total Nephron Glomerular Filtration and Tubular Reabsorption of Albumin in Early Diabetic Nephropathy Keita P Morii,1 Hideki Yokoi,1 Masato Kasahara,2 Takashige Kuwabara,1 Hirotsuka Imamaki,1 Akiha Ishii,1 Kazuwa Nakao,1 Tomomi Endo,1 Motoko Yanagita,1,4 Masashi Mukoyama,1 Kiyoshi Mori,1 1Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; 2Inst for Advanced of Clinical and Translational Science, Kyoto Univ Hospital, Kyoto, Japan; 3Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; 4Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Background: The early phase of diabetic nephropathy (DN) is characterized with hyperfiltration (or increased clearance) of creatinine or insulin. On the other hand, recent reports using microcapnograph technique or multi-photon microscope for superficial neprilysin indicated that glomerular filtration of albumin is not increased and tubular reabsorption is decreased in rodent models of DN.

Methods: Tamosifen (Tam)-inducible megalin knockout mice (mMegKO) were generated using tamoxifen (Tam) and cre-lox-mediated KI mice (from Professor T. Willnow, Max Delbrück Center) with Ndir1-CreERT2 mice (from Professor Yanagita), which enable efficient gene disruption in proximal tubules of adult mice. For analysis of DN, mMegKO mice were given low-dose Tam at 8 weeks after streptozotocin (STZ) treatment.

Results: Low-dose Tam treatment of mMegKO exhibited 15-fold increase of urinary albumin excretion (UA), which should represent total nephron glomerular filtration of albumin in normal mice. Megalin protein elimination was almost complete by high dose Tam, but some expression remained in S3 by low dose. By comparing STZ-mMegKO and non-STZ-mMegKO mice, total filtration of albumin was estimated to be elevated by 1.7-fold with STZ. Impartially, total reabsorption of albumin, calculated by subtraction of UA before Tam from that after Tam, was also elevated by 1.6-fold with STZ. These changes were normalized by insulin treatment.

Conclusions: By use of mMegKO, which allows overall quantitation of albumin handling in the whole kidney including juxtedudillary nephrons, total filtration and total reabsorption of albumin was markedly increased in STZ diabetic mice.

TH-PO373

Erythropoiesis Stimulating Agents Cannot Improves Circulating Endothelial Progenitor Cell Counts in Patients with End-Stage Renal Disease on Maintenance Hemodialysis Because of Erythropoietin Resistance Hong Tae Lee,1,4 Ji Young Moon,1,2 Sang Ho Lee,3 Chun-Gyoo Ihm,2 Tae Won Lee,2 Kyung-Iwan Jeong,2 1Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea; 2Dept of Nephrology, Kyung Hee Univ School of Medicine, Seoul, Republic of Korea.

Background: Decreased circulating endothelial progenitor cells (EPCs) associate with occurrence of cardiovascular disease and all cause mortality in end stage renal disease (ESRD) patients on hemodialysis. It is known that erythropoiesis stimulating agents (ESA) connect to vasculoprotective effects such as enhanced nitric oxide production in endothelial cells and mobilization of EPCs. Patients with ESRD on hemodialysis have markedly decreased EPC counts although they are often treated with ESA. We investigated that ESA can improve EPC levels in hemodialysis patients. Or not, we hypothesized that erythropoiesis resistance index (ERI) may associate with decreased effect of ESA on EPC.

Methods: We quantified ESA dose and EPCs in blood samples from 86 patients with ESRD on hemodialysis. The ERI was calculated by dividing the weekly erythropoietin dose per kilogram of weight (μg/wk/kg) by the Hb level (g/dl). Participants were divided into 4 groups based on the lowest, middle, highest ERI and no use of ESA group.

Results: The number of circulating EPCs at baseline ranged from 1 to 350 cells/200ml, with a mean ± SD of 26.0±4.8 cells/200ml. Without significant association with ESA dose and EPC counts. However, the EPCs counts of lowest ERI group were significantly higher than the medium, highest ERI and no use of ESA group. There was no different occurrence of cardiovascular events among the groups.

Conclusions: Administration of EPO may not always increase the number of circulating EPCs in ESRD patients on HD. The resistance to erythropoietin may associate with decreased circulation EPC counts.

TH-PO374

Dialysis with Medium Cut-Off Membranes (MCO) Modulates Endothelial Function In vitro: Findings from a Randomized Controlled “First in Man” Trial—Daniel Ziegler,1 Kevin Willy,2 Ralf Schindler,2 Matthias Girndt,1 Roman Fiedler,3 Markus Kusche,3 Christiane Streicher,4 Duska Dragun,4 Rusan Catur,5 1Dept of Internal Medicine II, Martin-Luther-University, Halle, Germany; 2Inst for Epidemiology and Applied Biometry, Eberhard-Karls-Univ Tübingen, Tübingen, Germany; 3NMI Technology Transfer GmbH, Reutlingen, Germany; 4Research & Development, Gambro Dialysatoren GmbH, Hechingen, Germany; 5Dept of Nephrology and Internal Intensive Care Medicine, Charité Univ Medicine, Berlin, Germany; 1Inst for Chemistry / Food Chemistry, Martin-Luther-Universitaet, Halle, Germany.

Background: Cardiovascular mortality in dialysis patients is in part caused by insufficient removal of proinflammatory interleukins. We examined the influence of serum samples from an RCT on markers of EC function. MCO membranes that allow elimination of 45 κd molecules were used for the first time.

Methods: Patients were dialyzed with a Highflux and a MCO membrane for 4 or 12 weeks. Serum samples were drawn and tested in an endothelial cell model. Neangiogenesis was assessed by the measurement of total segments length and KLF2 mRNA, a flow-responsive endothelial transcription factor, was measured. VEGF expression and VEGF protein release was investigated.

Results: Highflux serum enhances neangiogenesis in EC compared to healthy serum, with MCO serum showed markedly reduced expression of KLF2 mRNA and protein release was significantly altered.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Patients, the rate of mortality, access failure, maturation failure was 15.7%, 7.1% and 32.6%. The mortality benefit with RC AVF was superior to that with both BC AVF and AVG for all age. In elderly group, BC AVF has lowest access failure and highest 1yr patency rate compared with RC AVF or AVG. However, in very elderly group, there was no significant associations between access type and access failure or 2ndary outcomes when adjusted for confounding factors.

Conclusions: We concluded that AVF is the preferred form of vascular access for long term outcome in elderly patients. Nevertheless, BC AVF could be considered by individual characteristics in elderly patients who has complicated radiopaque site and a short life expectancy.

TH-PO377
Evaluation of Renal Perfusion in CKD Patients Using Arterial Spin Labelling (ASL) Magnetic Resonance Imaging (MRI)

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Background: The evaluation of renal blood flow in chronic kidney disease (CKD) is beneficial for the determination of drug efficacy and prognostic expectations of CKD. At present, radionuclide scanning or contrast agents are required for this purpose. In this study, we employed arterial spin labeling (ASL) MRI, which is a non-invasive method of measuring tissue perfusion using magnetized blood as an endogenous contrast agent, for the evaluation of CKD patients.

Methods: A total of consecutive 50 CKD patients (33 males and 17 females, 57±16.1 years) were subjected to MRI, including T1-weighted images, ASL and blood oxygen level-dependent (BOLD)-MRI. MRI was performed using a 3.0-T Imag (Skyra; Siemens, Erlangen, Germany). MATLAB, a technical computing language for data analysis, was used for the production of a perfusion map; while Osirix, image-processing software for digital imaging and communications in medicine (DICOM), was used for measuring the signal intensity on each map.

Results: The perfusion map showed that the signal intensity of the renal cortex is higher than that of the medulla. Similarly, T2* map obtained by BOLD MRI showed the same tendency. These findings appear to reflect the differences in the volume of blood flow and tissue oxygenation in each area. Mean cortical blood flow was 134.1±43.8 in G4-5 and 180.0±48.6 in G5a/b (ml/min/100g tissue weight, p<0.05), with significant differences observed between the two groups.

Conclusions: A reliable, non-invasive and repeatable system for monitoring renal blood flow is currently clinically unavailable. ASL MRI at 3.0 Tesla provides a method of measuring renal perfusion in CKD patients as well as healthy subjects without the need for the administration of exogenous compounds.

Funding: Government Support - Non-U.S.

TH-PO378
In-vivo Studies of the Microcirculation in Experimental Uremia

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Background: Endothelial dysfunction is a clinical hallmark of cardiovascular disease in patients with CKD. We analyzed morphology and function of the microcirculation in vivo in mice with experimental uremia.

Methods: In-vivo microscopy of the muscular cremaster capillary bed was performed in BALB/c mice with moderate to severe uremia due to 5/6 nephrectomy or adrenalin feeding (n=18), and in healthy controls (n=5). Morphological measurements included capillary length, capillary density, and the non-vascularized area. Functional parameters included the arterio-venous difference in oxygen saturation (avDO2) and the change in diameter (ΔD/D) before and after application of acetycholine, sodium-nitroprusside, papaverine and adenosine.

Results: Capillary length was inversely associated with the degree of experimental uremia, with a reduction of 15% per 100 mg/dl increase of serum urea. Overall, there was a heterogeneous pattern of capillary rarefaction, with areas of normal capillary density and capillary-free areas. The mean non-vascularized area in severely uremic animals (urea > 400 mg/dl) was 19.8±10 mm² ± 50.5±10 mm², and 3.1±10 mm² ± 3.7±10 mm² in controls. The ΔD/D after pharmacological vasodilatation was 15.4% ± 3.7% in controls, 12.4% ± 4.2% in moderately uremic animals and 7.9% ± 3.5% in severely uremic mice. The avDO2 was 13.1% ± 2.6% in controls, 11.8% ± 3.3% in moderately uremic and 9.8% ± 2.9% in severely uremic mice, indicating an arteriovenous shunt effect and a diminished oxygen delivery.

Conclusions: These in-vivo studies show a loss of microcirculation in the muscular cremaster of mice with experimental uremia, occurring in a heterogeneous “wipe-out” pattern. Morphological changes (capillary rarefaction) and functional changes (ΔD/D, avDO2) were associated with the degree of experimental uremia. These data suggest that a diseased microcirculation (uremic microangiopathy) contributes to endothelial dysfunction and precedes macrovascular disease in uremia.

173A
Arterial Biopsies of Children with CKD Show Altered Morphology,
Calcium Content and Gene Expression

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Background: The prospective 4C study investigates cardiovascular comorbidity in children with CKD. We have studied arterial biopsies of 4C-patients and age-matched controls.

Methods: Arterial biopsies were performed at the time of renal transplantation of patients aged 15.4 (8-21) years (n=21). Age-matched healthy control biopsies were obtained from a biobank (Deutsches Herzzentrum Berlin) collecting arterial biopsies from children undergoing elective cardiac surgery. Calcium concentrations were determined by the OCPM method. Intima-media thickness (IMT) was measured manually (Image J software) in H&E stained sections. Gene expressions were analyzed by a Custom RT Profiler PCR Array. Statistical significances were determined using the Holm-Sidak method, with α=5.000%.

Results: IMT was correlated with the calcium content of biopsies (r=0.41; P<0.05). Marked transcriptomic alterations were detected in the arteries of the CKD patients: Amongst 34 significantly regulated genes (P<0.05; 0.001), 20 (30%) contained 4CC contents (24.7, 52, NOX3 (35.8), RNUX2 (24.8), IL10 (11.3), TNF (8.3) and TRPV6 (7.7) were upregulated, whereas COL1A2 (0.7), TIMP2 (0.26) and ENPP1 (0.31) were downregulated.

Conclusions: Arterial biopsies from children with stage 5 CKD show an increased calcium content and an upregulation of osteogenic proteins (VSMC and matrix), calcium-transporting proteins, inflammatory cytokines, and downregulation of calcification inhibitors. These findings most likely reflect an early stage of a CKD-specific calcifying arteriopathy.

Capillary Rarefaction in Omental Biopsies of Children with CKD

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Background: Endothelial glycocalyx (Glx) contributes to the microvascular permeability barrier and its dysfunction correlates with diabetic nephropathy. Microalbuminuria represents a major risk factor for cardiovascular disease in diabetes. We hypothesised the albuminuria associated with glomerular endothelial Glx damage in diabetes would be accompanied by coronary microvascular Glx dysfunction in diabetic cardiomyopathy (DCP).

Methods: Coronary microvessels were treated with low doses of streptozocin (STZ) p. daily for 5 days. Echocardiography was applied to assess DCP by E/A ratio. A group of diabetic CD1 mice were treated with vitamin B, analogue Benefitamine (BTF, 70µg/kg/d) after DCP development.

Results: Microvessels from diabetic CD1 heart had decreased MOA lectin binding at 16 weeks after the development of DCP. Recovered MOA intensity was associated with BFT’s beneficial effect on DCP (Ctrl: 17.7±3.48; DCP: 2.5±1.21; DCP+BFT: 30.8±3.80, p<0.05, one-way ANOVA).

Conclusions: These findings suggest Glx damage is associated with DCP development. Recovered heart function with BFT treatment parallels with reversed Glx intensity. Identification of Glx with simpler technique is possible, i.e. specific lectin staining. Thus, correction of disarranged Glx may have therapeutic potential for DCP and other diabetic vascular complications, e.g. diabetic nephropathy.

Funding: Private Foundation Support

Monocyte Subpopulations of Hemodialysis Patients Exhibit Distinct Changes of Cold Shock Y-Box Protein-1 Expression

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Background: The cold-shock protein YB-1 is a ubiquitously-expressed RNA/DNA binding protein involved in proliferation, signal transduction, and inflammation. In monocytes YB-1 expression is regulated as part of the cellular differentiation process.

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TH-P0379

TH-P0380

TH-P0381

TH-P0382

TH-P0383

Vascular Biology: Atherosclerosis, Inflammation, Endothelium

Poster/Thursday
Upon acetylation YB-1 is secreted via a non-classical pathway, influencing inflammatory processes by acting as mitogen and chemokine. In dialysis patients prone to infections, we investigated monocyte populations and their YB-1 content and degree of acetylation.

Methods: The monocytic phenotypes Mo1/Mo2/Mo3 were differentiated by flow cytometry with the surface marker CD14 and CD16. After permeabilization and antibody staining, intracellular content of acetylated and non-acetylated YB-1 was measured.

Results: In dialysis patients (n=63; 63±17 years; n=41; 42) leukocyte numbers varied markedly (6.500±2.000/µl) while monocyte fractions were equal among control (n=100; 43±11 years, m: 59; f: 41) and patient cohorts. An analysis of the monocytic YB-1 content revealed that YB-1 levels were significantly lower in the dialysis cohort (healthy control: MFI 18000; dialysis cohort: MFI 12000, p=0.001).

Conclusions: These results were exerted independently of the increasing shear stress induced by increased vascular remodeling in media and intima in dialysis vs transplant patients suggests vascular remodelling in response to a changing cardiovascular risk factor profile after renal transplantation.

Funding: Private Foundation Support, Clinical Revenue Support, Government Support - Non-U.S.

TH-PO386
Polymorphonuclear Leukocytes' Priming a Prerequisite for Monocyte Activation and Transmigration, Initiating the Atherosclerotic Process

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Background: Endothelial dysfunction and monocytes transmigration underlie the development of atherosclerosis. Increased counts and priming of peripheral polymorphonuclear leucocytes (PMNLs) are associated with future or ongoing atherosclerosis, however, the role of PMNLs in the accelerated atherosclerotic process of hemodialysis (HD) patients is still unclear. We hypothesize that atherosclerosis is a circulatory disease, where circulating primed PMNLs activate monocytes and the endothelial layer, at the circulation. Our aims are to examine endothelial dysfunction, monocytes transmigration, post-transmigration activation and differentiation, induced ex-vivo by primed PMNLs (HD).

Results: A unique ex-vivo co-cultivation system of 3 cells types was developed, enabling interaction among: primary endothelial cells (HUVEC), in-vivo primed PMNLs and monocytes (THP-1), mimicking the initiation of the atherosclerotic process. The interactions among these cells was examined at the cellular, protein and gene expression level.

Results: THP-1 transmigration through pre-treated HUVEC with HD PMNLs showed a significant increase in: transmigration.

A, post-transmigration activation, B compared to transmigration through HUVEC pre-treated with PMNLs from healthy subjects (HC). THP-1 transmigration correlates with the PMNLs counts and priming state. Post-treatment with primed PMNLs induced higher MCP-1 expression (2-folds) in HUVEC.

Conclusions: The higher levels of monocytes transmigration, post-transmigration activation and endothelial MCP-1 expression mediated by primed PMNLs suggest a novel mechanism for the initiation of the atherosclerotic process, emphasizing the pivotal role of PMNLs in the initiation of the atherosclerotic process.

TH-PO387
The Effect of End-Stage Renal Disease (ESRD) on Differentiation of Circulating T Cell Subsets

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Background: Progressive loss of renal function is associated with a dysregulation of circulating T cells that may underlie their impaired T-cell immunity. However, it is not known how the differentiation of circulating T cells in ESRD relates to their T-cell immunity. In this study, we investigated the ESRD-related changes in subsets and differentiation of circulating T cells in ESRD patients.

Methods: Adult ESRD patients on HD and healthy subjects were recruited. Peripheral blood was collected and ESRD-related changes in subsets and differentiation of circulating T cells were investigated by flow cytometry.

Results: A total of 20 adult ESRD patients on HD (male: female 12:8, DM 65%) and 17 healthy subjects (male:female 6:11) were enrolled. The ESRD patients revealed an increased frequency of CD4+CD25+ Treg and CD14+ cell compared with healthy subjects. However, the frequency of CD4+ and CD8+ T cells decreased in ESRD patients. (Figure 1-B). Circulating naïve, central-memory(CM), effector-memory(EM), and terminal effector-memory(TEM) subsets of CD4+ and CD8+ T cells. The frequency of apoptotic cells was calculated by scoring annexin-V binding cells after back-gating of CD4/CD8 T cells. CD95(FAS) protein levels were confirmed by Western blot analysis and Flow cytometry.

In ESRD patients, the differentiation of effector memory CD8+ T cells increased (Figure 1-B). In ESRD patients, the differentiation of effector memory CD8+ T cells increased (Figure 1-B).

Conclusions: The higher levels of monocytes transmigration, post-transmigration activation and endothelial MCP-1 expression mediated by primed PMNLs suggest a novel mechanism for the initiation of the atherosclerotic process, emphasizing the pivotal role of PMNLs in the initiation of the atherosclerotic process.

TH-PO387

Determinants of Postprandial Inflammatory Response: Circulating Hemoglobin (Hb), Serum Insulin, and Leptin, and dysglycemic Scores in Children with CKD

Frida Dangardt, Devina Bhouruth, Daniela Thurn-Valsassina, Alicia Rapala, Marietta Charakida, Franz S. Schaefer, John Deanfield, Rukshana Shroff.

Methods: Affected children had a decreased CA MT (p = 0.001) but IT and lipid levels did not differ from the CKD group (p=0.01 for all). Transplanted patients had higher CA and RA levels associated with higher leptin levels (p=0.02).

Conclusions: Postprandial activation contributed to increased insulin, leptin and dysglycemic scores in children with CKD, showing a significantly higher percentages of CD4+ TEM (8.7–12.3%, P<0.05) and CD8+ TEM cells (26.8–34.2%, P<0.05). The FAS and apoptosis level showed a significantly decreased in ESRD patients (Figure 2).

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Underline represents presenting author.

175A
CB1 Cannabinoid Receptor Antagonist Attenuates Cardiac Hypertrophy and Fibrosis in Experimental Chronic Kidney Disease Yu-Juei Hsu, Sung-Sen Yang, Shih-Hua P. Lin. Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, Taipei, Taiwan.

Background: Cannabinoid receptor type 1 (CB1R) has been shown to participate in the development of myocardial hypertrophy and fibrosis—two main pathological features of uremic cardiomyopathy. However, it remains unknown whether CB1R is involved in the pathogenesis of uremic cardiomyopathy. Here, we aimed to elucidate the role of CB1R in the development of uremic cardiomyopathy via modulation of Akt signalling.

Methods: The myocardial hypertrophy and fibrosis were evaluated by echocardiography and immunohistochemical staining, respectively, in 5/6 nephrectomy chronic kidney disease (CKD) mice treated with a CB1R antagonist. CB1R and fibrosis marker expression levels were determined by immunoblotting in cardiac tissue obtained from CKD mice and in H9c2 cells exposed to the uremic toxin indoxyl sulfate (IS), with an organic anion transporter 1 inhibitor or a CB1R antagonist or agonist. Akt phosphorylation was also assessed to examine the signaling pathways downstream of CB1R activation in both in vitro and in vivo models of uremic cardiomyopathy.

Results: CKD mice exhibited marked left ventricular hypertrophy and myocardial fibrosis, which were reversed by treatment with the CB1R antagonist. CB1R, collagen I, transforming growth factor (TGF)-β, and α-smooth muscle actin (SMA) expression showed time- and dose-dependent upregulation in H9c2 cells treated with IS. The inhibition of CB1R by either CB1R antagonist or small interfering RNA-mediated knockdown attenuated the expression of collagen I, TGF-β, and α-SMA in IS-treated H9c2 cells, while Akt phosphorylation was enhanced by CB1R agonist and abrogated by CB1R antagonist in these cells.

Conclusions: CB1R blockade attenuates LVH and Akt-mediated cardiac fibrosis in a CKD mouse model. Uremic toxin IS stimulates the expression of CB1R and fibrotic markers and CB1R inhibition exerts anti-fibrotic effects via modulation of Akt signaling in H9c2 myoblasts. Therefore, the development of drugs targeting CB1R may have therapeutic potential in the treatment of uremic cardiomyopathy.

TH-PO389


Background: Cytotoxic CD4+CD28- cells have been linked to cardiovascular disease (CVD) but their origin remains unclear. We previously showed that in ANCA associated vasculitis (AAV) these cells are only present in CMV seropositive patients and are independently linked with mortality. CVD is a leading cause of mortality in AAV. Here we have characterised CD4+CD28- cells in AAV and examined their relationship to central pulse pressure (cPP), a marker of arterial stiffness and CVD risk.

Methods: We phenotyped CD4+CD28- cells after overnight stimulation with CMV lyse via flow cytometry and measured cPP using the Vicorder device in 43 CMV+ AA V patients in remission. We stained for CX3CR1, the fractalkine receptor implicated in myocardial and vascular remodeling, expressed in VSMC, and found a colocalization of ATRAP and AT1 receptor in Ang II-stimulated VSMC. The results of gain-of-function studies by adenoviral gene transfer for ATRAP overexpression. We used real time PCR, ELISA of TGFβ-p22phox,Rac1,1-Nox1 and BrdU incorporation assay for cell proliferation.

Results: We cloned a novel molecule interacting with carboxy-terminal domain of AT1 receptor, which we named ATRAP (for AT1 receptor-associated protein), using the yeast two-hybrid strategy. In this study, we tested the hypothesis that vascular smooth muscle cells express ATRAP and that ATRAP attenuates Ang II-induced proliferative activity and oxidative stress in vascular smooth muscle cells. We used rat smooth muscle cells and used adenoviral gene transfer for ATRAP overexpression. We used real time PCR,ELISA of TGFβ-p22phox,Rac1,1-Nox1 and BrdU incorporation assay for cell proliferation.

Conclusions: These results indicate that ATRAP significantly attenuates Ang II-mediated proliferative activity and oxidative stress in vascular smooth muscle cells, and suggests a novel strategy to inhibit cardiovascular disease such as arteriosclerosis and hypertension.
TH-PO391
Myostatin: A Playmaker in Chronic Kidney Disease and Vascular Damage
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Background: Patients with abdominal aortic aneurysms (AAA) have higher prevalence of chronic kidney disease (CKD), that may contribute to arterial deterioration in a mutual detrimental feedback. Myostatin (Mstn), a TGF-β family member with cell-cycle inhibitory effects, is up regulated by CKD, but its role in vascular remodelling is unexplored. We hypothesize that Mstn may play a role in the progression of vascular damage.

Methods: In human AAA (N=8), non atherosclerotic lesions (NAAL), samples (N=7) and normal abdominal aorta (N=3): rt-PCR for Mstn and Smoothelin, a protein with contractile function (Smtn), immunostaining for Mstn, Smtn, CD45 and αSMA. In vitro studies: A7R5 vascular smooth muscle cells (VSMC) and human monocytes exposed to normal sera (NS), sera from patients with AAA (AAAS) or Mstn (500 ng/ml) for 48 hours. VSMC: proliferation, rt-PCR for Mstn and Smoothelin. Human monocytes: rt-PCR for Mstn, α-SMA and MCP-1 dependent chemotaxis.

Results: Mstn mRNA was overexpressed (by 8 folds, p<0.05) in AAA. Mstn immunostaining was also higher in AAA and NAAL and associated with downregulated Smtn (p<0.05). Mstn colocализed with VSMC (αSMA) and leukocytes (CD45). In A7R5, AAAS upregulated Mstn and downregulated Smtn (p<0.05); Mstn exposure decreased Smtn mRNA. Proliferation of monocytes, AAAS upregulated Mstn and α-SMA and Mstn decreased αSMA expression (p<0.01).

Conclusions: Our data suggest that Mstn is overexpressed in atherosclerotic lesions at sites of leukocyte infiltration and de-differentiated VSMCs. Unrecognized circulating factors in AAA patients enhance Mstn expression in VSMCs and monocytes. In turn, Mstn leads to VSMC dedifferentiation, blunting their contractile function. In addition, Mstn activates monocytes, contributing to the inflammatory milieu in the aortic wall.

TH-PO392
Carbamylation of Plasma Proteins in Children with Chronic Kidney Disease
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Background: In adults with ESRD, Hct concentration predicts increased CV risk and mortality. In adults with CKD and ESRD, CV morbidity and mortality are affected by traditional risk factors which tend to override effects of uremia such as carbamylation due to enhanced post-translational carbamylation of lysine and histidine formation. Such mechanisms may be sensitively studied in children with CKD. Here, we analyzed plasma Hct levels in a large cohort of children with CKD followed as they progressed to RRT.

Methods: Plasma Hct and carbamylation levels was assessed, by mass spec, in 116 6 to 17 yo children from the 4C (Cardiovascular Comorbidity in Children with CKD) Study cohort with CKD stages 3-5 both cross-sectionally and longitudinally when treatment modality changed to dialysis (n=55) or transplantation (n=59). Factors predicting the change in Hct were modeled by multivariate linear modeling.

Results: Hct concentrations were independent of age but correlated with eGFR (r = -0.56, p<0.0001) urea (r = 0.61, p<0.0001) and albumin (r = -0.36, p<0.0001) successively increasing from 277±86 mmol/mmol Lys in CKD2 to 634±527 mmol Lys in CKD5. Hct levels declined by an average of 14.6% after initiation of dialysis, and by 58.1% after transplantation.

Conclusions: Carbamylation of plasma proteins appears to lower Hct more efficiently than intermittent HD. After transplantation Hct is strongly inversely correlated to eGFR and urea. Dialysis only decreases Hct more markedly in patients starting peritoneal dialysis (PD) than in those starting hemodialysis (-106±226 vs. -52±226 mmol/mmol Lys, p<0.05).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Conclusions: MPA has effects on MΦ cytokine release and cholesterol handling which are dependent on MΦ subtype and concentration. These effects may be important in modifying atherogenesis in patients with SLE and may have relevance in kidney transplantation as well.

Funding: Other NIH Support - 5 NCCAM R21 AT007032 02 Allison B. Reiss

TH-P0396
Mitochondria Derived Reactive Oxygen Species and Microvascular Dysfunction in Chronic Kidney Disease  Danielle L. Kirkman,1 Meghan G. Ramick,1 Bryce J. Math,1 Raymond R. Townsend,2 David G. Edwards.1 1Kinesiology and Applied Physiology, Univ of Delaware; 2Clinical and Translational Research Center, Univ of Pennsylvania.

Background: Endothelial dysfunction in chronic kidney disease (CKD) is characterized by reduced nitric oxide bioavailability as a consequence of oxidative stress. Damaged and dysfunctional mitochondria as a result of CKD are likely a large contributor to reactive oxygen species. The aim of this study was to determine if mitochondrial derived reactive oxygen species contribute to impairments in nitric oxide mediated microvascular function in CKD.

Methods: Cutaneous vasodilatation in response to local heating was assessed in 8 CKD patients (age:67±7 years; eGFR:48±11 ml/kg/1.73m2) and 8 matched healthy individuals (age:60±6 years; eGFR:91±11 ml/kg/1.73m2). Participants were instrumented with 2 intradermal microdialysis fibers for the infusion of 1) Ringers solution and 2) mitochondria specific superoxide scavenger mitoTempo. Skin blood flow in response to local heating (42°C) was assessed at the microdialysis sites by laser-Doppler flowmetry. Cutaneous vascular conductance (CVC) was calculated as a percentage of the maximum CVC achieved during sodium nitroprusside infusion at 43°C.

Results: CVC was attenuated in CKD patients compared to healthy controls (86±5 vs 95±3 %; p=0.01). MitoTempo significantly improved CVC in CKD patients (CKD Ringers vs CKD MitoTempo: 86±5 vs 93±6; p=0.05) to levels similar to that of healthy controls (CKD MitoTempo vs Healthy Ringers: 93±6 vs 95±3 %; p=0.67).

Figure 1. Cutaneous vascular conductance in response to local heating. *p<0.05 vs Healthy Ringers and CKD MitoTempo.

Conclusions: MitoTempo improved cutaneous microvascular function in CKD patients suggesting that mitochondria derived reactive oxygen species play a role in microvascular dysfunction in CKD. Improving mitochondria health and reducing mitochondria derived oxidative stress may be a potential therapeutic target for improving endothelial function in CKD.

Funding: Other NIH Support - National Heart Lung and Blood Institute R01HL115314

TH-P0397
Indolic Uremic Solutes-Aryl Hydrocarbon Receptor-Tissue Factor: A Novel Uremic Thrombosis Axis and Axis Aryl Hydrocarbon Receptor as an Emerging Antithrombotic Target  Moshe Shashar, Laith Al Rabadi, Mostafa Belgasm, Lawrence Prince-Wright, Jamaica Siwak, Jean M. Francis, Vipul C. Chitalia. Renal Section, Boston Medical Center, Boston, MA.

Background: Thrombosis, a highly prevalent complication in CKD patients, remains an area of high unmet clinical need with poorly defined pathogenesis. While recent work has implicated indolic uremic solutes as potent prothrombotic toxins acting through Tissue Factor (TF), a procoagulant protein, it also uncovers Aryl Hydrocarbon Receptor (AHR) as a key mediator of this regulation and a druggable target for thrombosis. Since AHR blockers (AHRBs) inhibited thrombosis in uremic milieu, we hypothesized that inhibition of AHR activity destabilizes TF through its ubiquitination.

Methods: Sera from 25 ESRD patients on hemodialysis matched with controls were used. RNA silencing oligos to carboxy terminus of hsc70-interacting protein (CHIP), full-length and a truncation of TF and full-length CHIP were expressed in various cell lines. Tissue factor expression and activity were examined using western blotting and a surface procoagulant activity assay, respectively.

Results: Our data showed that TF ubiquitination is inhibited in uremic milieu, a process substantially restored by AHRBs. The kinetic profile of this regulation suggested a post-translational mechanism. AHR is known to interact with CHIP, a RING-finger E3 ubiquitin ligase, and thus we posited that CHIP regulates TF. Binding and immunofluorescence studies supported an interaction of CHIP and TF in the cytosol. Deletion of the intracellular domain of TF substantially abrogated the interaction with CHIP suggesting that CHIP binds at the intracytosolic tail of TF. CHIP knock-out and silenced cells showed both significantly elevated TF expression and activity and prolonged TF half-life in uremic milieu supporting CHIP’s role as an E3 ligase of TF.

Conclusions: Our data suggest CHIP as a candidate E3 ligase of TF and raise a tantalizing possibility of AHRBs regulating TF ubiquitination and thrombosis through CHIP. While supporting a novel post-translational regulation of TF by CHIP, this work may uncover a potential mechanism of action of AHRBs, an emerging class of anti-thrombotics in CKD.

Funding: Private Foundation Support

TH-P0398
APOL1-B3 G2 Risk Variant Perturbs Cholesterol Homeostasis in THP-1 Macrophages  Alex Dinh,1 Hidefumi Wakashiu,1 Jurgen Heymann,2 Alessia Fornoni,2 Jeffrey B. Kopp.3 1NIDDK, NIH, Bethesda, MD; 2Dept of Medicine, Univ of Miami, Miami, FL.

Background: Apolipoprotein L1 (APOL1) circulates in human plasma bound to high-density lipoprotein (HDL). APOL1 G1 and G2 variants increase the risk of developing chronic kidney disease. We examined differences in cholesterol homeostasis in THP-1 macrophages stably expressing G0 and G2 variants of the APOL1-B3 (intracellular) isoform.

Methods: THP-1 cells were stably transfected with the G0 or G2 APOL1-B3 variants or an empty vector, and activated with phorbol myristate acetate (PMA) for 3 days. For cholesterol efflux assays, cells were incubated with 1 µCi/ml [3H]-cholesterol for 24 h. Endothelial microparticles were added to the media for 4 h, after which endothelial microparticles were quantified. For amphotericin B lysis, cells were exposed to amphotericin B for 5 h. Cell viability was assessed using the CellTiter-Glo luminescent assay. To generate foam cells, THP-1 cells were stimulated with PMA for 2-3 days and incubated with 20 mg/ml oxidized LDL for 18 h. Cells were stained with Oil Red O and quantified. The kinetic profile of this regulation suggested a novel post-translational regulation of TF, this work may unveil a potential mechanism of action of AHRBs, an emerging class of anti-thrombotics in CKD.

Funding: Private Foundation Support

TH-P0399
Indoxyl Sulfate-Induced Endothelial Microparticles Stimulate Vascular SMC Proliferation and Neointimal Hyperplasia Formation Through TGF-β Induction  Jung-hwa Ryu, Shina Lee, Dong-Ryed Ryu, Suk-Hee Kang, Kyu Bok Choi, Seung-Jung Kim. 1Internal Medicine, College of Medicine, Ewha Womans Univ, Seoul, Republic of Korea.

Background: Vascular access stenosis occurs frequently and predominantly as a result of neointimal hyperplasia formation caused by vascular smooth muscle cell (vascular SMC) proliferation. Previous reports showed that endothelial microparticle (EMP) is closely associated with vascular dysfunction and atherosclerosis. In this study, we investigated the effects of EMP on TGF-β signaling and its association with proliferation of vascular SMC and neointimal hyperplasia formation.

Methods: To produce EMPs, HUVECs were stimulated by indoxyl sulfate (IS). IS-induced EMPs were collected by ultracentrifugation of culture media and sorted by flow cytometry. Human aortic SMCs(1x10^4) were treated by EMPs of 2x10^6 particles Western Blot were done for Akt, ERK1/2, p38 MAPK, and Smad3. SMC proliferation was measured by Brdu cell proliferation assay. TGF-β production was measured by PCR and ELISA. Porcine internal jugular veins were cultured ex vivo in the presence of EMPs for 12 days, and immunohistochemistry for TGF-β and phospho-specific TGF-β signalings was performed.

Results: EMPs stimulated the proliferation of aortic SMCs in a dose-dependent manner. EMPs induced TGF-β secretion from aortic SMCs as well as the phosphorylation of its down-stream signaling molecules including Akt, ERK1/2, p38 MAPK, and Smad3. TGF-β expression and the phosphorylation of signaling molecules were significantly up-regulated in the area of neointimal hyperplasia.

Conclusions: IS-induced EMPs stimulated the proliferation of vascular SMCs and the production of TGF-β by vascular SMCs, and the proliferation of these cells was mediated by TGF-β. Accordingly, EMPs induced neointimal hyperplasia formation and TGF-β expression in cultured venous tissue. Further investigation is needed to demonstrate the role of EMPs on vascular access stenosis.
TH-PO400
Inflammation, Apoptosis, Fibrosis and Vascular Calcification in a Model of Balloon Injury in Rats with Chronic Kidney Disease
Artur P. Mendes, ISNI, CHLO, Lisboa, Portugal.

Background: Cardiovascular disease (CVD) is more prevalent and has a worse prognosis in chronic kidney disease (CKD) patients than in the general population and is the leading cause of morbimortality in those patients. Not only traditional risk factors of CVD but also uremia-related ones like inflammation, fibrosis and mineral disorder may contribute to the poor CVD prognosis.

Methods: We developed a model of accelerated vasculopathy in rats with CKD to study the vascular damage in CKD: inflammation, apoptosis, fibrosis and vascular calcification. The injury was induced by inserting a balloon injury (BI) with an outer diameter of 0.50 mm into the carotid arteries (CA) of 5/6 nephrectomy rats and compare the lesion with non-CKD rats (NR). We used 24 Wistar rats.

Results: We analyzed the normal and injured CA of NR and CKD rats with histology, immunohistochemistry (IH) and RT-PCR, 1 week after the BI. With HE, we saw similar intimal hyperplasia in the CA with BI in both groups. With Masson trichrome and sirius red we observed connective tissue mainly in adventitia layer. With IH for fibronectin we saw abundant expression in hyperplasia areas of the intima of the CA submitted to BI. The expression in the media layer was higher in CKD than NR. In cellular proliferation studies with MiB1 Ab we also appreciated a higher expression of the Ab in the neointima of CKD rats. In IH for activated caspase 3 no expression was noticed in both groups. In the anti-collagen III and VI antibodies we observed abundant expression in hyperplasia areas of the intima of the CA submitted to BI. In the anti-collagen and fibronectin in the non injured CA of the CKD rats than in the NR and much more in the injured CA than in the non injured CA of the NR, as expected, but also more type 1 collagen in the injured CA than in the non injured CA of the NR, as expected, but also more type 1 collagen and fibronectin in the non injured CA of the CA submitted to BI. The expression in the media layer was higher in CKD than NR. In cellular proliferation studies with MiB1 Ab we also appreciated a higher expression of the Ab in the neointima of CKD rats. In IH for activated caspase 3 no expression was noticed in both groups. In the anti-collagen III and VI antibodies we observed abundant expression in hyperplasia areas of the intima of the CA submitted to BI. In the anti-collagen and fibronectin in the non injured CA of the CKD rats than in the NR and much more in the injured CA than in the non injured CA of the NR, as expected, but also more type 1 collagen in the injured CA than in the non injured CA of the NR, as expected, but also more type 1 collagen and fibronectin in the non injured CA of the CKD rats than in the NR and much more in the injured CA than in the non injured CA of the NR.

Conclusions: In a model of accelerated vasculopathy we have shown a more intense activation of the inflammation and fibrosis pathways in the CKD rats than in NR.

TH-PO401
Post-Transcriptional Guidance of Monocyte to Macrophage Differentiation by the RNA-Binding Protein Quaking
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Background: Kidney injury is associated with excessive recruitment and influx of monocytes to sites of tissue damage and their ensuing differentiation into macrophages. This differentiation is associated with a striking increase in protein expression levels of the RNA-binding protein Quaking (QKI). We therefore set out to investigate the role of QKI in monocyte and macrophage function.

Methods: Monocytes expressing an shRNA against QKI were studied for their capacity to adhere, migrate and differentiate into macrophages. RNA-seq and microarray analysis of human monocytes and macrophages, including those of a unique QKI haploinsufficient patient, was performed to identify QKI-mediated signaling events. Identified splice variants of the actin capping protein γ-Adducin were validated using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK1-/-) mice were similarly protected using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay.

Results: Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK1-/-) mice were similarly protected using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK1-/-) mice were similarly protected using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK1-/-) mice were similarly protected using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK1-/-) mice were similarly protected using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay. Unilateral ureteral obstruction (UUO) on mice hypomorphic for QKI (QK1-/-) mice were similarly protected using a splicing reporter construct and were ectopically expressed in monocytes to study migration using a transwell migration assay.

Conclusions: Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Elevated Lp-PLA2 Plasma Activity Is an Independent Predictor of Subclinical Atherosclerosis in CKD-D Patients – No Correlation with Lp-PLA2 mRNA Expression in Isolated Monocyte Subsets

Christof Uhrich, Bogusz Trojanowicz, Roman Fiedler, Felix Kohler, Anna-Franziska Wolf, Eric Seibert, Matthias Girndt. Internal Medicine II, Martin-Luther-Univ Halle-Wittenberg, Germany;

Background: The continued search for biomarkers indicating future cardiovascular events among patients on renal replacement therapy is well-founded by the extraordinarily high cardiovascular mortality rate in these patients. The combination of inflammatory cells capable of expressing atherogenic molecules within the plaque makes the monocyte/Lp-PLA2-axis an interesting subject to study in patients on maintenance dialysis (CKD-D). Monocyte subsets were stratified upon the presence (A+) or absence (A-) of subclinical atherosclerosis by carotid artery ultrasound. Lp-PLA2 plasma activity was measured by an enzymatic kinetic and leucotic Lp-PLA2 mRNA expression by real time PCR. Monocyte subsets were analyzed flow-cytometrically and defined as classical CD14++CD16- (Mo1), intermediate CD14+CD16+ (Mo2) and non-classical CD14+CD16++ (Mo3). mRNA expression analysis of these subsets (N=24) was done after sorting of cells using ARIA II FACS-sorter.

Results: 60 CKD-D (62.3±15.5 years) patients and 39 healthy control subjects (54.0±8.4 years) were enrolled in a cross-sectional study. Lp-PLA2 mRNA expression in leucocytes and plasma Lp-PLA2 activity were significantly higher in CKD-D. CKD-D patients diagnosed with subclinical atherosclerosis (A+) had the most prominent Lp-PLA2 activity values, which even remained significantly different compared to A- after adjustment for age and HbA1c. Among different monocyte subsets Mo1 and Mo2 had the highest Lp-PLA2 mRNA expression level, but it was Lp-PLA2 mRNA expression on ‘patrolling’ Mo3 cells which was significantly elevated in A+ versus A-.

Conclusions: We conclude that Lp-PLA2 activity is an independent predictor of subclinical atherosclerosis in CKD-D patients. Among monocyte subsets Mo3 cells appear to have an exceptional position within the setting of atherosclerosis. These vessel patrolling cells may reflect a physiological response to vascular inflammation in CKD-D patients.

Funding: Private Foundation Support

TH-PO406
Hypoxanthine, a Uricemic Small Solute, Induces Cholesterol Accumulation in Hepatocytes and Incites Atherosclerosis in APO E Deficiency Status

Yong-ji Lim, 1 Hyo-M Yong, 1 Sukyung Lee, 1 Hee-Yeon Jung, 1 Se-Hee Yoon, 1 Ji-Young Choi, 1 Chan-Duck Kim, 1 Sun-Hye Park, 1 Ji-In Hee. 1

Background: Hypoxanthine which originates from purine metabolism is a small free water-soluble uric acid. Its biological functions remain unknown. In this study, we investigated the role of hypoxanthine on chronic kidney disease (CKD) and cholesterol synthesis with atherosclerosis development, particularly in apolipoprotein E (APOE)-deficient mice.

Methods: The effect of hypoxanthine on the regulation of cholesterol synthesis and atherosclerosis were evaluated in cultured HepG2 cells and ApoE knockout (KO) mice.

Results: Hypoxanthine had no effect on the renal interstitial fibrosis in CKD mouse. The effect of hypoxanthine on the regulation of cholesterol synthesis and atherosclerosis were evaluated in cultured HepG2 cells and ApoE knockout (KO) mice. In HepG2 cells, hypoxanthine increased intracellular ROS production. Hypoxanthine increased cholesterol accumulation and decreased APOE and ATP-binding cassette transporter A1 (ABCA1) mRNA and protein expression in HepG2 cells. Furthermore, H2O2 also increased cholesterol accumulation and decreased APOE and ABCA1 expression. This effect was partially reversible by pre-treatment with the antioxidant N-acetyl cysteine. Hypoxanthine and APOE knockdown using APOE-siRNA synergistically induced cholesterol accumulation and reduced APOE and ABCA1 expression. Hypoxanthine remarkably increased serum cholesterol levels and the atherosclerotic plaque area in ApoE KO mice.

Conclusions: Hypoxanthine induces cholesterol accumulation in hepatic cells through alterations in enzymes that control lipid transport and induces atherosclerosis in APOE-deficient mice and mice. These effects are partially mediated through ROS produced in response to hypoxanthine.

Funding: Government Support - Non-U.S.

TH-PO407
Atherosclerosis following Renal Injury Is Ameliorated by Pioglitazone and Losartan via Macrophage Phenotype

Suguru Yamamoto, 1,2 Jiyang Zhong, 1,3 Haichuang Yang, 1 Yiqin Zuo, 1 Ichiet Nairi, 1 Valentina Kon, 1 Dept of Pediatrics, Vanderbilt Univ Medical Center; Nashville, TN; 2 Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Science, Niigata, Japan; 3 Dept of Pathology, Vanderbilt Univ Medical Center, Nashville, TN.

Background: Chronic kidney disease (CKD) amplifies atherosclerosis which involves renin-angiotensin system (RAS) regulation of macrophages. RAS influences peroxisome proliferator-activated receptor-γ (PPARγ), a modulator of atherogenic functions of macrophages, however, little is known about its effects in CKD related vasculopathy.

Methods: Apolipoprotein E knockout mice were uninephrectomized (UNx) and treated with pioglitazone, losartan, or both (UNx+Pio/Los) for 10 weeks. Extent and characteristics of atherosclerotic lesions and macrophage phenotypes were assessed. Peritoneal macrophages and RAW264.7 cells were used to examine pioglitazone and losartan effects on macrophage phenotype and inflammatory response.

Results: UNx significantly increased atherosclerotic. Pioglitazone and losartan each significantly reduced the atherosclerotic burden by 29.6% and 33.5%, respectively; however the benefit was dramatically augmented by combination treatment (55.7%). Assessment of plaques revealed significantly greater macrophage area in UNx+Pio/Los with more apoptotic cells. Following extensive expanded macrophage-rich lesions of UNx+Pio/Los had more alternatively activated, Yim-1 and arginase 1-positive M2 phenotypes. There was no difference in plaque collagen content or calcifications. In vitro, pioglitazone alone and together with losartan was more effective than losartan alone in dampening lipopolysaccharide-induced cytokine production (mRNA and protein) while maintaining M1 phenotype change.

Conclusions: Combination of pioglitazone and losartan is more effective in reducing renal injury-induced atherosclerosis than either treatment alone. This benefit reflects mitigation in macrophage cytokine production, enhanced apoptosis, and a shift towards an anti-inflammatory phenotype.

Funding: NIDDK Support

TH-PO408
Differential Activation of Monocyte and Neutrophil Genomes Following Fistula Placement

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Background: Systemic inflammation is as an important regulator of flow mediated vascular adaptation. We evaluated the genomic response of circulating leukocytes after fistula (AVF) placement, hypothesizing that this severe flow environment induces unique monocyte (mon) and neutrophil (PMN) expression patterns.

Methods: Blood samples were collected pre-op, 2 weeks, and 6 weeks following AVF creation (n=74). Mon and PMN mRNA was isolated and analyzed for 44,699 genes using the HTA 2.0 microarray. BRB ArrayTools and Ingenuity Pathway Analysis was used to identify leukocyte genome changes, relevant ontologies, and upstream regulators.

Results: Compared to pre-op levels, 1,014 mon and 1,594 PMN genes were found to be differentially expressed 2 weeks after AVF placement (p<0.001), but returned to baseline by 6 weeks post-op [91 (mono) and 1 (PMN); p<0.001]. Mon and PMN showed a divergent, inversely correlated expression pattern (A+, p<0.001, with 892 genes upregulated in mono/downregulated in PMN (Group 1) and 138 genes upregulated in PMN/downregulated in mono (Group 2). Group 1 genes were mostly associated with intracellular translational control and cell survival; Group 2 genes were associated with the extrinsic stimulation of non-inflammatory systems (B). Upstream regulator analysis revealed enhanced interferon signaling in monocytes as the driver of these divergent expression patterns (C).

Conclusions: Following AVF creation and exposure to this new flow environment, there is a significant but divergent shift in the genomic profile of leukocytes. We hypothesize that this unique activation pattern has important implications in early AVF adaptation. Integration with the anatomic, physiologic and outcome data sets from the parent HFM study is ongoing.

Funding: NIDDK Support

TH-PO409
Identification of Angiotensin Peptides Modulating the Harmful Effects of Ang II In Chronic Renal Failure

Joachim Jankowski, Vera Jankowski. 1 Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, NRW, Germany.

Background: Angiotensin II (Ang II) is essential in the physiology and pathology of vascular regulation. Ang II is the principal vasoactive substance of the renin-angiotensin system (RAS), having a variety of physiological actions. In the past few years, the classical concept of the RAS system has experienced substantial conceptual changes. Angiotensin peptides such as Ang 1-7, Ang III and Ang IV were identified as mediators involved in vascular regulation. Progress of mass-spectrometric techniques affords the opportunity for identification of unknown angiotensin peptides. When screening the molecular mass range of Ang II for novel peptides, we observed two signals which could represent further angiotensin peptides.

TH-PO404
Vascular Biology: Atherosclerosis, Inflammation, Endothelium

Poster/Thursday

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

Underline represents presenting author.

180A
**Methods:** In order to identify novel angiotensin peptides, we isolated these peptides from human plasma. Using mass spectrometric analysis and protein structural analysis, we found several peptides. The peptide spectrum revealed Ang II like octapeptides Pro-Glu-Val-Tyr-Ile-His-Pro-Phc and Ala-Arg-Val-Tyr-Ile-His-Pro-Phc. We named these peptides Angiotenin-A and Angiotenin-Ala-Ang.

**Results:** Angiotenin-A antagonizes the contractile actions of Ang II. These physiological actions of angiotensinotex of Ang II by Angiotenin-A is mediated by the Mas receptor. Angiotenin-A has a stronger affinity to the Mas receptor than Ang-1-7. Plasma concentrations in healthy volunteers were about 15% and in CKD patients up to 50% of plasma Ang II concentrations. Ang A has the same affinity to the AT1 receptor as Ang II, but a higher affinity to the AT2 receptor. Ang II revealed a less vasoconstrictive effect than Ang II in vitro, which is not modificated in the presence of the AT2 receptor antagonist PD 123319, suggesting a lower intrinsinc activity at the AT2 receptor. In healthy subjects, Ang A concentrations are less than 20% of the Ang II concentrations, but the ratio Ang A / Ang II is higher in CKD.

The plasma concentration was significantly increased in renal and heart failure patients. The identification of Ang II modulating the vasoregulatory effects as a counter-regulatory effect to defend against hypertension. The identification of the renin-angiotensin-system and especially the angiotensin peptides has a stronger affinity to the Mas receptor than Ang-1-7. Plasma concentrations in healthy volunteers were about 15% and in CKD patients up to 50% of plasma Ang II concentrations. Ang A has the same affinity to the Mas receptor as Ang II, but a higher affinity to the AT2 receptor. Ang II revealed a less vasoconstrictive effect than Ang II in vitro, which is not modificated in the presence of the AT2 receptor antagonist PD 123319, suggesting a lower intrinsinc activity at the AT2 receptor. In healthy subjects, Ang A concentrations are less than 20% of the Ang II concentrations, but the ratio Ang A / Ang II is higher in CKD.

**Conclusions:** In conclusion, Angiotenin-A and Ang A are novel human, vasoconstrictive-angiotensin-derived peptides. Due to stronger agonism at the MAS and AT2 receptor, respectively, and -furthermore- their increased plasma concentration in CKD, Ang A may modulate the harmful effects of Ang II.

**TH-PO410**

**Phosphate (Pi)-Induced Endothelial Microparticles Express Histone H2B which Supports Thrombin Generation**


**Background:** Thrombosis is a common cause of death in patients with chronic kidney disease (CKD). A potent pro-thrombotic endothelial vasoconstrictr is Angiotensin II (AngII). The receptor affinity was analysed.

**Results:** MS analysis demonstrated that high Pi-induced EMPs contain nucleosome core histones (H2B, H2A, H2A.x, H3.2, and H4), enzymes, proteins involved in vesiculation and superficial phosphatidylserine (PSer) on their surface; however, a comprehensive characterization of the antithrombin composition of Pi-induced EMPs has been poorly defined.

**Conclusions:** EMPs that express histone H2B may be a novel pro-thrombotic endothelial mechanism through the expression of key pro-thrombotic factors expressed on EMPs.

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

**TH-PO411**

**Identification of the “Vasoconstriction Inhibiting Factor” (VIF) – A Potent Endogenous Cofactor of Angiotensin II Acting on the AT2 Receptor**

Joachim Jankowski, Vera Jankowski.

**Background:** The renin-angiotensin-system is a well-known cardiovascular factor which we have recently shown can induce the formation of pro-coagulant endothelial microparticles (EMP). These microparticles contain proteins that are expressed on EMPs expressing platelet activating factor, secretory phospholipidase A2, and surface phosphatidylserine (PSer) on their surface; the expression of these molecules on EMPs have been shown to support platelet aggregation, which although small can contribute to cardiovascular disease. The vasoconstrictor actions of Ang-II modulating the vasoregulatory effects as a counter-regulatory effect to defend against hypertension. The identification of the renin-angiotensin-system and especially the angiotensin peptides has a stronger affinity to the Mas receptor than Ang-1-7. Plasma concentrations in healthy volunteers were about 15% and in CKD patients up to 50% of plasma Ang II concentrations. Ang A has the same affinity to the Mas receptor as Ang II, but a higher affinity to the AT2 receptor. Ang II revealed a less vasoconstrictive effect than Ang II in vitro, which is not modificated in the presence of the AT2 receptor antagonist PD 123319, suggesting a lower intrinsinn activity at the AT2 receptor. In healthy subjects, Ang A concentrations are less than 20% of the Ang II concentrations, but the ratio Ang A / Ang II is higher in CKD.

**Conclusions:** In conclusion, Angiotenin-A and Ang A are novel human, vasoconstrictive-angiotensin-derived peptides. Due to stronger agonism at the MAS and AT2 receptor, respectively, and -furthermore- their increased plasma concentration in CKD, Ang A may modulate the harmful effects of Ang II.

**TH-PO412**

**A Novel Microfluidic System for Studying Human Microvascular Integrity**

Graham Marsh, Dr. Angela Huang, Jeremy Stuart Duffield.

**Background:** The microvascularature of the kidney plays a critical role in kidney physiology, injury, and disease. Proper hemodynamic and biochemical signals are pivotal for maintaining normal functions in kidney microvasculature, which are greatly altered during disease processes. In vitro models are useful to study the function of the kidney capillary network and cannot accurately examine the microvasculature in injury conditions. To bridge the gap between *in vitro* and *in vivo* models, we developed a novel platform to study kidney microvasculature by building a 3D capillary using a Noris microfluidic system.

**Methods:** We seeded primary kidney endothelial cells from a human fetal donor into a 120 mm tube in a collagen matrix. We then flowed media through the device with a controlled shear stress to mimic *in vivo* conditions. The system allows for cells to be grown in confluent monolayers, allowing for tightalistic, such as permeability, shear stress, and EC50 response to agonists and antagonists. In this engineered microenvironment, we are able to derive growth factors or stimulators in controlled doses to observe changes in microvasculature function and morphology. This platform has allowed us to visualize the microvasculature with a high resolution by confocal microscopy, to observe cell-cell interactions, study the basement membrane composition, and measure vessel integrity. We evaluated the barrier function of the capillary network by examining vascular leak under normal conditions and in an injury model with TNFα activation.

**Conclusions:** There was a significant increase in the permeability of the vessels when they are activated with TNFα compared to resting conditions, and microvessels co-cultured with mesangial cells had significantly increased microvessel integrity and vessel wall leak. The microfluidic platform has enormous potential to study the human kidney microvasculature *in vitro* while maintaining the structure and morphology observed in vivo.

**Funding:** Pharmaceutical Company Support - Biogen

**TH-PO413**

**The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherosogenesis by Regulating Plasminogen Activator Inhibitor-1 and Cellular Adhesion Molecules Generation**

Hidevuki Negoro, Medicine, Harvard Medical School, Boston.

**Background:** The circadian clock is a molecular mechanism that confers 24 hours variation in gene expression and function to regulate number of physiological functions in humans. Circadian disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunctional endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence plasminogen activator inhibitor-1 (PAI-1) and cellular adhesion molecules, such as monocyte chemotactic protein-1 (MCP-1) and intracellular adhesion molecule-1 (ICAM-1) which play an important part in the progression of vascular diseases.

**Methods:** Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of PAI-1, MCP-1 and ICAM-1 in the knockdown cells.

**Results:** Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in MCP-1 and ICAM-1 expression in mice with a dysfunctional clock. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include circulating fibrinogen and PAI-1, which are significantly elevated in Bmal1 KO mice. We confirmed that the PAI-1 levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice. These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherosogenesis by regulating PAI-1 and cellular adhesion molecules generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

**Funding:** Other U.S. Government Support

**TH-PO414**

**TNF-Alpha Receptor 1 Is Associated with Mortality in Persons with Coronary Artery Disease**

Meyeon Park, Daniela Maristany, Eric Vittinghoff, Mary Whooley, Michael Shlipak.

**Background:** Inflammation is a possible mechanism to explain the association between atherosclerosis and mortality. Chronic kidney disease is associated with high levels of inflammation. This study evaluated circulating tumor necrosis factor receptor type 1 (TNFRA1), a marker of inflammation, as a risk factor for mortality.

**Methods:** In the Heart and Soul Study, a cohort of established coronary artery disease (CAD), we measured TNFRA1 from baseline serum samples and defined elevated levels of TNFRA1 by the highest quartile (Q4, > 3.4 ng/ml). Our outcomes were myocardial infarction, stroke, renal failure hospitalization, and lower vascular mortality. High levels of TNFRA1 with outcomes using Poisson regression and adjusting for age, race, smoking, hypertension, diabetes, cholesterol, albuminuria, and baseline estimated glomerular filtration rate (eGFR).

**Results:** Among 981 participants who had TNFRA1 measurements at baseline, median TNFRA1 was 2.47 ng/ml (IQR 1.9-3.4). Median TNFRA1 in individuals with eGFR < 60 was 2.9 (3.8-5) and 1.7 (2.1-2.7) in those with eGFR > 60. Median follow-up time was 8.9 years. Higher levels of TNFRA1 (Q4 v. Q1-3) were associated with a higher risk of MI in...
TH-PO415
Blood Monocyte Profiles and P2X7 Receptor Expression in Chronic Kidney Disease and End-Stage Renal Disease Serika D. Naicker, Susan Logue, Deirdre Cotter, Matthew D. Griffin. REMEDI, School of Medicine, National Univ of Ireland, Galway, Ireland.

Background: Monocytes are innate immune cells with 3 subsets [Classical (CD14+CD16-), Intermediate (CD14+CD16+) and Non-classical (CD14+CD16+)] which have distinct pathogenic roles in chronic inflammation and atherosclerosis. We quantified blood monocyte subsets in a cohort of patients with CKD and ESRD/chronic hemodialysis (cHD) and evaluated their expression of the inflammasome-activating ATP receptor P2X7.

Methods: CKD stage 1-5 was assigned based on MDRD eGFR. PBMCs from healthy adults (CTRL, n=25), patients with CKD stages 1-5 (n=100) or ESRD prior to and after HD (n=32) were analyzed by 8-colour flow cytometry to quantify monocyte subsets and their surface expression of P2X7 receptor. PBMC stimulation cultures were carried out using optimized concentrations of TLR ligands ± ATP.

Results: Total monocyte numbers progressively increased from CTRL through CKD stages 1-5. Expression of P2X7 among the subsets, Intermediate monocytes were most highly expanded in CKD in a stage-dependent manner. ESRD patients additionally demonstrated higher numbers of non-classical monocytes which diminished significantly following HD. Surface expression of P2X7 was readily detected on all monocyte subsets in CTRL. CKD Stages 1-5 and ESRD but was most highly expressed by Non-classical monocytes. Compared to CTRL, all stages of CKD were associated with higher monocyte expression of P2X7 but, in ESRD, this was further increased on Non-classical monocytes following HD. High-level interleukin (IL)-1β release by monocytes from CTRL and CKD/ESRD patients was observed upon brief exposure to the P2X7 ligand ATP following priming with ligands for TLR4 (highly expressed by Classical monocytes) or TLR7/8 (highly expressed by Non-classical monocytes) indicating active inflammasome response in multiple monocyte subsets.

Conclusions: CKD is associated with a stage-dependent increase in circulating monocytes that is greatest for the Intermediate subset. Non-classical monocytes are also expanded in ESRD and modulated by HD. The P2X7 receptor, which mediates inflammasome activation via extracellular ATP, is expressed by all monocyte subsets in CKD/ESRD but most highly by Non-classicals.

Funding: NIDDK Support

TH-PO416
Activation of CXCL16/CXCR6 Pathway by Inflammation Accelerates the Progression of Atherosclerosis in ESRD Patients Zhebo Hu, Kun ling Ma, Yangqi Shi, Xi Wang, Bi-Cheng Liu, 1 Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China; 1 Inst of Nephrology, Southeast Univ, Nanjing City, Jiang Su Province, China.

Background: Objective Chronic inflammation plays a crucial role in the progression of atherosclerosis (AS). The current study aimed to observe the effects of inflammation on lipid accumulation in the radial arteries of end-stage renal disease (ESRD) patients with arteriovenostomy and further investigate whether inflammation accelerates the progression of AS via the dysregulation of the CXCL16/Cxcr6 pathway.

Methods: Forty-seven ESRD patients were divided into control group (n=20) and inflamed group (n=27) according to plasma C-reactive protein (CRP) level. Biochemical index and lipid profile of patients were measured. Surgically removed tissues from the inflamed group (n=27) were analyzed by 8-colour flow cytometry to quantify monocyte subsets and their surface expression of P2X7 receptor. PBMC stimulation cultures were carried out using optimized concentrations of TLR ligands ± ATP.

Results: Total monocyte numbers progressively increased from CTRL through CKD stages 1-5. Expression of P2X7 among the subsets, Intermediate monocytes were most highly expanded in CKD in a stage-dependent manner. ESRD patients additionally demonstrated higher numbers of non-classical monocytes which diminished significantly following HD. Surface expression of P2X7 was readily detected on all monocyte subsets in CTRL. CKD Stages 1-5 and ESRD but was most highly expressed by Non-classical monocytes. Compared to CTRL, all stages of CKD were associated with higher monocyte expression of P2X7 but, in ESRD, this was further increased on Non-classical monocytes following HD. High-level interleukin (IL)-1β release by monocytes from CTRL and CKD/ESRD patients was observed upon brief exposure to the P2X7 ligand ATP following priming with ligands for TLR4 (highly expressed by Classical monocytes) or TLR7/8 (highly expressed by Non-classical monocytes) indicating active inflammasome response in multiple monocyte subsets.

Conclusions: CKD is associated with a stage-dependent increase in circulating monocytes that is greatest for the Intermediate subset. Non-classical monocytes are also expanded in ESRD and modulated by HD. The P2X7 receptor, which mediates inflammasome activation via extracellular ATP, is expressed by all monocyte subsets in CKD/ESRD but most highly by Non-classicals.

Funding: Government Support - Non-U.S.

TH-PO417
Ablation of Pericytes Induces Capillary Rarefaction and Proximal Tubular Injury Janewit Wongboonsin, Rafael Kramann, Susanne V. Fleig, Flavia G. Machado, Benjamin D. Humphreys. Renal Div, Brigham and Women’s Hospital, Boston.

Background: We recently showed that Gli1+ cells in the pericyte niche are the predominant source of myofibroblasts in kidney fibrosis. One hypothesis for the mechanism of capillary rarefaction observed in fibrotic kidney disease is that injury induces pericyte dedifferentiation and shifts pericytes from a potential capillary progenitor to a myofibroblastic cell type. To test this, we first performed unilateral ischemia reperfusion injury (IRI) in bicipic Gli1CreER;SFlt1mice and performed fluorescence microangiography (FA) at 2 weeks after injury to delineate the renal microvasculature and quantify detachment of Gli1+ cells from capillaries. In a second set of experiments we ablated Gli1+ in Gli1CreER, iDTR mice by diphtheria toxin injection, performed FA and analyzed pericytial capillary detachments by automated software-based quantification over a time course of 56 days.

Results: After IRI, Gli1+ cells proliferate and detach from the renal microvasculature. Specific genetic ablation of Gli1+ cells triggers pericytial capillary rarefaction and induces focal macrophage tubular injury. While pericytial capillary number decreased, pericytial capillary perimeter and area remained unchanged. Injured tubules were characterized by focal Ki67+ expression in cortical areas with decreased Gli1+ expression. Renal Ki67 and Hif1α mRNA expression increased early after Gli1+ cell ablation. Interestingly, while mRNA expression of collagen-I mRNA expression decreased early after ablation, confirming the role of Gli1+cells as myofibroblasts progenitors, we detected increased expression of both fibrinogen and fibronectin at 56 days after ablation. Immunostaining for aSMA showed focal cortical areas with myofibroblast expansion and scar formation.

Conclusions: Ablation of Gli1+ pericytes in healthy kidney causes pericytial capillary rarefaction, focal tubular epithelial injury and focal fibrosis in the outer cortex most likely due to hypoxia.

Funding: NIDDK Support

TH-PO418
Activation of Tie2 by Deletion of VE-PTP Increases GFR in Mice Isabel Anna Carota,1,2 Chengjin Li,1 Vera Eremina,1 Tuncer Onay,1 Susan E. Quaggin.1 1Div. of Nephrology/Hypertension and Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago; 2Eli Lilly and Company; 1Samuel Lunfenfeld Research Inst, Mount Sinai Hospital, Toronto, Canada.

Background: With an increasing number of patients suffering from CKD, there is an urgent need for new therapeutic targets. The Angiopoietin-Tie2 signaling pathway has been implicated in the development of renal disease. In CKD patients elevated levels of circulating Angpt-2, the antagonist of the tyrosine kinase receptor Tie2, correlate with a decrease in glomerular filtration rate (GFR). Additionally it has been shown that loss of Angpt-1, the Tie2 agonist, leads to enhanced glomerular scarring in diabetic Angpt-1 KO mice. These findings suggest that an imbalance of Tie2 ligands is associated with progression of renal disease. Here we investigate the impact of Tie2 activation on baseline renal function by genetic deletion of its negative regulator the endothelial specific phosphatase-VE-PTP in an inducible KO mouse model.

Methods: To study the effect of Tie2 activation following loss of VE-PTP, we generated inducible VE-PTP KO mice. Kidneys were examined histologically and phosphorylation level of Tie2 was quantified by IP from lung lysates followed by Western blot analysis. GFRs were measured using the FITC-Sinistrin clearance method (n=7 KO, 6 contr. at 10 weeks).

Results: Knock-out of VE-PTP enhances Tie2 phosphorylation 2-fold resulting in enhanced Tie2 activity in a ligand-independent manner. Deletion of VE-PTP before embryonic day 13.5 leads to the formation of dilated glomerular capillaries, which are not observed in kidneys of mice when VE-PTP is deleted after E18.5. In contrast, mGFRs of VE-PTP iKO mice (deletion after E18.5) were increased from 298.6±28.0 in controls to 458.1±27.9 in KO litter mates (p<0.016). Both groups showed no difference in blood pressure, albuminuria or renal histology.

Conclusions: Inhibition of VE-PTP leads to elevated Tie2 phosphorylation suggesting VE-PTP is a potential target to rescue the effects of increased Angpt-2 levels that occur in CKD patients. The increased GFR observed in VE-PTP iKO mice suggest that disrupting VE-PTP–Tie2 interactions may be a strategy to slow progression of CKD.

Funding: Other NHF Support - RC1HL124120, Pharmaceutical Company Support - Eli Lilly and Company

TH-PO419
Circulating VEGF-C Levels Are Associated with Insulin Sensitivity in End Stage Renal Disease Patients Sernhil Musu Depen,1,2 Adriana Hung,1 Edward D. Segal,1 Hang Sha,1 Charles L. Stump,1 Talat Alipkizer,1,3 Vanderbilt Univ, Nashville, TN; 1VA, Nashville, TN.

Background: Insulin resistance (IR) is a common metabolic derangement in advanced kidney disease. We have previously demonstrated that inflammation is a key mediator of IR in end-stage renal disease (ESRD). Vascular Endothelial Growth Factor C (VEGF-C) is a key regulator of lymphangiogenesis that may contribute to IR. Recent experimental data suggest that the VEGF-C pathway may have important effects on adipose tissue IR by promoting macrophage recruitment. The relationship between VEGF-C and IR in humans

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not been well characterized. We aimed to examine the relation between circulating VEGF-C and insulin sensitivity by the gold standard hyperinsulinemic euglycemic clamp (HEGC) in patients on chronic dialysis.

**Methods:** Fourteen HD and 10 PD patients who participated in HEGC were included in this analysis. Serum VEGF-C values were measured by ELISA.

**Results:** Characteristics of study population are summarized in (table 1).

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>PD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55(38, 60)</td>
<td>48(35, 55)</td>
<td>0.21</td>
</tr>
<tr>
<td>Gender(M,%)</td>
<td>93</td>
<td>50</td>
<td>0.03</td>
</tr>
<tr>
<td>Racer(AA,%)</td>
<td>79</td>
<td>60</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>29(26, 33)</td>
<td>30(26, 35)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes(%)</td>
<td>21</td>
<td>10</td>
<td>0.43</td>
</tr>
<tr>
<td>GDR by HEGC(mg/kg/min)</td>
<td>5.4(3.5, 6.2)</td>
<td>6.46(8.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>hs-CRP(mg/L)</td>
<td>4.8(2.5, 11.3)</td>
<td>2.5(1.5, 13.4)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Median serum VEGF-C levels were 350 (270, 638) pg/mL in PD and 230 (184, 270) pg/mL in HD patients (p = 0.029). The median glucose disposal rate (GDR) derived by HEGC tended to lower in HD compared to PD patients. There was a significant positive correlation between serum VEGF-C and GDR by HEGC (r=0.495, p=0.016).

The association remained significant after adjusted by age, gender, and hs-CRP (p=0.026).

**Conclusions:** Our data suggest that the lymphangiogenic growth factor VEGF-C may be an important contributor to IR in the chronic uremia and a potential therapeutic target.

**Funding:** Other NIH Support - Grant R01HL124210

TH-PO420

**Role of Macrophage in Hyaluronic Acid-Induced Lymphangiogenesis in UUO Model**

**Won Kim, Jong-Hwan Jung, Yujin Jung, Kyung Pyo Kang, Sik Lee, Sung Kwang Park. Chonbuk National Univ Medical School.**

**Background:** Hyaluronic acid (HA) is one of important component of extracellular matrix proteoglycan, has many biologic and pathologic effects such as inflammation, angiogenesis, wound healing and tissue remodeling. Renal lymphangiogenesis has been demonstrated in a rat remnant kidney model and in mouse unilateral ureteral obstruction (UUO) model. However, there is few data about role of macrophage in HA-induced lymphangiogenesis in UUO. We investigated the effect of macrophage in HA-induced lymphangiogenesis in UUO.

**Methods:** RAW 264.7 cells (RAW cell, macrophage cell line) were incubated with TFG-b1. For in vivo production was evaluated by ELISA. LYVE-1-positive lymphatics, HA, vascular endothelial growth factor (VEGF)-C were evaluated by immunofluorescence and ELISA in UUO-induced fibrotic kidney treatment with or without clodronate (macrophage depleting agent).

**Results:** To evaluate the changes in HA expression in macrophages, RAW cell were treated with TGF-b1. We found that TGF-beta1 (1, 5, and 10 ng/mL) increased hyaluronic acid synthase (HAS1), HAS2 and HAS3 mRNA expression in the cells. ELISA data demonstrated that treatment of RAW cells with TGF-b1 (10 ng/mL) increased HA production in a time-dependent manner. In UUO model, renal HA level was higher in ureteral obstruction operated kidney than that of sham-operated kidney. Our immunofluorescence finding showed that HA is expressed on interstitial space in UUO kidney. HA accumulation is correlated with the number of LYVE-1-positive lymphatic vessels after ureteral obstruction. HA expression was also costained with F4/80-positive renal macrophages 7 days after ureteral obstruction. Depletion of macrophage with clodronate significantly decreased UUO-induced renal HA expression and UUO-induced increased density of LYVE-1-positive lymphatic endothelial cells. We also found that VEGF-C expression in the kidney was significantly decreased in UUO kidney after treatment with clodronate compared to that after treatment with control buffer.

**Conclusions:** These results suggest that macrophage has a partial role in HA production and HA-induced renal lymphangiogenesis in UUO model.

TH-PO422

**Disruption of Angiopoietin-Tie2 Signaling Leads to Cystic Kidney Disease**

**Yael Kenig-Kozlofsky,1 Rizaldy P. Scott,1,2 Benjamin R. Thomson,1 Shinji Yamaguchi,1 Christine Jiang Wu,1 Stefan Heiman,1 Susan E. Quaggin,**

**1Div of Nephrology-Hypertension and Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; 2Lunenfeld-Tanenbaum Research Inst, Toronto, Canada.**

**Background:** Angiopoietin ligands Angpt1 and Angpt2 and their cognate receptor Tie2/Tek are essential for development of the heart and systemic blood vasculature. While investigating their function in the shaping of the complex renal vasculature, we uncovered that mid-gestational inactivation of the Angpt1/Angpt2-Tie2 signaling axis remarkably causes cystic kidney disease.

**Methods:** Using a transcytosis-inducible gene targeting approach we deleted both Angpt1 and Angpt2 or Tie2 at embryonic stage E16.5 in the mouse.

**Results:** Compound deletion of Angpt1 and Angpt2, or loss of Tie2 led to kidney cyst formation detectable as early as 2 weeks after birth. By 8 weeks of age, enlarged cysts had severely distorted the renal architecture and glomerular filtration rate dropped by ~40%. Surprisingly, mutants did not manifest proteinuria, urine concentrating defects or renal lymphangiogenesis, in contrast to other models. Notably, renal angiogenesis, extrarenal lymphatic electrolyte clearance, and the salt-sensitive hypertension in mice were less than those in control mice. Surprisingly, mutants did not manifest proteinuria, urine concentrating defects or renal lymphangiogenesis, in contrast to other models. Notably, renal angiogenesis, extrarenal lymphatic electrolyte clearance, and the salt-sensitive hypertension in mice were less than those in control mice.

**Conclusions:** Our data suggest that increasing the expression of Angpt1 and Angpt2 or Tie2 in renal stem cells significantly reduced proteinuria and urine concentrating defects and might contribute to the pathogenesis of renal cysts and suggest this pathway as a potential therapeutic target to alleviate cystic kidney disease.

**Funding:** Other NIH Support - Grant R01HL124210

TH-PO42

**Nfat5/TonEBP Deficiency in B Cells Results in Reduced Antibody Formation, Hypoplastic Cutaneous Lymph Capillary Formation, and Salt-Sensitive Hypertension**

**Jens Tirze,1,2 Liljana Rovick,1 Patrick Neubert,1 Kento Kitada,2 Wolfgang Schuh,2 Hans-Martin Jack,1 Friedrich C. Luft,1,2 1Disciplinary Center for Clinical Research, UC Erlangen; 2Dept of Clin. Pharm, Vanderbilt Univ; 2Div. of Mol. Immun., UC Erlangen; 2MDC, Charite Berlin.**

**Background:** Intestinal Na+ storage induces pro-inflammatory responses in macrophages (Mφ), which are mediated by the osmoprotective transcription factor Nfat5 to promote host defense. However, Mφ also reduce salt concentration in the subcutaneous barrier by Nfat5/VEGF-C driven lymphatic clearance of electrolytes, protecting the organism from excess intestinal Na+ storage and hypertension. The role of Nfat5 in B cells is unknown. We hypothesized that Nfat5 in B cells boosts pro-inflammatory and homeostatic immune responses.

**Methods:** We fed control (mb1+/Nfat5cre-flox/flox) and 5 mb1+/Nfat5cre-flox/+ (genetic deletion of Nfat5 in B cells) mice a high-salt diet (4% NaCl chow/ 0.9% saline; HSD) for 8 weeks and studied their ability to produce antibody after vaccination with trinitrophenyl conjugated to keyhole limpet hemocyanin (TNP-KLH; 100µg i.p.), followed by a boost injection (50 µg) after 6 weeks. We also studied the size of cutaneous lymph capillaries and mean arterial blood pressure (MAP) in these mice fed a HSD.

**Results:** On HSD, mb1+/Nfat5cre mice showed a >30% reduction in total IgM / IgG (p<0.05), and TNP-KLH-specific IgM / IgG (p<0.05) antibody production versus control, indicating reduced pro-inflammatory immune function. Additionally, these mice showed reduced lymph capillary diameters (40/9µm vs. 25/8µm, p<0.05), accompanied with increased MAP (117±8mmHg vs. 129±6mmHg, p<0.05), indicating reduced homeostatic immune function.

**Conclusions:** Nfat5 in B cells is important for specific antibody formation, suggesting that Na+ storage and B cell osmoreprotection is relevant for the T cell/Dendritic Cell (DC)-mediated adaptive immune response in secondary lymphatic organs. We currently study Mφ, DC, or T-cell driven modulation of the cutaneous lymph capillary network to better understand hypoplastic cutaneous lymph vessel formation, extrarenal lymphatic electrolyte clearance, and the salt-sensitive hypertension in mb1+/Nfat5cre-flox/+ mice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Novel Mechanisms for Salt Sensitive Hypertension in Humans: Effects of Salt Loading on Skin Sodium, VEGF-C and Blood Pressure

Vikesh Selvarajah,1 Kaisa Maki-Petaja,1 Liliana Domingues Pedro,2 Sylvaine Fa Brugger,2 Carmel M. McEnery,1 Ian Wilkinson.2 1Di of Experimental Medicine and Immunotherapeutics, Univ of Cambridge, Cambridge, United Kingdom; 2MBM Human Nutrition Research Unit, Fulbourn, Cambridge, United Kingdom.

Background: Dietary sodium is an important trigger for hypertension. Animal studies show that the skin buffers dietary salt and salt-loading induces lymphangiogenesis mediated by VEGF C from macrophages, helping to maintain BP in response to salt load.

The relevance of these mechanisms in humans is unclear.

Methods: We conducted a double-blind randomised crossover trial examining the effects of acute dietary salt loading on skin sodium, skin sodium dynamics, ambulatory BP and plasma VEGF-C in 48 healthy participants. Participants were placed on a low salt diet (70mmol sodium/day). Dietary compliance was checked using 24hr urine collections.

Results: Skin biopsies were taken after placebo and salt-loading treatment (200mmol daily for 7 days). Skin Na and K concentrations (mg/g tissue) were analysed by ICP-OES. Results were expressed as the ratio of Na:K to correct for variability in sample hydration. Plasma VEGF-C was analysed by ELISA.

Results: Skin data was available for 47 individuals. Mean age was 29.9 ± 8.3 with mean baseline urinary sodium 98.8 ± 55.0 mmol/24hrs. 24hr urine sodium excretion increased from 71.4 ± 43.1 to 225.9 ± 89.0 mmol/p (p<0.001) with salt loading. Ambulatory MAP showed a non-significant increase from 88 ± 7.0 to 89 ± 7 mmHg (p=0.10). Office MAP was unchanged. Skin Na:K increased from 2.91 ± 0.56 to 3.12 ± 0.62 (p=0.001). Percentage change in Na:K was negatively correlated with baseline Na:K (r = -0.40, p=0.007). Changes in ambulatory MAP correlated positively with baseline skin Na:K (r = 0.30, p=0.048). Stroke volume correlated with skin Na:K post placebo (r = -0.42, p=0.002) and slow sodium (r = -0.53, p<0.0001) respectively. No significant change was noted in plasma VEGF-C.

Conclusions: Skin data appears to increase with dietary salt loading and the degree of change correlates with baseline Na:K levels. Ambulatory blood pressure change with dietary salt loading correlates with baseline skin Na:K, supporting a possible role for the skin as a buffer for dietary sodium.

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Underline represents presenting author.

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well as αENaC protein level, whereas the expression of glucocorticoid receptor (GR) is
increased. A diet rich in Na+ and low in K+ does not restore plasma aldosterone to control
levels, but is sufficient to restore body weight, plasma and urinary electrolytes.
Conclusions: In conclusion, MR expression along the nephron and in the collecting
duct system during adulthood is crucial for Na+ and K+ homeostasis, and its deletion cannot
be compensated neither by sodium transporters including ENaC, nor by GR overexpression,
but solely by a high Na+ and low K+ rescue diet.
Funding: Government Support - Non-U.S.

TH-PO428
The Succinate Receptor 1 Is a Physiological Regulator of the ReninAngiotensin Aldosterone System Peter M.T. Deen,1 Claudia Carmone,1
Ana Carolina Ariza,1 Steef Kurstjens,1 Olivier Devuyst,2 Joris Hubertus
Robben.1 1Physiology, Radboud Univ Medical Centre, Nijmegen, Netherlands;
2
Physiology, Univ of Zürich, Zürich, Switzerland.
Background: It has been shown that oxidative cell stress in diabetes type I (T1DM)
induces tubular release of mitochondrial succinate and that subsequent activation of the
SUCNR1 in the juxta-glomerular apparatus is needed for renin release and T1DM-induced
hypertension. Here, we tested whether the SUCNR1 also has a physiological role in renal
water and electrolyte handling.
Methods: Wild-type (wt) and SUCNR1-/- mice 10 weeks old were placed in metabolic
cages and 24h clinical parameters were analyzed in order to assess physiologically relevant
differences. After sacrifice, kidneys were weighed and collected for further analysis.
Results: Blood and urine analysis of wt and SUCNR1-/- mice showed that loss of
SUCNR1 increased sodium and urea excretion, reduced renal renin and plasma angiotensin
II (AngII) and aldosterone levels. Immunoblotting revealed a downregulation of the most
crucial sodium transporters (NHE3, NCC and ENAC) in SUCNR1-/- mice. Fractional
excretion of urea and water were increased in absence of the receptor, coinciding with
reduced AQP2 abundance. With an unchanged overall morphology, wet, but not dry, weights
of kidneys of SUCNR1-/- mice were significantly increased than of wild-type littermates.
Conclusions: Our data reveal that the SUCNR1 is essential for the physiological
maintenance of renin and AngII levels, and proper proximal tubule and collecting duct
sodium reabsorption. The increased wet kidney mass is likely due to tubular dilation due
to increased tubular pressure because of life-long diuresis. Our data thus indicate that
the mammalian SUCNR1 is a physiological regulator of water and volume homeostasis.
Funding: Government Support - Non-U.S.

TH-PO429
Adult Nephron-Specific Beta- and Gamma-ENaC Knockout Mice Develop
a Severe Pseudohypoaldosteronism Type 1 (PHA1) Emilie Boscardin,1
Romain Perrier,2 Chloe Sergi,1 Bernard C. Rossier,1 Edith Hummler.1 1Dept of
Pharmacology and Toxicology, Univ of Lausanne, Lausanne, S itzerland; 2Inst
of Chemistry and Biology of Membranes and Nano-Objects, Univ of Bordeaux,
Pessac, France.
Background: The epithelium sodium channel (ENaC) consists of three subunits (alpha,
beta and gamma ENaC) that are expressed at the apical side in tight epithelia in the kidney,
and is limiting for sodium reabsorption. Mutations in ENaC subunits is causative for the
human pseudohypoaldosteronism type 1 (PHA-1), a salt-losing syndrome. Since mice
with ubiquitous and constitutive gene inactivation of beta- and gamma-ENaC die soon
after birth, the consequences of a kidney-specific deletion of either beta- or gamma-ENaC
cannot studied in adulthood. Therefore, we aimed to unveil the specific role of these ENaC
subunits in the adult kidney using an inducible and kidney-specific CreloxP-mediated
recombination system.
Methods: We used 4-weeks old doxycycline inducible nephron-specific beta- and
gamma-ENaC knockout mice obtained by crossing the double transgenic mouse (PAX8/
LC1), which express the reverse tetracycline transactivator under the control of a tetracycline
response element (Traykova-Brauch et al., 2008) with the floxed Scnn1b and Scnn1g mice,
respectively (Mérillat et al, 2009).
Results: Already following 3-4 days of doxycycline treatment, beta- and gamma-ENaC
KO mice develop a severe and lethal PHA-1, characterized by severe body weight loss,
severe hyperkalemia (beta-ENaC KO: 11mM, n= 7, Ctl: 5 mM, n= 21, p<0.001; gammaENaC KO: 11mM, n=6:, Ctl: 5mM; n=7, p<0.001), and dehydration. Beta-ENaC KO
additionally suffer from severe hyponatremia, while the gamma-ENaC KO present with
significant decreased plasma sodium concentration.
Conclusions: Our data demonstrate that the single beta- and gamma-ENaC subunits
are crucial for daily maintaining sodium and potassium balance in adulthood.
Funding: Government Support - Non-U.S.

TH-PO430
New Mechanistic Insights into the Regulation of ENaC by AMPK in Kidney
Epithelial Cells Hui Li,1,2 Kenneth R. Hallows.1,2 1Medicine, Univ of Pittsburgh
School of Medicine, Pittsburgh, PA; 2Medicine, Univ of Southern California
Keck School of Medicine, Los Angeles, CA.
Background: Renal collecting duct epithelial Na+ channels (ENaCs) play a key role
in total body volume and blood pressure control. The metabolic sensor AMP-activated
protein kinase (AMPK) inhibits ENaC currents in kidney and other epithelial cells, but

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the mechanisms involved are unclear. We hypothesized that AMPK regulation of ENaC
could occur via modulation of ENaC degradation, ENaC subunit cleavage status, and/or
ENaC protein synthesis.
Methods: Mouse polarized kidney cortical collecting duct (mpkCCDc14) cells were
cultured on Transwells for immunoblot analysis and equivalent short-circuit current (Isc)
measurements of ENaC following AMPK activity modulation and proteasomal or lysosomal
inhibitor treatments. Apical domain biotinylation assays were performed to measure changes
in ENaC apical membrane expression, and cycloheximide chase assays were performed
to investigate ENaC stability.
Results: AMPK activation decreased cellular ENaC stability in cycloheximide chase
assays. ENaC-dependent Isc was inhibited by the AMPK activators AICAR and A769662
(Abbott), and these effects were blocked by the proteasomal inhibitor MG132, but not by
the lysosomal inhibitor leupeptin. Western blot analyses revealed that AMPK activation
decreased both mature and immature b-ENaC expression as well as cleaved g-ENaC
expression, while increasing uncleaved g-ENaC expression. Moreover, treatment of
mpkCCDc14 cells with AMPK activators decreased pP70S6K expression, suggesting
decreased signaling of the mTOR pathway involved in protein synthesis and cell
proliferation. Finally, AMPK activation decreased apical cell surface expression of both
mature b- and cleaved g-ENaC, the active forms of ENaC, an effect that was blocked by
MG132.
Conclusions: AMPK-dependent regulation of ENaC in mpkCCDc14 cells occurs by:
1) increased targeting of ENaC for proteasomal degradation, thereby decreasing cellular
ENaC stability; 2) inhibition of g-ENaC cleavage and g-ENaC surface expression; and 3)
inhibition of ENaC protein synthesis along with mTOR pathway inhibition.
Funding: NIDDK Support

TH-PO431
Sodium Retention in Nephrotic Syndrome Occurrs Independly of
Proteinuria Alexey Larionov,1 Geraldine Mollet,2 Corinne Antignac,3 Franziska
Theilig.1 1Medicine, Anatomy, Fribourg, Switzerland; 2Inserm U1163, Paris,
France; 3Inserm U983, Paris, France.
Background: Patients with nephrotic syndrome often present symptoms of volume
retention, such as edema formation or hypertension. The primary dysregulation was localized
to the renal cortical collecting duct and involves an inappropriate activation of the epithelial
sodium channel, ENaC. Plasma proteases passing the leaky glomerular filter were made
responsible; however, clinical observation demonstrated signs of volume retention before
the initiation of proteinuria.
Methods: To elucidate the relationship between sodium retention and proteinuria
tamoxifen-inducible podocinCre; Nphs2fl/fl were used and metabolic cage experiments for
4 weeks were performed and functional renal parameters were determined. Additionally,
morphological and biochemical analysis were performed on kidneys harvested 9 days or
21 days after the beginning of the treatment. Results: Compared to Nphs2fl/fl, podocinCre;
Nphs2fl/fl demonstrated reduced sodium excretion on day 7 (Na+/creatinine: 246±10 vs. 220±8
µmol/mg) while proteinuria occurred on day 11 (protein/creatinine: 13±1 vs. 6.85±0.8 mg/
mg). Blood pressure started to increase on day 10 (BP: 120±12 vs. 74±10 mmHg) and
remained high till the end of the experiment. In mice with nephrotic syndrome western
blot analysis of kidneys harvested on the day 9 of the experiment demonstrated no change
in the full length ENaC subunit abundance and a 3-fold increase in the 30 kDa αENaC
cleavage product. Nephrotic kidneys at the day 21 of the experiment demonstrate strongly
increased abundance of full length and cleaved forms of α- and γENaC.
Conclusions: Our experiments demonstrate the occurrence of a possibly endogenous
protease responsible for cleaving αENaC which may lead to increased sodium retention
and hypertension in the early phase of the nephrotic syndrome.
Funding: Government Support - Non-U.S.

TH-PO432
Altered Renal Electrolyte Handling in Mice with Genetic Knockout of the
Insulin-Like-Growth Factor-1 Receptor (IGF1R) from the Collecting Duct
Principal Cell Carolyn M. Ecelbarger, Marcus J. Byrd, Patrice Dixon, Lijun
Li. Dept of Medicine, Georgetown Univ, Washington, DC.
Background: IGF1, produced predominantly in liver, can be increased in the circulation
during metabolic syndrome (MetS) due to hyperinsulinemia. In addition to anabolic effects,
IGF1 has been shown to activate the epithelial sodium channel (ENaC) in the renal collecting
duct (CD); however, the role of the IGF1R in these effects is uncertain, since the insulin
receptor can also bind IGF1.
Methods: To address the role of IGF1R in the CD, we produced CD-principalcell-select knockout (KO) mice, by crossing mice with Cre-recombinase driven by an
aquaporin-2 promoter with mice with loxP sites flanking IGF1R gene. Adult KO mice were
of normal body weight and had no overt alterations in kidney structure/function. To test
the impact of IGF1 infusion on urinary electrolytes, anesthetized male WT and KO mice
were infused via the jugular vein with either saline vehicle (V) or a 290 µM solution of
IGF1 (I) in saline at a rate of 15 µl/min for 60 minutes (n = 5/genotype/treatment). Urine
was collected via a cannulated bladder.
Results: Urine volume was reduced by IGF1 and the reduction was blunted in the
KO (µl/60 min): 142 ± 41 (WTV), 45 ± 9 (WTI), 86 ± 9 (KOV), 73 ± 8 (KOI), p < 0.018
for treatment. In WT, IGF1 infusion led to a significant 42, 65, and 67% reduction in the
concentration of Na+, K+, and Cl-, respectively in urine. Total urine Na+ in the WTI was
20% of WTV. In contrast, the excretion of electrolytes was relatively maintained in KO, i.e.,
IGF1 led to a 19, 21, and 17% reduction in Na+, K+, and Cl- concentrations, respectively,
and means (KOV verus KOI) were not significantly different. The ratio of Na+ to K+ in
the urine was also affected by genotype, i.e., increased by 76% in the WT, but reduced

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The defect in the KO is likely upstream of the inhibitory purinergic receptor since ENaC significantly inhibited by benzamil. ENaC activity in the KO is uncoupled from Na intake. KO and control mice fed a 0, 0.2, or 2.0% Na diet.

CCD by cell-attached patch clamp and measurements of urinary ATP were performed on and control mice fed a 0.2% Na diet. Single channel analysis of ENaC activity in split open

The apical BK channel in the CCD mediates flow-induced K secretion and compromised purinergic signaling in the CD are Na homeostasis. The lack of response to Na intake implies that renal Na excretion and impairment of renal H,K-ATPases. We hypothesized that HKα, HK-ATPase knockout (KO) would affect ENaC activity.

Methods: Na reabsorption was measured by in vitro microperfusion in CCD from KO and control mice fed a 0.2% Na diet. Single channel analysis of ENaC activity in split open CCD by cell-attached patch clamp and measurements of urinary ATP were performed on KO and control mice fed a 0, 0.2, or 2.0% Na diet.

Results: Na reabsorption in the KO was significantly less than in controls and was not significantly inhibited by benzamil ENaC activity in the KO is unaltered from Na intake. When fed a 2.0% Na diet ENaC activity is higher in the KO vs. controls; and is lower on a 0% Na diet in KO vs. controls with no difference in activity in the KO on any of the Na diets. Preliminary results suggest that purinergic regulation of ENaC by a local signaling system is abnormal in the KO contributing to inappropriate channel responses to changes in dietary Na. KO mice have lower urinary ATP than controls and show no dietary Na-effect on ATP in contrast to controls where ATP is proportionally related to dietary Na intake. The defect in the KO is likely upstream of the inhibitory purinergic receptor since ENaC in the KO responds normally to exogenous ATP.

Conclusions: These results implicate the HKα, HK-ATPase in the maintenance of Na homeostasis. The lack of response to Na intake implies that renal Na excretion and BP in the KO are expected to be abnormal particularly at extremes in dietary Na intake. Dysfunctional regulation of ENaC by a local signaling system is abnormal in the KO contributing to inappropriate channel responses to changes in dietary Na.

TH-PO434

High Cholesterol Diet (HCD) Impairs K Secretion in the Rabbit Cortical Collecting Duct (CCD) Rolando Carrizo-Gayan, David Flores, Lisa M. Satlin. Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The apical BK channel in the CCD mediates flow-induced K secretion (FKS). BK channels possess multiple cholesterol recognition/interaction motifs in the α subunit and, in non-renal cells, are inhibited by enhanced cholesterol content in the lipid membrane and hypercholesterolemia. Cholesterol determines membrane fluidity, and changes in membrane cholesterol are expected during postnatal development and in response to HCD. We speculated that HCD, via enhanced incorporation of cholesterol into the plasma membrane (PM), inhibits BK channel-mediated FKS in the CCD.

Methods: NZW rabbits were randomized after weaning to receive either a standard diet (0.3%) or a cholesterol enriched diet (HCD; 0.3%) for 4-5 wks, at which time the animals were sacrificed. Kidneys were dissected for (i) isolation of renal cortical membranes for immunoblotting of BKα, ROMK and ENaCβ, and (ii) microperfusion of isolated CCDs in mice of before and after IP injection of furo. Fluorescent immunohistochemistry (FIHC) and western blotting were used to determine BK-α and Na-K-Cl cotransporter (NKCC2) expressions.

Results: In WT on a control diet, K clearance was higher in furo-treated mice compared to veh due to increased distal flow. However, in WT on LNaHK, K clearance was significantly lower in furo-treated mice despite increased distal flow, and furoami decreased K clearance more than either drug alone. In KO on LNaHK, K clearance was not different between furo and veh groups. Micropuncture studies showed that furo decreased [K] in EDT of WT on control diet but increased [K] in EDT of WT on LNaHK. In WT on LNaHK, K clearance was higher and urine osmolality lower in furo-treated mice compared to veh, indicating NKCC2 was still active. NKCC2 expression in medullary TAL was higher in WT on LNaHK compared to control diet. FIHC showed that BK-α was expressed in the apical membranes of MCD of WT on LNaHK, but not KO, which may mediate K recycling in MCD.

Conclusions: These results suggest that there is a furosemide-sensitive BKJ4-dependent net K secretion in the thick ascending limb of mice on LNaHK diet. Funding: NIDDK Support

TH-PO435


Background: It has been long understood that thick ascending limb (TAL) reabsorbs Na, Cl, and K, and high K diet inhibits NaCl reabsorption in TAL. In the present study, however, we found a persistent NaCl reabsorption and a net K secretion in TAL of mice on a low Na high K diet (LNaHK) that is dependent on jum4 subtype of large Ca-activated K channels (BK). We hypothesized that K secretion in the TAL was the result of K recycling via BC-J4 from the mediallucillary collecting ducts (MCD).

Methods: Wild-typed (WT) and mice with a knock-out of BKJ4 (KO) were fed either a control or LNaHK diet for 7-10 days. They received intraperitoneal (IP) injections of vehicle (veh), furosemide (furo), amiloride (ami), or furosemide + amiloride (furoami) and were placed in metabolic cages for 12 hours to collect urine. Urine and plasma [Na] and [K] were measured with flame photometry. Micropuncture was used to measure [K] in the outer medullary tubule (EMT) and NKCC2 was demonstrated a greater abundance of ROMK and ENaC in total membranes and lower expression of Na-K-Cl cotransporter (NKCC2). Na delivery.

Results: Under a control diet, K clearance was higher in furo-treated mice compared to veh due to increased distal flow. However, in WT on LNaHK, K clearance was significantly lower in furo-treated mice despite increased distal flow, and furoami decreased K clearance more than either drug alone. In KO on LNaHK, K clearance was not different between furo and veh groups. Micropuncture studies showed that furo decreased [K] in EDT of WT on control diet but increased [K] in EDT of WT on LNaHK. In WT on LNaHK, K clearance was higher and urine osmolality lower in furo-treated mice compared to veh, indicating NKCC2 was still active. NKCC2 expression in medullary TAL was higher in WT on LNaHK compared to control diet. FIHC showed that BK-α was expressed in the apical membranes of MCD of WT on LNaHK, but not KO, which may mediate K recycling in MCD.

Conclusions: These results suggest that there is a furosemide-sensitive BKJ4-dependent net K secretion in the thick ascending limb of mice on LNaHK diet. Funding: NIDDK Support

TH-PO436

A Decrease in ENaC and ROMK Activity in the Late Distal Convoluted Tubule/Connecting Tubule May Contribute Hyperkalemia in PHAII NIDDK Support Vladislav V. Bugay, Charles S. Wingo, I. Jeanette Lynch, Gaytan D. Gainesville, FL; 1University of Florida, Gainesville, FL.

Background: Pseudohypoaldosteronism type II (PHAII) is caused by mutations in with-no-lysine kinase 1 (WNK1) and WNK4. Mice harboring PHAII WNK4 mutant mice have PHAII WNK4 mutant by genmic manipulation (TgWNK4+/−) developed typical PHAII phenotypes characterized by hypertension and hyperkalemia. While the hypertension is caused by an excessive Na absorption through NCC in the distal convoluted tubule (DCT), hyperkalemia has been attributed to a low Na delivery to the distal nephron. However, the role of ENaC and ROMK in causing hyperkalemia is not explored.

Methods: In the present study, we used the whole-cell patch-clamp technique to examine the ROMK and ENaC activity in the late DCT (DCT2) and early connecting tubule (CNT). The tubule was split open to expose the apical membrane and was bathed in a solution containing 135 K-gluconate and 10 KCl. The pipette contains a symmetrical K solution.

Results: Western blot confirmed that NCC expression is upregulated in TgWNK4+/− mice in comparison to the WT and TgWNK4−/− mice. The whole cell recording detected chloride-sensitive K currents in the DCT2/CNT, the basolateral K currents in the DCT1 were similar among WT, TgWNK4−/− and TgWNK4+/− mice in comparison to the WT and TgWNK4−/− mice. We also measured the whole cell K currents in the DCT1 which lacks apical ROMK and ENaC channels. In contrast to Na and ROMK currents in the DCT2/CNT, the basolateral K currents in the DCT1 were similar among WT, TgWNK4−/− and TgWNK4+/− mice. This suggests that the upregulation of NCC in TgWNK4+/− mice did not stimulate the basolateral K+ currents.

Conclusions: We conclude that ENaC and ROMK channel activity are inhibited in TgWNK4+/− mice and that WNK4+/−-induced inhibition of ENaC and ROMK may contribute to the suppression of K secretion in the DCT2/CNT in addition to a reduction of Na delivery.

Funding: NIDDK Support

TH-PO437

Gilz Regulates Sodium and Potassium Balance During Dietary Sodium Restriction Priyanka Rashami, Michael Ng, David Pearce. Univ of California San Francisco, San Francisco, CA.

Background: The hormonal regulation of ion transport by the kidney tubules is critical for regulating sodium and potassium balance in blood, extracellular fluid volume and blood pressure. The renin-angiotensin-aldosterone (RAAS) system is the primary regulator of Na reabsorption and K secretion. RAAS regulates multiple transporters involved in electrolyte homeostasis such as NaCl cotransporter (NCC) and epithelial sodium channel (ENaC). While both ENaC and NCC mediate Na reabsorption, they affect K differently: Electrogenic Na reabsorption via ENaC stimulates K secretion, while

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electro-renal reabsorption of Na via NCC inhibits K secretion by competing with ENaC for Na transport. Glucocorticoid-induced leucine zipper protein (Gilz) is an aldosterone-regulated gene product reported to cause changes in ion balance but the mechanism has not been explored. In this study we use the Gilz knock out (Gilz−/−) mouse generated in our laboratory to show that during sodium deprivation Gilz−/− mice come into sodium balance more quickly than wild type (WT) and become significantly hyperkalemic. These observations raised the possibility that loss of Gilz results in hyperactivation of an electro-nal transport, which does not stimulate K secretion. Indeed, Gilz knock out mice are more sensitive to thiazide diuretics suggesting increased NCC activity.

Conclusions: These results suggested that aldosterone up-regulates NCC expression by disruption of 14-3-3 γ binding to NCC that leads to decreasing NCC ubiquitination. Funding: Veterans Administration Support, Private Foundation Support

TH-PO440
Calcineurin Inhibitors Upregulate the Thiazide-Sensitive NaCl Cotransporter in Urinary Exosomes of Kidney Transplant Patients

Omar Tunakel,1 Mathijs de van der Vle,1 Marco Valdez Flores,2 Ewout J. Hoorn,2 Luuk Hilbrands,1 Joost Hoenderop,1 René J. Bindels.1,2 1Physiology and Nephrology, Radboud Univ Medical Center, Nijmegen; 2Div of Nephrology & Transplantation, Erasmus Medical Center, Rotterdam, Netherlands.

Background: Calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (Tac), are the cornerstone of immunosuppression and superior in preventing acute allograft rejection. This benefit, however, comes at the cost of common adverse effects including hypertension. Recently several studies have shown that CNI-induced hypertension is largely mediated by activation of the thiazide-sensitive NaCl cotransporter (NCC). The aim of the present study was to further substantiate the role of NCC in CNI-induced hypertension by assessing the abundance and activity of NCC in urinary exosomes of CNI-treated patients.

Methods: Kidney transplant patients were enrolled 6 months after transplantation and treated with CsA (n=14), Tac (n=18) or a CNI-free immunosuppressive regimen (n=13). Six healthy subjects were also included. Urinary exosomes were isolated from 10 ml midstream urine samples by ultracentrifugation and normalized by urinary creatinine. The corresponding immunoblot were probed with antibodies specifically recognizing NCC and pNCC-T58. To confirm equal loading of the samples the abundance of the somatodendritic marker CD9 was determined.

Results: NCC was detected in urinary exosomes by immunoblot as two bands of ~260 and ~130 kDa representing the dimeric and monomeric forms, respectively. Abundance of both NCC and pNCC-T58 in urinary exosomes of CsA and Tac groups was significantly increased in comparison to patients treated with a CNI-free immunosuppressive regimen and healthy subjects. Moreover, both the NCC and pNCC-T58 abundance was 2.5-fold higher in CsA group compared to Tac group. CD9 abundance in urinary exosomes was similar between the various groups.

Conclusions: The present study demonstrates that: (i) total and phosphorylated NCC abundance is increased in urinary exosomes of CNI-treated kidney transplant patients; (ii) urinary exosomes can be used as a novel biomarker to assess NCC abundance and activity in CNI-treated kidney transplant patients.

Funding: Government Support - Non-U.S.

TH-PO438
Pharmacological Inhibition of the Circadian Regulatory Casein Kinases 1α/ε Prevents Aldosterone-Mediated Induction of Na-Cotransporter Activity

Michelle L. Gunz,1,2 Kristen Solocinski,1,2 Robert S. Hoover,1,4 Benjamin S. Ko.1,2 Medicine/Nephrology, Univ of Florida, Gainesville, FL; 3Biochemistry and Molecular Biology, Univ of Florida, Gainesville, FL; 2Medicine/Nephrology, Emory Univ, Atlanta, GA; 4Research Service, Atlanta Veteran’s Administration Medical Center, Atlanta, GA; 5Medicine, Univ of Chicago, Chicago, IL.

Background: The circadian clock protein Per1 transcriptionally regulates the Na-Cl co-transporter NCC in response to aldosterone. We previously showed that disruption of 14-3-3 γ binding to NCC altered aldosterone-mediated but not AngII-mediated induction of NCC activity.

Methods: In HEK293T cells, overexpression of Gilz isoform 1 (Gilz1) inhibits NCC activity in response to hypotonic low-Cl conditions as assessed by its phosphorylation at T53 and T58. Gilz mediated NCC inhibition is lost in the presence of constitutively active casein kinase 1∆/İ (CK1∆/İ) in order to enter the nucleus. Previously, we showed that co-expression of Gilz inhibits SAPK phosphorylation at S373. Together, our results suggest that during sodium restriction, Gilz1 shifts sodium reabsorption from NCC to ENaC, thus favoring K+ excretion. This effect may be critical for the maintenance of eukalemia in the face of Na+ restriction.

Funding: Other NIH Support - T32

TH-PO439
Disruption of 14-3-3 γ Binding to NCC Altered the Aldosterone-Mediated Regulation of NCC Protein Expression

Xiuyan Feng,1 Zhizhi Zhuang,2 Courtney Marie Caroti,1 Hui Cai,1 medicine/Emory School of Medicine, Atlanta, GA; 2Section of Nephrology, Atlanta Veterans Administration Medical Center, Decatur, GA.

Background: 14-3-3 γ belongs to a family of multifunctional regulatory proteins that mainly bind to phosphorylated Ser/Thr residues in the target proteins. Previous data have shown that 14-3-3 γ proteins regulate renal ion channel and transporter such as ENaC and UT-A1 by altering their ubiquitinations. We have previously shown that aldosterone increases both total and surface expressions of sodium chloride co-transporter (NCC) via reducing NCC ubiquitination. Thus, we investigated whether 14-3-3 γ is involved in the aldosterone-mediated regulation of NCC.

Methods: Cell culture, transfection, western blot analysis, immunostaining, confocal microscopy, co-immunoprecipitation and C57/Bl6 mice were used for this study.

Results: Co-immunoprecipitation (co-IP) in Cos-7 cells showed that 14-3-3 γ is the strongest one binding to NCC among all isoforms of 14-3-3. Immunostaining and confocal microscopy also showed that 14-3-3 γ is localized in distal convoluted tubule in mice. Co-IP experiments in Cos-7 cells showed that wild-type (WT) 14-3-3 γ binds to NCC, whereas 14-3-3 γ K50E mutant almost completely loses its binding to NCC. Western blot analysis showed that WT 14-3-3 γ significantly decreased total NCC expression by 63 % compared to the control group, whereas 14-3-3 γ K50E mutant did not change NCC protein expression. WT 14-3-3 γ increased NCC ubiquitination by 1.5 fold (1.5 ± 0.44 vs 1.0), whereas 14-3-3 γ K50E mutant did not alter NCC ubiquitination compared to the control group. In addition, we implanted aldosterone osmotic mini-pump to WT mice for 14 days and then harvested the samples. Western blot analysis showed that whether SPARK increased total NCC expression by 1.68 folds (1.0 ± 0.28 vs 1.68 ± 0.15) and decreased the ubiquitinated NCC by 56 %. Co-IP also showed aldosterone decreased the 14-3-3 γ binding to NCC by 57 % without changing total 14-3-3 γ expression.

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Conclusions: These results suggested that aldosterone up-regulates NCC expression by disruption of 14-3-3 γ binding to NCC that leads to decreasing NCC ubiquitination.

Funding: Veterans Administration Support, Private Foundation Support

TH-PO441
Generation of Hypertension-Associated STK39 Polymorphism Knock-In Cells Lines with the CRISPR/Cas9 System

Shintaro Mandai, Takayasu Mori, Eisei Sotara, Tatemitsu Rai, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Previous genome-wide association studies identified STK39, encoding STE20/SPS1-related proline/alanine-rich kinase (SPAK), as one of a limited number of hypertension-associated susceptibility genes. The physiological function of this polymorphism is yet to be clarified.

Methods: To investigate whether SPAK and the downstream targets are modulated by this polymorphism, we generated homozygous (A/A) and heterozygous (G/A) knock-in human embryonic kidney (HEK293T) cell lines with the clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system, using a double-nickase (Cas9-D10A), single guide RNAs targeting STK39 intron 5 around SNP, and a 100-bp donor single-stranded DNA oligonucleotide.

Results: Homozygous (A/A) and heterozygous (G/A) knock-in cell lines were generated. Reverse transcription-polymerase chain reaction (RT-PCR) with sequencing analyses revealed the identical STK39 transcripts across the wild-type and both knock-in cell lines. Quantitative RT-PCR showed increased STK39 mRNA expression, and immunoblot analysis revealed increased total and phosphorylated SPAK with increased phosphorylated Na-K-Cl cotransporter isoform 1 (NKCC1) in both knock-in cell lines. The largest increases in these molecules were observed in the homozygous cell line.

Conclusions: STK39 intronic polymorphism rs3754777 increases STK39 transcription, leading to activation of the SPAK-solute carrier family 12 (SLC12A) signaling cascade. Activation of the target cation-chloride co-transporters may be responsible for hypertension susceptibility in individuals with this polymorphism.

Funding: Private Foundation Support, Government Support - Non-U.S.
The Major Contribution of WNK4 to the Pathogenesis of Pseudohypoaldosteronism Type II (PHAI) Caused by the KLHL3 Mutation R258H
Koichiro Sasa, Eisui Sohara, Daiwei Takahashi, Tatemitsu Rai, Shinichi Uchida.

Background: Recently, we reported that KLHL3<sup>R258H</sup> knock-in mice, a PHAII model mouse, exhibit the activation of OSR1/SPAK-NCC signaling by the increased protein levels of both WNK1 and WNK4. Our data is improved protein localization by the mutant KLHL3. Previously we have demonstrated that the amount of phosphorylated and total NCC decreased to almost undetectable levels in the WNK4<sup>−/−</sup> mice, indicating that WNK4 plays the major role in NCC regulation and that other WNKs including WNK3 and WNK7 cannot compensate for the absence of WNK4. In this study, we sought to determine the contribution of WNK4 to the activated OSR1/SPAK-NCC signaling in the KLHL3<sup>R258H</sup> knock-in mice.

Methods: We generated WNK4<sup>−/−</sup>KLHL3<sup>R258H</sup> mice by crossing the WNK4<sup>−/−</sup> mice with the KLHL3<sup>R258H</sup> mice. In addition, we also generated WNK4<sup>−/−</sup>KLHL3<sup>R258H/R258H</sup> mice. Therefore, WNK4-OSR1/SPAK-NCC phosphorylation signal cascade was examined in kidneys from these mice.

Results: As previously reported, compensatory increased WNK4 was observed in the WNK4<sup>−/−</sup> mouse kidney, compared to WNK4<sup>+/+</sup>. Expectedly, both WNK4<sup>−/−</sup>KLHL3<sup>R258H</sup> mice and WNK4<sup>−/−</sup>KLHL3<sup>R258H/R258H</sup> mice showed further increases in WNK4 in the kidney, due to the KLHL3 mutation. However, although phosphorylated SPAK was increased in the whole kidney to the levels comparable with that in wild-type mouse, total NCC and NCC phosphorylated at S71 were almost completely absent even in WNK4<sup>−/−</sup>KLHL3<sup>R258H</sup> mice.

Conclusions: As in the wild-type mice, WNK4 plays the major positive role in the regulation of NCC in the KLHL3<sup>R258H</sup> PHAII model mice.

Mechanism of Regulation of WNK Kinases Elizabeth J. Goldsmith

Background: WNK4 is a protein kinase on pathway for the regulation of cation-chloride cotransporters. We demonstrated that the kinase domain of WNK1 binds chloride ion and inhibits WNK1 autophosphorylation (Piala et al. Sci. Signaling 7 ra414 2014). New crystallography improves our understanding of the mechanism of this regulation.

Methods: New crystals of the kinase domain of WNK1 (210-483) (phosphorylated) were obtained using peg-ion screening, that yielded crystals diffraction to 2.1 Å. Data were collected at the APS Beamline 19, and data were processed in HKL2000; the structures were solved by molecular replacement. In addition, the structure of a chloride sensing mutant was solved in an unphosphorylated form of the same construct on diffraction to 2.5 Å.

Results: The structure of the phosphorylated form reveals conformational changes associated with dislodging the chloride from the active site of WNK1, and how a ATP analog, AMP-PNP, binds to the unique WNK1 active site. The structure adopted however, associated with dislodging the chloride from the active site of WNK1, and how a ATP

Conclusions: The new structural data confirms the chloride regulation of WNK1, and strongly suggests that activation is a multistage process.

Funding: NIDDK Support, Private Foundation Support

Characterisation of the Cullin-3 Mutation That Causes a Severe Form of Familial Hypertension and Hyperkalaemia Keith Siew, Frances-Rose Schumacher, Thimo K. Kurz, Kevin O'Shaugnessy.

Background: Deletion of exon-9 from Cullin-3 (CUL3, residues 403-459: CUL3<sup>∆403-459</sup>) causes pseudohypoaldosteronism type IIE (PHA2E), a severe form of Familial Hyperkalaemia and Hypertension (FHH). CUL3 binds to KLHL3 ubiquitylates WNK kinases, promoting their ubiquitin-mediated proteasomal degradation. Mutations in both KLHL3 and WNK4 cause Knl1 and WNK5. CUL3 binds and ubiquitylates WNK, and also natriuresis. The natriuretic effect of EX-4 has been associated with phosphorylation and potential inhibition of Na-H-exchanger 3 in proximal tubules, but the quantitative contribution has not been defined.

Methods: Tubule-specific NHE3 knockdown mice were generated (Pax8-Cre/NHE3<sup>fl/fl</sup>) and compared with littermate controls (NHE3<sup>fl/fl</sup>). a) EX-4 (10 mg/kg) or vehicle was applied i.p. in a cross-over design together with an oral NaCl load (30 mg/ml of 0.85% saline) and the urine quantitatively collected over 3 hours in metabolic cages. b) Terminal 1/6-inulin clearance studies determined tubules of EX4 on GFR, blood pressure (BP), and fractional fluid excretion (FE).

Results: Western blotting revealed non-detectable renal NHE3 in tubNHE3<sup>−/−</sup>, tubNHE3<sup>−/+</sup> and WT showed a) similar diuresis and natriuresis during vehicle application (not shown) and EX-4-induced increase in diuresis (50±14 vs 60±17 %) and natriuresis (10±13.44 vs 20±3.28 %) (P<0.01 vs vehicle; n=9-10/group), and b) similar basal values (not shown) as well as EX4-induced changes in GFR (14.6±6 vs 13.9±9 %) and blood pressure (-3±3 vs -7±2 %); EX-4-induced similar increase in FE in NHE3<sup>−/−</sup> (1.1±1.0 to 3.1±0.8 %) and WT (1.1±0.4 to 2.5±0.5 %) (P<0.01 vs basal); n=7-8/group).

Conclusions: The acute EX-4-induced diuresis and natriuresis does not require tubular NHE3 in mice.

Funding: NIDDK Support, Pharmaceutical Company Support - Astra-Zeneca

Protein Carbonylation of a Single Amino Acid Residue of Na/K-ATPase α1 Subunit Dictates Na/K-ATPase Signaling and Sodium Transport in Renal Proximal Tubular Cells Yanling Yan, Anna P. Shapiro, Jiaan Tian, Deepak K. Malhotra, Zi-jian Xie, Joseph I. Shapiro, Jiang Liu.

Background: We have demonstrated that direct carbonylation modification of the Na-K ATPase α1 subunit regulates Na-K ATPase signaling and subsequent transsplanchnical sodium transport in renal proximal tubules.
Methods: Mutation of Pro224 of rat α1 subunit. Assays for protein carbonylation, e-Src phosphorylation, and α1-ATPase activity, active transphilaeelix, Na+ transport, cellular redistribution of ion transporters, etc. Results: Cardiotoxic steroids (CTS, such as ouabain) signaling through Na+-ATPase, regulate sodium reabsorption in renal proximal tubule (RPT). By direct carbonification modification of the activator (A) domain of the Na+-ATPase α1 subunit, reactive oxygen species (ROS) are required to initiate ouabain-stimulated Na+-ATPase/e-Src signaling and subsequent regulation of active transphilaeelix Na+ transport. A single mutation of Pro224 to Ala in rat α1 subunit was established into a stable cell line, and the mutant cell line was competed to the wild-type RPT cells by characterization with Na+-ATPase α1/β1 expression, [H] ouabain binding and ouabain-sensitive 86Rb+ uptake assays. The mutation of Pro224 to Ala abolishes ouabain-stimulated Na+-ATPase/e-Src signaling, protein tyrosine phosphorylation, protein carbonylation, redistribution of Na+-ATPase and sodium/proton exchanger isoform 3 (NHE3), and inhibition of active transphilaeelix Na+ transport. However, a mutation of Ala146 to Pro in rat α1 subunit, as characterized as aforementioned, does not affect ouabain-mediated Na+-ATPase signaling and sodium handling. The data indicates that carbonification modification of Pro224 in rat α1 subunit dictates ouabain-mediated RPT Na+-ATPase signal transduction and subsequent sodium transport.

Conclusions: Direct carbonification of a single amino acid dictates ouabain-mediated Na+-ATPase signaling and related sodium handling in renal proximal tubules.

TH-PO448
The Mineralocorticoids Receptor Regulates the Expression of Na+-K+-ATPase β Subunit in Kidney Collecting Duct Cells
Pablo Diaz, Cristian Degregorio, Luis F. Michea, Magdalena Gonzalez. Unv de Chile, Chile.

Background: Aldosterone modulates the activity of the Na+-K+-ATPase (NKA) in principal cells (PC) of kidney collecting duct (CD) via activation of the mineralocorticoids receptor (MR). The NKA is a heterodimer with a catalytic α subunit and a regulatory β subunit. β1 subunit is absent in the kidney. However, the NKA β subunit may be a determinant of subcellular localization and trafficking of the αβ heterodimers, and also may have a role in the cell-cell adhesion that may be relevant in paracellular permeability. Previous studies addressed the modulation of α and β expression in response to aldosterone. However the role of aldosterone in the regulation of the β subunit has not been analyzed. We tested the hypothesis that the activation of the MR modulates the expression of NKA β subunit in CD.

Methods: C57BL/6 mice underwent adrenalectomy (ADX) or sham surgery (SHAM). The ADX mice received either salt diet or hormone replacement therapy (HRT) with deoxycorticosterone (ADX+DOCA, 10mg/mL/day). In a second set of experiment mice received spironolactone (Spi, 50 mg/Kg/day) or vehicle (Control). Treatment after 3 days we obtained the kidneys (cortex and medulla) for the analysis of NKA α, β, and β subunits (mRNA and protein abundance by qRT-PCR and Western blot). Finally, we studied the effect of aldosterone (0.1-100 nM) in primary culture of inner medullary collecting ducts (IMCD, 24 hours).

Results: Adrenalectomy increased β-subunit mRNA and protein abundance in mouse renal medulla but not in kidney cortex (200% vs control, P<0.05 n=4 for mRNA and 65% vs control, P<0.001, n=9 for protein). Similarly, Spi treatment increased the abundance of β-subunit mRNA and protein in renal medulla only (205% vs control, P<0.01, n=8 for mRNA and 100% vs control, P<0.05, n=5 for proteins). Both the ADX mice as the Spi treated mice showed no significant changes in the abundance of α, β, or transcripts and proteins. The treatment with Aldosterone decreased β mRNA in IMCD cells (50% vs control,P<0.01, n=5).

Conclusions: We conclude that the NKA β subunit expression is downregulated by the activation of the MR.

Funding: FONDECYT 1130550, IMH P09-016F, BECA CONICYT 21120658.

TH-PO449
Purified Recombinant ApoL1 Forms Anion Channels in Phospholipid Bilayers
John C Edwards. Internal Medicine, Saint Louis Univ, Saint Louis, MO.

Background: Variants in the protein ApoL1 confer the increased risk of certain types of chronic kidney disease that is observed in people of African ancestry. ApoL1 has been reported to function as an ion channel but reports vary on the nature of this activity. We sought to characterize ApoL1 channels with anticipation that detailed properties of the channel activity of WT and variant ApoL1 may provide insight into the pathophysiology of ApoL1-associated kidney disease.

Methods: Recombinant ApoL1 was expressed in bacteria with a N-terminal GST tag replacing the signal sequence and separated from the ApoL1 coding region by a thrombin cleavage site, and with a C-terminal V5-His tag. N-octyl glucoside-solubilized protein was bound to glutathione agarose. The bound fusion protein was cleared with thrombin, releasing ApoL1-V5His which was further purified by Ni-affinity. Channel activity was assessed using vesicle-based voltage dependent Cl and K efflux assays employing ion selective electrodes. Single channel properties were investigated using the Tip-Dip lipid bilayer approach with ApoL1 added to the bath solution.

Results: The preparation yields highly purified soluble ApoL1. Introduction of ApoL1 into phospholipid vesicles either by reconstitution via detergent dialysis, or by direct insertion into pre-formed vesicles yields a Cl channel selectivity that supports voltage-driven chloride transport through ApoL1. The Cl channel activity activates the GluCl in the lipids at low pH (5.0). We do not find potassium-selective permeability when assayed at either pH 5 or 7.5. In tip-dip bilayer, ApoL1 spontaneously inserts at low pH, generating transitions with single channel conductance of about 5 pS, and with a non-rectifying I-V relationship. We do not find enhanced channel activity if the bath solution is changed to pH 7.5.

Conclusions: Purified recombinant ApoL1 can insert directly into phospholipid membranes at low pH and function as an anion selective channel. A prominent difference between our preparation and that of others reported to function as a cation channel is that our method avoids denaturation and refolding. Whether the disease associated variants show altered channel properties remains to be determined.

Funding: Other NIH Support - NHLBI

TH-PO450
Using ChlopHensor to Measure Intracellular Cl- in a Transporting Renal Epithelium
Aylvín R. Rodan,1 Qifei Sun,1 Drew Stenesen,2 Helmut Kramer.1 Internal Medicine, UT Southwestern, Dallas, TX; 2Neuroscience, UT Southwestern.

Background: Drosophila melanogaster eat a K+-rich diet and secrete a KCl-rich fluid from the main segment of the renal tubule. We have previously shown that ~1/3 of transepithelial K+ flux through the cation-conducting principal cell is via the basolateral NKCC and is regulated by the WNK-SPAK/OSR1 kinase cascade. This pathway is activated under hypotonic conditions. Cl- is a key regulator of WNK activity. Here, we measured intracellular Cl- in the fly tubule using the transgenic Cl- sensor, ChlopHensor.

Methods: The GAL4-UAS system was used to drive tubule expression of ChlopHensor, a pH- and Cl-sensitive GFP linked to a pH- and Cl-insensitive dBiF. Fluorescence after excitation at 488 nm (green), 458 nm (cyan) and 543 nm (red) was quantified using Imager. Calibration curves of the green/cyan ratio (to measure pH) and cyan/red ratio (to measure Cl-) were created at varying intracellular pH and Cl- by equilibrating in the presence of 5 mM nigericin, CCCP, valinomycin and 10 mM tributylthionocarbamoyl. Fluorescence emission was then measured in the tubule principal cells under varying conditions.

Results: In standard bathing medium (SBM), intracellular Cl- concentration was 27±2 mM (n=21 cells in 7 tubules), similar to previous measurements made with double-barreled whole-cell patch electrodes. In hypotonic medium, Cl- decreased to 16±1 mM (p<0.0001, paired t-test). pH was unchanged. In a time-course experiment, initial Cl- was 30±4 mM in SBM, then decreased to 20±3, 16±2, and 15±2 mM at 10, 30 and 60 minutes of hypotonic exposure. The decrease in Cl- was hypotonic in conditions brought by increasing [K+] in the hypotonic medium (A, 8±1 mM) and increased by decreasing [K+] and [Cl-] in the hypotonic medium (A, 17±2 mM, p<0.05 compared to usual hypotonic and p<0.001 compared to high-K+ hypotonic, one-way ANOVA with Bonferroni correction).

Conclusions: Activation of the WNK-SPAK/OSR1-NKCC pathway in the Drosophila renal tubule under hypotonic conditions correlates with decreased intracellular Cl- concentration. The decrease in Cl- is accentuated when both K+ and Cl- are lowered, suggesting Cl- efux in hypotonic conditions, perhaps due to regulatory volume decrease mechanisms.

Funding: NIDDK Support, Private Foundation Support

TH-PO451
Potassium-Induced Dephosphorylation of Renal Sodium Chloride Cotransporter Is NOT Dependent on the Anions Nao Hiro Nomura, Wakana Shoda, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida. Dept of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan.

Background: Dietary potassium intake is strongly associated with blood pressure and cardiovascular death. High-potassium diets decrease phosphorylation of sodium-chloride cotransporter (NCC) and induce lower blood pressure. In many experimental studies using high-potassium diets, potassium chloride was added to make high-potassium diets. On the other hand, there is a recent report that a high-potassium diet made of potassium citrate increased phosphorylation of NCC. It is also known that chloride itself affects NCC phosphorylation. Thus, the accompanying anion might modulate the NCC phosphorylation. Therefore, the accompanying anion might modulate the NCC phosphorylation response to the high potassium diets, and aldosterone also might be involved in the discrepancy. In this study, we clarified the change of NCC phosphorylation with potassium compounds accompanying different anions, and confirmed the association between potassium intake and NCC phosphorylation with acute oral infusion.

Methods: Adult C57BL/6 mice were fed potassium chloride, potassium gluconate, and potassium citrate with oral gavage. Kidneys were collected after 15 min infusion, because plasma aldosterone level did not show significant difference at this point time. Western blotting was performed with anti-phospho-NCC antibody.

Results: All potassium compounds infusion showed significant decrease of NCC phosphorylation. Sodium gluconate and sodium citrate acute infusion showed very little and no reduction of NCC phosphorylation respectively.

Conclusions: Rapid potassium infusion decreases phosphorylation of NCC. It is not depend on the anions at least in acute potassium infusion.

Funding: Government Support - Non-U.S.
Association of Birth History and BMI with APOL1 Risk Alleles in CKiD

Rebecca C. Hoert,1 Kimberly J. Reidy,1 Derek Ng,2 Robert Wroniecki,3 Susan L. Furr,2 Bradley Warady,1 Craig S. Wong,2 Larry A. Greenbaum,1 Marva M. Moxey-Mims,4 Jeffrey B. Koppi,1 Sourav Lipimou,1 Cheryl Ann Winkler,1 Frederick J. Kaskel,6 1Pediatrics/Nephrology, Montefiore, Bronx, NY; 2Epidemiology, Johns Hopkins, Baltimore, MD; 3Pediatrics/Nephrology, Stony Brook Univ, Stony Brook, NY; 4Pediatrics/Nephrology, Children’s Hospital of Pennsylvania, Philadelphia, PA; 5Pediatric/Nephrology, Children’s Mercy, Kansas City, MO; 6Pediatrics/Nephrology, Univ of New Mexico, Albuquerque, NM; 7Pediatrics/Nephrology, Emory Univ, Atlanta, GA; 8NHI, Bethesda, MD.

Background: In the Chronic Kidney Disease in Children (CKiD), there is a high prevalence of abnormal birth history (BH) and poor growth. American Americans (AA) have increased rates of prematurity. APOL1 risk alleles are associated with risk of glomerular CKD in AA patients, but the association with BH or growth is unknown.

Methods: Children of AA descent were genotyped for APOL1 risk alleles (G1, G2). High risk (HR) was defined as 2 risk alleles (G1, G1; G1,G2 or G2,G2) Low risk (LR) was defined as no risk alleles or one G1/G2 allele. Demographics and growth parameters were compared between APOL1 HR vs. LR groups.

Results: 28/84 AA children with glomerular disease had HR APOL1, 28 had LR APOL1 and 28 did not have APOL1 measured. 26.9% (7/28) with HR APOL1 were premature, versus 3.5% (1/28) in AA LR APOL1 patients and 6.9% (13/191) in non-AA LR APOL1 patients. Also in AA children with HR APOL1, 29.2% (7/28) were small for gestational age, vs. 36.3% (9/28) in AA LR APOL1 patients and 15.4% (27/179) in non-AA LR APOL1 patients (p=0.011). Overall, 48.1% (13/28) AA children with HR APOL1 had an abnormal BH, versus 35.7% (10/28) in AA LR APOL1 patients and 20.5% (39/191) in non-AA LR APOL1 patients (p=0.007). HR APOL1 risk alleles were also associated with increased BMI in patients with FSGS (p<0.04).

Conclusions: HR APOL1 in CKiD is significantly associated with an abnormal BH and further BMI. Analysis of the interaction of APOL1 genotype with BH and BMI in CKiD is warranted.

Funding: NIDDK Support

TH-PO453

Relationships of Serum Growth Hormone, Insulin-Like Growth Factor-I and IGF-1 Binding Proteins (BP’s) in Children with CKD on Growth Hormone Therapy

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Background: We evaluated children with chronic kidney disease (CKD) enrolled in the Viva La Familia Study to determine relationships between Serum Growth Hormone (GH), Insulin-Like Growth Factor-1 (IGF-1) and IGF-1 Binding Proteins (BP’s), with/without recombinant GH therapy, to assess values that might be useful to guide individual treatment decisions.

Methods: 266 CKD children: 206 - normal height; 26 - short stature; 34 [18 short; 16 normal height] on recombinant (r) GH therapy were selected for gender, age and GFR matching. Normal height = Height Standard Deviation Score (SDS) > -1.88. GH, IGF-1, and IGBP-1 were measured by chemiluminescence and ELISA.

Results: Children with CKD on GH display lower IGF-1/GH than normal height and short children not on rGH therapy.

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<tr>
<td>IGF-1/GHF-1 BP *</td>
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</tr>
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</table>

Conclusions: IGF-1/GHF-1 BP is closer to that in normal height CKD children than in short CKD children. Height SDS correlates with serum IGF-1 in children on rGH better (r = 0.374) than normal height (r = 0.329) and short children (r = 0.048).

Funding: NIDDK Support, Private Foundation Support

TH-PO454

Two-Year Kidney Outcomes of Teen-LABS Participants

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Background: A significant amount of severely obese adolescents undergoing weight loss surgery have evidence of early kidney damage. The objective of this study was to determine if early kidney injury is reversible following weight loss surgery.

Methods: We analyzed data two years following bariatric surgery in the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort, a prospective multicenter study of 242 severely obese adolescents undergoing bariatric surgery. Primary outcomes were change in 24-hour albuminuria (urinary albumin to creatinine ratio > 30 mg/mg) and cystatin C-estimated GFR (cGFR) were compared to baseline values to determine the effect of bariatric surgery on kidney injury.

Results: At surgery, the mean (± SD) age of the patients was 17 ± 1.6 years, 76% were female, and 72% were white race. Procedures included gastric bypass (67%), sleeve gastrectomy (28%), and adjustable gastric band (5%). Median BMI (IQ) at baseline was 51 (45, 58) kg/m², and this decreased to 35 (30, 43) kg/m² two years follow-up. Cystatin C-based GFR was 108 ± 27 mL/min/1.73m² at baseline and by two years post-operatively, GFR had increased by 10% to 119 ± 27 mL/min/1.73m² (p<0.01). Low cGFR (< 90 mL/min/1.73m²) was observed in 25% at baseline, and this improved to 12% at two years follow-up (p=0.01); 71% with low baseline cGFR experienced normalization of cGFR at follow-up. Alternatively, 7% of subjects with normal baseline cGFR developed incident CKD (eGFR < 90 mL/min/1.73m²) two years follow-up (p=0.03). Among those with baseline albuminuria, 69% experienced normalization of albuminuria at follow-up. In contrast, 7% of subjects were observed with incident albuminuria at two years post-op.

Conclusions: Two years following surgery, improvements in kidney function and albuminuria were observed in our cohort. Further study will permit assessment of durability of improvements and longer-term kidney outcomes of severely obese adolescents undergoing bariatric surgery.

Funding: NIDDK Support

TH-PO455

Genetic Variation Underlying Uric Acid Clearance in Hispanic Children: The Viva La Familia Study

Geetha Chittoor,1 Sandra L. Laston,2 Nitish R. Mehra,3 Karin Haack,1 Shelley A. Cole,4 Anthony Gean Comuzzie,4 Nancy F. Butte,4 V. Saroja Voruganti,4 1Nutrition and Nutrition Research Inst, Unv of North Carolina at Chapel Hill, Kannapolis, NC; 2South Texas Diabetes and Obesity Inst and Regional Academic Health Center, UTHSC at San Antonio/Univ of Texas Rio Grande Valley, Brownsville, TX; 3Pediatrics and USDA/ARS Children’s Nutrition Research Center, Baylor College of Medicine, Houston, TX; 4Genetics, Texas Biomedical Research Inst, San Antonio, TX.

Background: Variation in renal excretion of uric acid is a key factor in the development of gout, hyperuricemia, and nephropathy. Hyperuricemia (increased serum uric acid concentrations) and hyperuricosuria (increased urinary uric acid concentrations) can lead to uric acid nephrolithiasis. These are two common multifactorial disorders that have been shown to be associated with progression to kidney disease and have a familial inheritance. The genetic determinants of renal handling of uric acid are poorly elucidated.

Methods: We investigated the genetic factors that influence the excretion of uric acid and its related indices in 769 Hispanic children of the Viva La Familia Study. We conducted a genome-wide association analysis for uric acid clearance after accounting for family kinships. All methods were implemented in SOLAR.

Results: All renal uric acid clearance measurements were significantly heritable (p < 2 x 10^-10). We observed a strong association of uric acid clearance with a single nucleotide polymorphism (SNP) in the zinc finger protein 446 (ZNF446) gene on 19q13 (p < 8 x 10^-13, rs2033711 (A:G), minor allele frequency (MAF) of 0.30). The minor allele (G) was associated with increased uric acid clearance. We also found suggestive associations of uric acid clearance with SNPs in ZNF324, ZNF584, and ZNF132 (within 72kb region of 19q13, 1 x 10^-6, MAFs between 0.28 and 0.31).

Conclusions: Our study indicates, for the first time, the importance of the chromosomal region 19q13 in the regulation of renal clearance of uric acid in Hispanic children.

Funding: Other NIH Support - DKO80457; USDA/ARS [ Cooperative Agreement 6250-51000-053]

TH-PO456

Association Between Height and Clinical Outcomes in Children at Time of ESRD Onset

Elaine Ku,1 Richard N. Fine,2 Chi-yanu Hsu,3 David V. Glidden,4 Barbara A. Grimes,1 Kirsten L. Johansen.1 1UCSF; 2Stony Brook Univ.

Background: Short and tall stature are associated with adverse outcomes in the general adult population. The aim of this study was to examine risk of mortality and transplantation in children with short and tall stature at time of ESRD onset.

Methods: Using data from US Renal Data System, we performed a retrospective analysis of children ages 2-19 years undergoing transplantation therapy during 1995-2011. We used Cox models adjusted for demographic and socioeconomic factors, calendar year, and cause of ESRD to determine the association between short (<3 percentile) and tall
TH-PO457
Genital Organ Anomalies in Female Pediatric Patients with End-Stage Renal Disease Shoichiro Kanda,1 Naoya Morisada,2 Yuji Tomii,1 Keichii Takizawa,1 Naoto Kaneko,3 Tomoo Yabuuchi,2 Hirotaka Hama,4 Eiji Nakano,5 Norimasa Tada,6 Kiyonobu Ishizuka,7 Yuki Akioka,8 Hiroko Chikamoto,9 Kazumoto Iijima,10 Toshio Hattori,1
1Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan; 2Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.

Background: In the general population, the rate of prevalence of genital organ anomalies in females is 1.0 per 1000 births. Although female pediatric patients with end-stage renal disease (ESRD) appear to occasionally have genital organ anomalies, the clinical features of them have not been examined.

Methods: We performed a retrospective analysis of female pediatric ESRD patients attending the Department of Pediatric Nephrology, Tokyo Women’s Medical University (TWMU) Hospital. The study was in accordance with the ethical guidelines of the Ministry of Health, Labour and Welfare, Japan. The study was also approved by the central ethics board of TWMU and Kobe University.

Results: Eighty-two patients were included in this study. Genital organ anomalies were found in eight (9.7%) patients and consisted of bicornuate uterus in three patients, double uterus or vaginal atresia in two, and double uteri in one. Renal phenotypes were congenital anomalies of the kidney and urinary tract in six patients and FSFS in two patients. In seven (87.5%) patients, genital organ anomalies were diagnosed after the start of renal replacement therapy. Two patients complained of acute abdomen associated with their first menstrual period. Genetic and chromosome analyses revealed hypothyroidism, deafness, and renal dysplasia syndrome (GATA3, c.1013G>T) in one patient, Turner syndrome in one, Frasier syndrome (46XY, WT1, IVS9+5G>A) in one, and FSFS carrying a mutation of WT1 (c.745C>A) in one.

Conclusions: Our study showed that female pediatric ESRD patients had a frequency of genital organ anomalies of approximately 10%. Additionally, genetic disorders responsible for kidney and genital organ development were detected in four out of eight patients. Therefore, physicians need to be aware of the possibility of genitourinary syndrome and investigate genital organ anomalies in the medical care of female pediatric patients with ESRD.

TH-PO458
Intestinal Microbiota in Pediatric Patients with End Stage Renal Disease Janice Crespo-Salgado,1 Tyrus Stewart,1 Mike J. Ferris,2 Mahmoud Kallah,3 Larry A. Greenbaum,4 V. Matti Vehaskari,5 Diego H. Aviles,6 1Pediatric Nephrology, LSUHSC, New Orleans, LA; 2Pediatric Nephrology, Women & Children’s Hospital of Buffalo, Buffalo, NY; 3Pediatric Nephrology, Emory Children’s Center, Atlanta, GA.

Background: Cardiovascular mortality is increased in children with end stage renal disease (ESRD). Studies in adult population suggest that uremia increase intestinal permeability and alters the intestinal microbiota. These changes could facilitate the translocation of endotoxin and bacterial metabolites to the systemic circulation leading to inflammation. We hypothesized that children with ESRD have an altered intestinal microbiota that lead to increased bacterially derived uremic toxins, and renal transplantation will reverse those changes.

Methods: Serum p-cresyl sulfate and indoxyl sulfate (P<0.05). Multivariate regression also showed each unit of DEHP and HMW p-cresyl sulfate exposure was associated with an increase in PWV of 0.034 m/s (p=0.037) and 0.024 m/s (p=0.041), respectively.

Conclusions: This is the first demonstration of oxidative stress and vascular dysfunction related to environmental chemicals in otherwise healthy children. The link with replacement compounds such as BPS suggests that the consequences of exposure to these chemicals will be a long-term public health problem.

Funding: NIDDK Support, Other NIH Support - NIEHS Pilot study Award

TH-PO459
Cardiorenal Effects of Exposure to Environmental Chemicals in Children Angilina Kataria,1 Suzanne M. Vento,1 Leonardo Trasande,2 Dow Levine,1 Debra J. Morrison,2 Rachel Brody,2 Kurunthachalam Kaman,1 Jingchuan Xue,1 Howard Trachtman,1 1Pediatrics, NYU Langone Medical Center; New York, NY; Office of Collaborative Sciences, Human Specimen Resource Center, NYU Langone Medical Center, New York, NY; 2Environmental Health Sciences, School of Public Health, State Univ of New York at Albany, Albany, NY.

Background: Exposure to short-lived organic chemicals such as bisphenol A and B (BPA/BPS) and phthalates is ubiquitous in the US. Graded exposure to BPA and di-(2-ethylhexyl) phthalate (DEHP), based on urinary excretion, is associated with an increased low-grade albuminuria. Oxidant stress is hypothesized as the mediator underlying these associations. We conducted the following study to assess (1) the mechanism of action of these compounds and (2) the extent of exposure on vascular function in children.

Methods: A cross-sectional study recruiting 10–13 year old children was conducted at Bellevue Medical Center. Demographic information was obtained and height, weight and BP were measured. A first morning and spot urine samples were collected for determination of BPA, BPS, phthalate, 8(0H)-deoxyguanosine, and F2-isoprostane excretion (normalized to creatinine excretion). Pulse wave velocity (PWV) was measured non-invasively (SphygmCor). Multivariate analysis was used to evaluate the relationship between exposures and the laboratory tests.

Results: There were 41 participants, 19 M:22 F, age 12±1 yr. 31 Hispanic, 7 Caucasian, and 3 Other. The mean BMI was 21.7±5.0 and albuminuria 11.4±23.6 mg/L and 10 (25%) were pre-hypertensive (BP≥90th percentile). The degree of exposure to BPS, total bisphenols, DEHP, and high molecular weight (HMW) phthalates correlated with F2-isoprostane excretion (p<0.05). Multivariate regression also showed each unit of DEHP and HMW phthalate exposure was associated with an increase in PWV of 0.034 m/s (p=0.037) and 0.024 m/s (p=0.041), respectively.

Conclusions: This is the first demonstration of oxidative stress and vascular dysfunction related to environmental chemicals in otherwise healthy children. The link with replacement compounds such as BPS suggests that the consequences of exposure to these chemicals will be a long-term public health problem.

Funding: NIDDK Support, Other NIH Support - NIEHS Pilot study Award

TH-PO460
Safety of Eculizumab in Pediatric Patients with Atypical Hemolytic Uremic Syndrome Gema Ariceta,1 Larry A. Greenbaum,2 Jimmy Wang,3 John F. Kincade,1 Christoph Licht, 1 1Hospital Univ Vall d’Hebron, Barcelona, Spain; 2Emory Univ, Atlanta, GA; 3Aexion Pharmaceuticals, Inc, Cheshire, CT; 2The Hospital for Sick Children, ON, Canada.

Background: The safety of eculizumab, a terminal complement inhibitor approved for treatment of children and adults with aHUS, was characterized in 4 prospective trials. This post hoc analysis further evaluates its safety in pediatric participants in 3 of the trials.

Methods: Treatment-related adverse events (TRAEs) and serious AEs (SAEs) reported for patients (pts) (<18 yr) after 1 year and after end of study (EOS) in studies C08-002, C08-003, and C10-003 were pooled.

Results: Pediatric pts (N=28) received eculizumab for a mean (SD) of 67 (42) weeks. TRAEs occurred in 13 pts (46.4%) after 1 year (Table). SAEs are listed in the Table. Elevated levels of alanine transaminase and aspartate aminotransferase were noted in some pts before and after receiving eculizumab, levels generally were higher before treatment and normalized over time. BY EOS after 433 cumulative months of treatment, there were

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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no deaths or meningococcal infections; 6-infection-related serious TRAEs occurred in 4 pts, all upper respiratory tract infection (n=2), influenza, peritonitis (patient on peritoneal dialysis), respiratory syncytial virus infection, and pneumonia (n=1 each).

Conclusions: Eculizumab appears well tolerated in pediatric pts with aHUS. The safety profile of eculizumab in pediatric pts is similar to that in the broader pt population of adult studies. Although more infection-related serious TRAEs were noted, most were mild to moderate in severity, none led to treatment discontinuation, and all pts recovered. Some TRAEs might have been manifestations of underlying aHUS disease.

Medical writing support - Kristen W. Quinn, PhD, of Peloton Advantage, funded by Alexion.

Table 3: Baseline Demographic and Clinical Characteristics and Eculizumab Safety in Pediatric Patients (N=28)

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<th>Characteristic</th>
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</tr>
<tr>
<td>CFH C2</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>CFH autoantibodies</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CFHR1 or CFHR3 polymorphism</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Mean time from diagnosis to screening, months (SD)</td>
<td>67 (17)</td>
<td>88 (79)</td>
<td>53.5 (60.9)</td>
</tr>
<tr>
<td>Newly diagnosed, n (%)</td>
<td>15 (79)</td>
<td>4 (44)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>No PSE1 during the current manifestation, n (%)</td>
<td>11 (61)</td>
<td>2 (22)</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Diastolic at baseline, n (%)</td>
<td>9 (50)</td>
<td>3 (33)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>History of renal transplant, n (%)</td>
<td>2 (11)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Safety Findings

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAEs</td>
<td>Pediatric (n=19)</td>
</tr>
<tr>
<td>16 (84)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Serum</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Serious</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>1 (5)</td>
</tr>
<tr>
<td>TRAEs*</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Serious</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>1 (5)</td>
</tr>
<tr>
<td>0.05 mg/gCr</td>
<td>1 (5)</td>
</tr>
<tr>
<td>SAFEs</td>
<td>10 (53)</td>
</tr>
</tbody>
</table>

Most common TRAEs by organ system include skin and subcutaneous tissue (n=8 (33)), infections and infections (n=5 (22)), gastrointestinal (n=2 (11)), nervous system (n=1 (5)), eye (n=1 (5)), and renal and administration site conditions (n=1 (5)).

Results: Twenty-seven subjects (11 early-and 16 late-treated) were prescribed with eculizumab. Among the early-treated subjects (stage 2) were studied (26 males and 27 females, age 3 to 38 years, median 17). Blood GFR periods were defined as GFR slope = 0 or positive. Fifty-three pediatric CKD patients (stage ³2) were studied (26 males and 27 females, age 3 to 38 years, median 17). Blood GFR was estimated by equation for Japanese children and adults. Stable GFR may prevent CKD progression although the influence of age and underlying disease cannot be ruled out.

**TH-PO462**

Novel Urinary Biomarkers for Detecting Renal Scar in Children with Febrile Urinary Tract Infection Takahisa Kimata, 1 Tetuya Kitao, 1 Solsakum Yamanouchi, 1 Jiro Kino, 1 Hirokazu Kurosawa, 1 Yoshiaki Hirayama, 1 Akihiko Saito, 1 Kazunari Kaneko 1 Pediatrics, Kansai Medical Univ, Osaka, Japan; 2Denki Kagaku Kogyo K.K., Tokyo, Japan; 3Applied Molecular Medicine, Niigata Univ, Niigata, Japan.

Background: Recurrent febrile urinary tract infections (fUTI) during infancy cause renal scar. Renal scar can be diagnosed through renal scintigraphy while it seems impractical to perform it for all infants with fUTI. Therefore, exploring biomarkers that can identify the patients at high risk of developing renal scar is worthwhile. Urinary excretions of total proteins, beta-2 microglobulins (BBM), and N-acetylated-3-D-glucosaminidase (NAG) have recently been reported as sensitive biomarkers for various kidney injuries. This study was undertaken to explore sensitive urinary biomarkers to diagnose renal scar.

Methods: Thirty one infants who underwent renal scintigraphy during the chronic phase after fUTI were enrolled. The following measurements were performed using urine samples: total proteins, BBM, NAG, NAG-L, FABP, C-meg and AGT. The values were corrected by creatinine and compared between the patients with renal scar (n=20) and those without renal scar (n=10).

Results: Among urinary biomarkers, AGT and C-meg in the group with scar (median value 14.4 mg/gCr and 6.7 pmol/gCr) demonstrated significantly higher levels than those without scar (median value 4.5 mg/gCr and 1.9 pmol/gCr) (P=0.021 and 0.0046). Among the area under the curves in receiver operating characteristic curve calculated for each urinary biomarker, C-meg yielded the highest value as following: C-meg (0.81) > AGT (0.76) > NAG (0.60) > protein (0.50) > BBM (0.54) > NAG-L (0.50) > L-FABP (0.46).

Nagai et al. 2012 calculated that the test had 80% (70%) sensitivity, 72.7% (81.8%) specificity.

Conclusions: Urinary C-meg and AGT are useful for renal scar screening.

**TH-PO463**


Background: Microalbuminuria is common in the general population with a prevalence of 6% and in a proteinuric indicator of renal disease. Whether microalbuminuria is acquired during life (as a result of hypertension/diabetes) or is congenital and already present at birth is unknown. We studied the prevalence of microalbuminuria in toddlers and compared distributions of albuminuria with the general adult population.

Methods: We collected urine samples from 1352 children (20-40 months old) from the GECKO Drenthe cohort. Albuminuria distribution was compared with the distribution in 4805 participants of the general adult cohort PREVEND. Difference in prevalence of increased albuminuria (Uₐₐ > 20 mg/L) was tested with chi-square. Associations between logarithm of Uₐₐ and antenatal, postnatal and maternal factors explaining albuminuria variations.

Results: The urinary albumin (Uₐₐ) was measured in 1352 children (20-40 months old) from the GECKO Drenthe cohort. Albuminuria distribution was compared with the distribution in 4805 participants of the general adult cohort PREVEND. Difference in prevalence of increased albuminuria (Uₐₐ > 20 mg/L) was tested with chi-square. Associations between logarithm of Uₐₐ and antenatal, postnatal and maternal factors were tested with linear regression analysis.

Conclusions: The median Uₐₐ in GECKO was 2.3 mg/L [5-95th percentile: 2.1-25.5] and in PREVEND 6.0 mg/L [2.3-28.6] (P distribution comparison 0.053). Prevalence of Uₐₐ > 20 mg/L was 6.9% in GECKO and 7.8% in PREVEND(Figure; P=0.195). Uₐₐ was lower in boys and not associated with other factors.

Conclusions: The distribution of Uₐₐ in toddlers and the prevalence of microalbuminuria in toddlers and general adult population are comparable. These findings suggest that microalbuminuria is a congenital condition which may predispose those at a higher renal/cardiovascular risk later in life.

Figure: Prevalence of different Uₐₐ levels in toddlers (GECKO) vs adults (PREVEND).

Funding: Pharmaceutical Company Support - Hutchinson Whampoa Ltd, Hong Kong, Government Support - Non-U.S.

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

Underline represents presenting author.

192A
TH-PO464
Validation of a Novel Device to Collect Urine for Albuminuria Assessment in Young Children  
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Background: Urine collection for albuminuria measurement in babies and toddlers is cumbersome. Taped plastic bags are complicated and may come loose. Old-fashioned cotton wool (pantyliner) or a felt (PeeSpot) are used as collection devices in a disposable diaper. We compared the analytical performance of these two methods.

Methods: The pantyliner and urine collection felt were placed in the diaper; 81 different standard urines with a wide range of albuminuria were applied by hand (in duplicate); incubated for 3 hours at 37°C (simulating the baby), and 72 hours at room temp (simulating transport); extracted by centrifuging. Urinary Albumin Concentration was measured Analytical performance of two methods was tested according National Committee for Clinical Laboratory Standards (NCCLS) guidelines for method comparison, and compared with the standard urine. Performance measures assessed were bias, precision and accuracy.

Results: Median albumin concentration was: standard: 66.0 mg /L (IQR 25.0–211.0 mg/L), pantyliner method 32.0 mg /L [4.7–165.0 mg/L], and PeeSpot method 61.0 mg /L [27.0–216.0 mg/L]. Bias and precision were higher in pantyliner (-34.2% and 32.4 mg/L) than in PeeSpot (3.3% and 5.0 mg/L) and accuracy was lower in pantyliner (48.1%) vs PeeSpot (96.3%). Passing-Bablok regression and Bland-Altman plot showed a systematic underestimation for pantyliner method, but not for PeeSpot method (Figure).

Conclusions: The PeeSpot method is a reliable method for the collection of urine in babies and toddlers albuminuria measurement. This technique should be used in future research into this subject.

Figure: A: Passing-Bablok regression for pantyliner and PeeSpot. B: Bland-Altman plots for pantyliner and PeeSpot on logarithm of albuminuria. LoA = Limit of Agreement.

Funding: Government Support - Non-U.S.

TH-PO465
A Distinct Urinary Lipid Profile in Patients with FSGS  
Elif Erkan, Xueming Zhao, Prasad Devarajan. Pediatrics, Children’s Hospital of Cincinnati.

Background: Focal segmental glomerulosclerosis (FSGS) accounts for the majority of patients with end-stage renal disease (ESRD) during adolescence. Treatment of FSGS has been a great challenge for pediatric nephrologists due to interwoven molecular pathways underlying its complex pathophysiology. In FSGS patient kidney biopsy sections display increased tubular apoptosis a hallmark for tubular injury. We hypothesize that tubulointerstitial injury caused by the uptake of lipogenic mediators in glomerular filtrate contributes to the progressive nature of FSGS.

Methods: We explored urinary lipid profile of patients with FSGS, minimal change disease (MCD) and healthy controls by High Performance Liquid Chromatography. Normalized data from GC/MS and UPLC/MS analysis including 625 metabolites were compared by Multivariate analysis. We discovered a unique signature characterized by increased concentration of fatty acid (FA) and lyso phosphatidylcholine (LPC) and a decrease in urinary concentration of phosphotidylcholine (PC) in patients with FSGS. Patients with FSGS had lower urinary acylcarnitine levels. Patients with FSGS were divided into two groups (four patients in each group) based on their estimated GFR, to normal GFR (105.29 ± 4.11 ml/min /1.73m²) and low GFR group (69.25 ± 6.49 ml/min /1.73 m²). Low GFR group had higher urinary FA concentration and lower urinary acylcarnitine concentration (p<0.05).

Conclusions: We speculate that these findings indicate increased metabolism of membrane phospholipid PC by phospholipase A2 (PLA2) resulting in higher urinary concentrations of LPC and FA. We propose that decrease in urinary acylcarnitine levels in FSGS implicates an arrest at mitochondrial fatty acid oxidation despite high FA levels. 

believe increased by products of PC metabolism further potentiate tubular and podocyte toxicity in FSGS. Validation of urinary lipids as a biomarker in predicting the diagnosis and progression of FSGS in a larger patient population is warranted.

Funding: NIDDK Support

TH-PO466
Steroid Dependency in Childhood Steroid-Sensitive Nephrotic Syndrome – Clinical Characterization of a Large Single Center Cohort  
Aanya K. Büscher, Mareen Sadau, Rainer Büscher, Peter F. Hoyert. Pediatric Nephrology, Univ of Duisburg-Essen, Pediatrics II, Essen, Germany.

Background: Steroid-sensitive nephrotic syndrome (SSNS) is characterized by preservation of renal function and recurrent disease. Clinical course depends on the number of relapses which is highly variable. A subset of patients presents with relapses during or shortly after steroid therapy (steroid-dependency, SDNS). Mostly, childhood SSNS is of idiopathic origin with minimal change glomerulopathy (MCN) in renal histology. Aim of our study was the characterization of SSNS patients with regard to differences between SDNS and non-SDNS.

Methods: We retrospectively analyzed 100 SSNS patients treated at our hospital. Data collection comprised age at onset, number/trigger of relapses, dose/duration of steroid therapy, time to response, further immunosuppressants, renal function, renal histology, and family history.

Results: 89% of patients experienced relapses (mean 9 (range 0–34)), 55% developed SDNS after (15–245) months from onset. In 80% of cases, several infections triggered SSNS relapse. 60% of patients received further immunosuppressants (95% cyclophosphamide, 58% ciclosporinA; sustained disease remission in 24/51%, respectively). Renal biopsy was performed in 70% (93% MCN, SDNS and non-SDNS). SDNS patients were significantly younger at disease onset (4.16y vs. 5.34y (non-SDNS), P<0.05; all patients 4.7y). Mean time to first relapse was significantly shorter in SDNS (6.3months vs. 16.3months non-SDNS, P<0.001; all patients 9.8months). Response to steroids at disease onset was faster in non-SDNS (6.9days vs. 11.7days SDNS, P<0.001). SDNS patients developed secondary steroid resistance in 20% (2% non-SDNS, P<0.01, all patients 12%). 

Conclusions: 55% of patients developed SDNS and differed from non-SDNS patients by a younger age at disease onset, a shorter time until first relapse and a slower therapy response. The clinical course in general was influenced by therapy regimen.

Funding: Clinical Revenue Support

TH-PO467
Dyslipidemia in Pediatric CKD Patients from KNOW-PedCKD Study  
Seong heon Kim,1 Yo Han Ahn,2 Eujin Park,3 Kyoung Hee Han,4 Heeyoon Cho,3 Joo Hoon Lee,5 Hee Gyu Kang,6 Young seop Park,6 Hae Il Cheong,1 Curie Ahn,3 IL Soon Ha.1 1Dept of Pediatrics, Pasan UniV Natl Univer Children’s Hospital, Yangsan, Republic of Korea; 2Dept of Pediatrics, Jeju National Univ School of Medicine, Jeju, Republic of Moldova; 3Dept of Pediatrics, Seoul National Univer Children’s Hospital, Seoul, Republic of Korea; 4Dept of Pediatrics, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea; 5Dept of Pediatrics, Yonsei Univ College of Medicine, Severance Children’s Hospital, Seoul, Republic of Korea; 6Dept of Pediatrics, Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea; 7Dept of Pediatrics, Kangyook National Univ School of Medicine, Daegu, Republic of Korea.

Background: Children with chronic kidney disease (CKD) exhibit various co-morbidities, including dyslipidemia. We investigated the prevalence and characteristics of dyslipidemia in pediatric CKD patients.

Methods: Seven major pediatric nephrology centers of Korea enrolled children younger than 20 years who had CKD. From July 2010 to December 2013, 322 children (MF 218:104) were enrolled.

Results: Baseline lipid analysis found a high prevalence of dyslipidemia in 49%.

Several factors were analyzed including age, gender, CKD stage, primary renal disease, height, weight, BMI, social economic status, hypertension, co-morbidity, Z score of height, z score of weight, z score of BMI, gestational age at birth, birth weight, estimated GFR and duration of underlying diseases. Univariate logistic regression analysis demonstrated that several factors including BMI, co-morbidity, Z score of weight and Z score of BMI were associated with dyslipidemia. After multivariate adjustment, social economic status and Z score of BMI were significantly associated with dyslipidemia. A subset of patients presented with relapses during or shortly after steroid therapy.

Conclusions: Among children with CKD, dyslipidemia is quite common and is associated with factors such as social economic status and Z score of BMI.

Funding: Government Support - Non-U.S.
Hyper trophy (LVH) and diastolic dysfunction. In children with chronic kidney disease correlated with higher medication adherence (β = .499, p = .000, R² = .262). The outcomes/health services utilization measures were adherence (Morisky et al., 1986) and number/length of hospitalizations in the last year.

Results: Higher STAR-QoL total score correlated with higher medication adherence (β = .301, p = .000, R² = .070). Higher STAR, Medication Management Subscale correlated with higher medication adherence (β = .499, p = .000, R² = .224). Greater STAR, Disengagement Knowledge Subscale correlated with higher medication adherence (β = .216, p = .001, R² = .044), fewer number of hospitalizations (β = .453, p = .000, R² = .262) and inpatient days in the past year (β = .432, p = .000, R² = .187).

Conclusions: The strong reliability of the STAR-QoL in AYA with a variety of conditions treated in either the pediatric or adult-focused clinics, correlates with health outcomes and health services utilization.

Funding: Private Foundation Support

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Emotional-Behavioral Functioning of Children Enrolled in the Chronic Kidney Disease (CKiD) Study Group.

Background: CKiD is a longitudinal study examining medical, neurocognitive, and psychosocial outcomes for children with mild to moderate CKD ages 1-16 years at study entry. Little is known about how CKD affects emotional-behavioral functioning (EBF), although data from the CKiD study indicate that these children are at increased risk of attention and executive functioning deficits. In one of the largest studies to date, we report EBF of participants at baseline and over time.

Methods: Parents of participants completed the Behavior Assessment System for Children (BASC-2) at baseline and every 2 years. 835 participants had BASC-2 data, including 797 at baseline. Linear mixed models predicted participants’ scores on BASC-2 summary measures (Internalizing, Externalizing, Behavioral Symptoms Index, Adaptive Skills Index, Health-related Quality of Life) from confounders (medication adherence, comorbid conditions). Analyses controlled for key demographic (age, sex, ethnicity, maternal education, household income, Full Scale IQ) and medical (GFR, hypertension [HTN], low birth weight, anemia, seizures, proteinuria, glomerular diagnosis, time since CKD onset) covariates.

Results: Children with mild to moderate CKD have EBF scores generally within normal limits at baseline and over time. At baseline, the proportion of scores with at least 1 SD above the mean was 24% for internalizing problems and 27% for attention problems, higher than would be expected in a typical sample. In an adjusted linear mixed model, persistent hypertension was related to attention problems (β = 1.81, 95% CI = 0.40-3.21, p = .02).

Conclusions: Children with mild to moderate CKD have parent-reported EBF that is within normal limits, at baseline and over time. However, the proportion with scores more than 1 SD above the mean is higher than would be expected, suggesting that this population may be at slightly increased risk for internalizing symptoms and attention problems, particularly in the context of HTN, which was associated with increased risk of parent-reported attention problems.

Funding: NIDDK Support, Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI)

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Echocardiographic Findings in Hypertensive Children with Kidney Disease or Essential Hypertension.

Gabriel Parisi, Wachhare Seerunnougva,2,3 Jeanette Arenas Morales,2,3 Marcia J. Defreitas,2,3 Carolyn L. Abitbol,2,3 Michael Freundlich,2,3 Sethuraman Swaminathan,1,4 Gaston E. Zilleruelo,2,3 Pediatric Cardiology, Univ of Miami;2 Pediatric Nephrology, Univ of Miami, Miami, FL.

Background: Hypertension (HT) is a major risk factor causing left ventricular hypertrophy (LVH) and diastolic dysfunction. In children with chronic kidney disease (CKD), the cardiovascular morbidity exceeds that of peers without CKD.

Methods: Children with diagnosis of HT underwent echocardiography with concurrent tests of HT and LV mass, systolic and diastolic function were reviewed. Diastolic transmitral early (E), late (A), septal E’, lateral-leaflet E’ velocities measured. Calculated E/A=1 and or E/E’ Z-score>2 defined diastolic dysfunction.

Results: 52 HT children (11±5yr, 29 had CKD [CKD-HT] and 23 essential HT (eHT). No difference in age, gender, body mass index (BMI), %obesity, degree HT between groups. Prevalence LVH (25% & 30%) and LVM+Z were similar. LVM+Z was strongly correlated with BMI-Z in both groups (r = 0.6, p<0.01) and to a lesser degree with SBP-Z (r = 0.3, p = 0.05). No correlation of LVM+Z with GFR. Diastolic dysfunction was identified in 16/52 HT and 23/29 CKD-HT (25%) whereas systolic function was preserved in both groups. Changes of E/A and aortic root diameter were subtle but significantly different between eHT and CKD-HT (see figure). Additionally, a significant decline in E/A (p = 0.01) and Septal E/E’<Z (p = 0.03) was observed with worsening GFR.

Conclusions: High prevalence of LVH and diastolic dysfunction noted in HT children with or without CKD. Severity of LVH associated with obesity and to a lesser extent to CKD and severity of HT but significantly related to E/A ratio and larger aortic root diameter which could be related to poor renal function.

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Glomerular Capillary Changes in Thin Basement Membrane Disease.

Yusuke Kajimoto, Michiko Aoki, Go Kanazaki, Kiyotaka Nagahama, Akira Shimizu. Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.

Background: Thin basement membrane disease (TBMD) is diagnosed by diffuse reduction in the thickness of glomerular basement membrane (GBM) in electron microscopy (EM), and characterized clinically by benign familial hematuria. However, some cases progress to end-stage renal disease. In the present study, we performed the clinicopathological analyses of TBMD, especially focusing on glomerular capillary injuries, including morphological and qualitative alterations of GBM and glomerular capillaries, and correlated with clinical findings.

Methods: In our department, 27 renal biopsy cases of TBMD (1.9%) was identified. We investigated clinical characteristics using clinical records. We also examined pathological characteristics using light and EM, immunostaining for CD34, which can detect glomerular capillaries, immunostaining for α5 (IV) chains of type IV collagen, which is one of the main component of GBM, and low-vacuum scanning electron microscopy (LV-SEM), which allows detailed three-dimensional observation of GBM surface.

Results: The average age was 37.3 ± 19.5 (5-64yr) years. 26 cases had hematuria and 21 cases had proteinuria. 17 cases (63.0%) indicated hematuria or proteinuria under 20 years of age. In 6 cases, the eGFR declined in G3a to G4 in clinical CKD stage. In immunofluorescence, α5 (IV) expression was significantly reduced in the GBM with partial enhancement of α2 (IV). In LV-SEM observations, thinning and flattering of GBM was noted with multiple small holes and manufactures in the surface of GBM. In CD34 and PAS staining, narrowed glomerular capillaries increased with accumulation of glomerular extracellular matrix (ECM), associated with glomerular endothelial cell injuries.

Conclusions: In TBMD, narrowing glomerular capillaries developed with increased glomerular ECM, in association with glomerular endothelial injuries. In addition, qualitative (reduced α5 (IV) expression) and ultrastructural alterations of GBM (small holes and manufactures) were noted. These glomerular capillary injuries might be associated with the clinical findings including urinary abnormalities and renal dysfunction.

Clinical Significance of IgM Disposition in Kidney Biopsy of Paediatric Minimal Change Disease, Single-Centre Case-Control Study.

Dana Alrothri, Mohammed Alshareh, Fatima Al Robot, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Background: In many cases of Minimal change nephrotic syndrome, or Minimal change disease (MCD), immunoglobulin M (IgM) is abnormally deposited in the mesangium, and can be seen under the electron microscopy (EM) and immunofluorescence (IF). Based on many studies, the rule of IgM is controversial in minimal change disease MCD which is one of the histopathological types of INS. The aim of this study is to explore the clinical significance of mesangial IgM deposits in pediatric MCD cases.

Methods: We reviewed a sample of 313 cases children with MCD who underwent a native kidney biopsy (NKB) at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia from 2003 to 2014. The sample is divided furtherly according to the presence of IgM deposits under EM and IF to IgM+ IF and IgM-IF, which are labeled as case- control groups respectively. We reviewed the clinical course as per the response to the steroid treatment. Initial adjuvant therapies included: Cyclosporine, Tacrolimus and Cyclophosphamide.

Results: MCD IgM-IF has shown a significant association with the presence of hypertension at the time of diagnosis, where a p-value of 0.03. MCD IgM+IF showed
Correlation Between Age-Dependent Expression of Oxidant Handling Genes and Sensitivity to Nicotine Exposure in the Mouse Kidney
Istvan Arany, Samuel Hall, Mehul P. Dixit. Pediatrics, Univ of Mississippi Medical Center; Jackson, MS.

Background: Studies have shown that childhood exposure to secondhand smoke may increase adulthood renal risk. Other studies also suggest that children may be more vulnerable to secondhand smoke exposure than adults, which may imply augmented sensitivity to renal oxidative stress. Accordingly, we tested the status of oxidant handling genes and extent of oxidative stress in the kidneys of adolescent mice exposed to active or passive smoking-equivalent nicotine and compared to the kidneys of adult mice.

Methods: 4- and 24-week-old male C57BL6/J mice - that are equivalent to early adolescence and early adulthood, respectively- had ad libitum access to NIC in their drinking water (200 or 5 µg/ml) for 4 weeks that results in either active (~150 µg/ml) or passive (~10 µg/ml) smoking-equivalent cotinine (stable metabolite of NIC) levels in their plasma. Renal oxidative stress (4HNE content), injury (KIM-1 expression) and function (plasma creatinine) were determined. Expression of select pro- and antioxidant genes were determined by Western blotting and microarray.

Results: Active smoking-equivalent NIC exposure resulted in 2.5 fold increase in renal 4HNE content in adolescent mice compared to vehicle, which is significantly higher (p<0.05) than in adult mice (4 fold). Similarly, renal KIM-1 expression increased 2.2 vs 1.5 fold (p<0.05), respectively, while renal function was unchanged. In contrast, passive smoking-equivalent NIC exposure increased renal 4HNE content only in young (1.4x) but not in adult mice. Interestingly, baseline expression of select pro-oxidant genes (p60hsc) was higher, while expression of some anti-oxidant genes (Nrf2, MrSOD) was lower in the young kidney compared to the adult kidney. In vitro experiments confirmed that high level of p60hsc or low level of Nrf2 or MnSOD exacerbates NIC-mediated ROS production and consequent mitochondrial depolarization-dependent injury in renal proximal tubule cells.

Conclusions: Our results imply that the young kidney exhibits a more pro-oxidant environment than the adult kidney, which may explain their higher sensitivity to NIC exposure-dependent oxidative stress.

Maternal Nutrient Restriction Aggravates Renal Tubular Necrosis and Interstitial Fibrosis After Unilateral Ureteral Obstruction in Rat Offspring
Mariko Hida,1 Tokiya Abe,2 Akinori Hashiguchi,3 Midori Awazu.1 1 Dept of Pediatrics, Keio Univ School of Medicine, Tokyo, Japan; 2 Dept of Pathology, Keio Univ School of Medicine, Tokyo, Japan.

Background: Maternal nutrient restriction not only reduces nephron number but may also affect tubules, interstitium, capillary density, endothelial function, and response to oxidative injury. These changes may become apparent only after a secondary injury to the kidney. We examined the response to unilateral ureteral obstruction (UUO) in the kidney of offspring from control and nutrient restricted rats.

Methods: Six-week old offspring from rats given food ad libitum (CON, n=3) and restricted to 50% food restriction throughout pregnancy (NR, n=6) were subjected to left ureteral obstruction. After 7 days, blood pressure, serum creatinine, urea nitrogen, and urine from the left kidney were examined. Kidneys were stained with Masson trichrome, elastica van Giessen, or CD31. Collagen was quantified by analyzing the color distribution of whole-slide images after color classification of the pixels. The expression of nitrotyrosine was assessed by immunoblot of kidney lysate.

Results: There was no difference between CON and NR in body weight, blood pressure, serum creatinine, and urine protein or osmolality. Blood urea nitrogen was significantly higher in NR than CON (20.8±0.8 vs 17.5±0.1 mg/dL, P<0.05). Macrophocytosis, dilution of similar degree was noted in the obstructed kidney of CON and NR. Tubular necrosis, however, was more extensively observed in NR. There was no difference in the collagen area ratio of the contralateral kidney between CON and NR. The collagen area ratio of the obstructed kidney was increased in NR, while it was a contralateral kidney, and the increase was significantly greater in NR compared to CON (6.8±3.3 vs 2.6±0.5%, P<0.05). There was no difference in immunohistochemical expression of endothelial marker CD31 between CON and NR. The expression of nitrotyrosine, a marker of oxidative stress, was increased in the obstructed kidney in both CON and NR, and the extent was greater in NR.

Conclusions: NR kidneys are more susceptible to ischemia and fibrosis secondary to UUO, which may be due to increased oxidative stress.

Funding: Government Support - Non-U.S.
Methods: Six week old Upk1b/+ mice and wild type mice were intravesically inoculated with a low dose of bacteria. Besides high levels of intravesical bacteria burden and histopathology were analyzed at baseline, 1 and 7 days post infection (dpi). Urothelial permeability was evaluated at baseline using 10,000 dalton FITC-Dextran.

Results: Deletion of Upk1b led to absent urothelial plaques and umbrella cells, as well as reduced expression and apical localization of Upk1a protein. UPEC established intracellular bacterial communities in wild type but not Upk1b/mutant urothelium 1 dpi. Upk1b/+bladders demonstrated reduced urothelial neutrophil infiltrates 1 dpi. Whereas bacterial recovery from urine, bladder, ureters and kidneys was significantly reduced in Upk1b/+ mice (p<0.05, Maren Nestler), comparable burden was observed 7 dpi. Upk1b/+ but not wild type bladder urothelium was permeable to FITC-dextran.

Conclusions: Upk1b serves an essential role in plaque assembly and terminal differentiation of umbrella cells. Whereas umbrella cells and uroplakin plaques facilitate FITC-dextran.

Funding: NIDDK Support

TH-PO478

3D Modeling of the Urinary Tract to Better Understand Urothelial Development and Pathology  
Leah D. Hunter, 1,2 Claudia F. Mosley, 1,2 Ashley R. Jackson, 3 Kirk M. McHugh, 4,10*  
1Div of Anatomy, Ohio State Univ; 2Center for Human and Molecular Genetics, Nationwide Children’s Hospital; 3Biomedical Sciences Graduate Program, Ohio State Univ

Background: Recent evidence implicates a role for urothelium in the pathogenesis of chronic kidney disease (CKD). To better understand these processes, we plan to three-dimensionally (3D) reconstruct and electronically annotate the expression of urothelial markers throughout development.

Methods: Embryonic day E13.5 (undifferentiated), E14.5 (urothelial differentiation onset) FVB/N mice were 3D reconstructed electronically from 10mm serial sections labeled with urothelial antibodies. Molecular annotations were electronically generated using Stereo Investigator software and visualized using Neurolucida Explorer.

Results: E13.5 urothelium displayed highly undifferentiated characteristics, lacking keratin (Krt14 and Krt15) and uroplakin expression, while E14.5 exhibited significant urothelial identity expressing a wide range of markers. Bladder basal urothelial cells express sporadic Krt5, Krt14 and K67. Unexpectedly, Krt5 also localized to intermediate and select superficial cells at E14.5. Shh and p63 uniformly localized to basal and most intermediate urothelial cells. Shh and K67 localized to some superficial urothelial cells. Intermediate and superficial bladder urothelial cells expressed uroplakins. Interestingly, uroplakin expression was more prominent in the dorsal urinary tract, while Shh exhibited more ventral patterning, and Krt14 commonly localized to anterior portions of the caudal bladder urothelium. Krt20 was only minimally expressed at E14.5. Overall, E14.5 bladder urothelial cells expressed 13% Krt14, 5% uroplakins, 1% Krt20, 79% p63, 66% Shh, 21% Ki-67, and 34% Krt13, when normalized to E-cadherin.

Conclusions: Molecular annotation and 3D modeling of the entire embryonic urinary tract will provide novel insight into the expression pattern of urothelial-specific proteins temporally and spatially. Future studies will include 3D mapping of these tissues and markers throughout development.

Funding: NIDDK Support

TH-PO479

Cardiac Hypertrophy Causes Elevation in Circulating c-FGF23 Levels in Mice  
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Background: Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate and calcium metabolism. Besides its bone-sparing effect, intact FGF23 induces left ventricular hypertrophy (LVH). However, it remains unclear whether ventricular hypertrophy affects circulating levels of FGF23.

Methods: The activation of the calcineurin-NFAT (nuclear factor of activated T-cells) pathway plays pivotal roles in the pathogenesis of LVH. Using cardiomyocyte-specific calcineurin targeting transgenic (CnA-TG) mice, we assessed whether ventricular hypertrophy affects circulating levels of FGF23.

Results: CnA-TG mice at 6 weeks developed ventricular hypertrophy. Heart weight-to-body weight ratio was 0.11 ± 0.0014 in CnA-TG mice and 0.0843 ± 0.0033 in wild type (WT) mice. Real time PCR analyses demonstrated that cardiac tissues of CnA-TG mice had higher levels of atrial natriuretic peptide, brain natriuretic peptide, and β myosin heavy chain. Serum C-terminal FGF23 levels of CnA-TG mice was significantly higher than those of WT mice (214.7 ± 68.7 vs. 137.2 ± 19.8 pg/mL; P<0.002), whereas the levels of intact FGF23 were not different between the two groups (CnA-TG mice 26 ± 14.4 pg/mL vs. WT mice 24.7± 6.1 pg/mL; P=0.943). All parameters — body weight, food intake, water intake, urine volume, creatinine clearance, serum phosphate/calcium levels, urinary phosphate/calcium excretion, and fractional excretion of phosphate/calcium were—were not different between the two groups. Although iron deficiency has been reported to decrease serum FGF23, but not cardiac expression. CnA-TG mice had higher transferrin saturation than WT mice (91.5 ± 6.3 vs. 71.7 ± 15.5%, P<0.001).

Conclusions: Cardiac hypertrophy causes elevation in circulating c-FGF23 levels through yet-unidentified mechanisms.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO480

Soluble Klotho and Cardiac FGF23 Modulate Left Ventricular Hypertrophy in CKD Patients  
Maren Leijteh-Nestler, 1 Christian Faul, 1 Dieter Haffner, 1

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Background: Elevated levels of circulating fibroblast growth factor 23 (FGF23) are strongly associated with chronic kidney disease (CKD) mortality, and left ventricular hypertrophy (LVH), a major cause of cardiovascular death in CKD patients. Existence and role of a paracrine cardiac FGF23/Klotho system in the heart, however, remain elusive.

Methods: We conducted a retrospective case-control study in 25 deceased patients with end-stage renal disease, and 25 age and sex-matched healthy controls. At the time of death 18 patients were on dialysis treatment, and 7 patients were transplanted. Myocardial autopsy samples of the left ventricle (LV) were evaluated for endogenous FGF23 expression, FGF1-4, Klotho, calcineurin-NFAT signaling mediated LVH, and genes regulating pathological cardiac remodeling by immunohistochemistry and quantitative real-time PCR analysis. The expression of brain natriuretic peptide (BNP) served as a marker of LVH.

Results: Here, we find that FGF23 is expressed in human cardiomyocytes, and that myocardial expression of FGF23 in concert with Klotho deficiency strongly correlates with the presence of LVH in CKD patients. Enhanced cardiac FGF23 expression is associated with chronic phosphate load, up-regulation of FGF4 expression, and activation of calcineurin-NFAT signaling, an established inducer of cardiac remodeling and LVH. Most important, these changes are reversed after renal transplantation. Using in vitro studies, we observe that cardiomyocytes express and release full-length biologically active FGF23, and that enhanced FGF23 secretion results in cardiac myocyte hypertrophy, which is blocked in the presence of soluble Klotho.

Conclusions: Our results indicate that enhanced levels of FGF23 induce LVH via a paracrine mechanism in settings of Klotho deficiency. In CKD patients, this process is reversed after renal transplantation.

TH-PO481

Role of FGF23 Mediating LVH in a Mouse Model of Klotho Deficiency  
Maren Leijteh-Nestler, 1 Melis Basaran, 2 Makoto Kuro-o, 3 Ioana Alexeanu, 1 Jakob Völk, 1 Florian C. Lang, 1 Dieter Haffner, 1 Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; 2Center for Molecular Medicine, Jichi Medical Univ, Shimotsuke, Japan; 3Dept of Physiology, Univ of Tuebingen, Tuebingen, Germany

Background: In patients with chronic kidney disease (CKD), high serum concentrations of the phosphaturic hormone fibroblast growth factor 23 (FGF23) result in high mortality rate and left ventricular hypertrophy (LVH). FGF23 signals via FGF receptors (FGFR) in the presence of its cofactor Klotho. Recent studies reveal a Klotho independent pathway of calcineurin-NFAT pathway mediating LVH. Our results indicate that enhanced levels of FGF23 induce LVH via a paracrine mechanism in settings of Klotho deficiency. In CKD patients, this process is reversed after renal transplantation.

TH-PO482

Cardiac FGF23 in Concert with Klotho Deficiency Affect Myocardial Fibrosis in Dialysis Patients  
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Background: Pathologic cardiac remodeling, i.e. left ventricular hypertrophy (LVH) and myocardial fibrosis, is a major cause of cardiovascular (CV) death in patients with chronic kidney disease (CKD). Increased circulating levels of fibroblast growth factor 23 (FGF23) are associated with increased mortality in CKD coinciding with enhanced CV Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FGF23 is causatively involved in the development of age-related LVH. A recent translational study from our group demonstrated that VDRAs, particularly paricalcitol, reduced cardiac fibrosis acting on COL1A1, MMP2 and CTGF expression, probably through the regulation of miR-29b and miR-30c. These miRNAs could be useful serum biomarkers for cardiac fibrosis and also potential new therapeutic targets.

**Results:** All VDRAs prevented cardiac fibrosis, achieving statistically significant differences as compared to the paricalcitol-treated group. A reduced expression of miR-29b and miR-30c was observed in heart of both paricalcitol treated groups, and associated with both improved cardiac function and reduced LVH. However, the extent of cardiac remodeling was greater in the paricalcitol-treated groups as compared to controls.

**Conclusion:** The VDRAs, particularly paricalcitol, reduced cardiac fibrosis acting on COL1A1, MMP2 and CTGF expression, probably through the regulation of miR-29b and miR-30c. These miRNAs could be useful serum biomarkers for cardiac fibrosis and also potential new therapeutic targets.

**Funding:** National Institutes of Health, National Heart, Lung, and Blood Institute (HL108502, HL110156) and K08 HL117291 (S.G.S.).

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

**Underline represents presenting author.**

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Memorandum KO phenotype, and we established kidney-specific Memo KO mice. Uremia (normal 1.0, uremic 3.01 -//- mice failed to mitigate FGF23 increments with CKD progression, as CD14 mice with CKD exhibited comparable serum FGF23 concentrations to WT mice with CKD (9598.7 ± 504.7 pg/ml, p=NS; n=9 per group).

Conclusions: Bacterial endotoxin stimulates FGF23 production by bone by a mechanism that is partially dependent on CD14 signaling; however, the deletion of CD14 in a CD14 mouse model fails to attenuate the rise in serum FGF23 that accompanies kidney injury.

Funding: NIDDK Support

TH-PO490

Inflammation Affects FGF23 Production in Uremia

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Background: FGF23 increases since early stages of chronic kidney disease (CKD). In CKD, other factors as inflammation may affect the phosphaturic action of FGF23, and higher FGF23 may be required to control P. We aimed to determine if the production of FGF23 is affected by LPS-induced inflammation in experimental CKD.

Methods: 5/6 Nx rats on diets with 0.2% or 0.4%P received LPS for 15 days. Sham rats also received LPS. Blood, urine, and kidney samples were collected.

Results: Nx rats on a 0.2%P diet had lower FGF23 compared to sham, whereas a 0.4%P diet increased FGF23 levels. LPS-treated groups had more than a 3-fold increase in plasma levels of FGF23 as compared with their respective controls. Fractional excretion of P in sham and Nx rats was not modified by the administration of LPS. No differences in renal Klotho expression were found between sham and rats on a 0.2%P diet. A 50% reduction in Klotho was seen in 5/6 Nx rats on the diet containing 0.4%P. The administration of LPS to sham rats reduced Klotho expression by approximately 25%. In 5.6 Nx rats on 0.2% and 0.4%P, LPS reduced Klotho by 70% and 50%, respectively.

Conclusions: The prevention of the increase in FGF23 associated with CKD is not possible in the presence of inflammation.

Funding: National Institute of Diabetes and Digestive and Kidney Disease.
Methods: Sprague Dawley rats (250 g) were acclimatized to a powdered 1.2% Ca, 0.6% P diet for 2 weeks. These rats were either continued on this diet supplemented with 3% NaCl (n=9) or 3% NaHCO3 (n=10) for an additional 8 d. Blood was then obtained by cardiac puncture for measurement of FGF23 by ELISA (intact FGF23, Immutopics) as well as standard metabolic parameters.

Results: Feeding rats NaHCO3, lead to a significant fall in serum FGF23 and an increase in serum HCO3 compared to feeding NaCl (Table; values are mean±SE; *, p< 0.05; **, p<0.01). Serum POx fell with NaHCO3 as did both serum Ca and creatinine with NaHCO3 compared to NaCl fed rats.

Conclusions: Provision of oral NaHCO3, sufficient to raise serum HCO3, led to a significant fall in serum FGF23 in normal rats supporting the hypothesis that (pH or HCO3) directly regulates FGF23; however, we cannot exclude that a NaHCO3-induced change in POx contributed to the change in FGF23. If comparable acid-base regulation of FGF23, now demonstrated in vitro and in vivo, is confirmed in humans, it suggests that correction of acidosis in patients with CKD may lower their elevated FGF23 levels.

Funding: NIDDK Support

TH-PO492

Metabolic Acidosis Increases Osteoblastic MEPE Expression in Parallel to the Increase in Fibroblast Growth Factor 23

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Background: Serum fibroblast growth factor 23 (FGF23) increases with the severity of chronic kidney disease (CKD), leading to decreased renal tubular phosphate (Pi) reabsorption and serum 1,25(OH)2D. FGF23 is synthesized in osteoblasts and osteocytes; however, the primary factors regulating its production are not clear. Patients with CKD have decreased renal net acid excretion leading to metabolic acidosis (MET). During MET, acid is buffered by bone with release of mineral calcium and Pi. MET directly stimulates FGF23 in mouse bone and primary osteoblasts after the same signaling pathways that lead to MET-induced bone resorption. To further characterize the regulation of FGF23 by MET we utilized primary osteoblasts to study gene expression pathways upstream of FGF23 production, including the major extracellular phospholipid, MEPE, and the phosphate-regulating endopeptidase, PHEX.

Methods: Confluent osteoblastic cells isolated from neonatal mouse calvariae were incubated in neutral (NTL, pH=7.50, Pco=39 mmHg, [HCO3]=30 mmHg) or acid (MET, pH=7.20, Pco=39 mmHg, [HCO3]=14 mm) medium. Specific RNA gene expression was analyzed by real time PCR with expression normalized to RPL13A and calculated relative to non-incubated cells.

Results: Maximal stimulation of FGF23 was found at 24h (MET=7.26±1.55 vs NTL=7.35±0.64, p<0.05). MET significantly increased MEPE RNA expression as early as 6h compared to NTL (relative expression: MET=2.23±0.41, vs NTL=1.19±0.16, p<0.05) with a further increase observed after 24h. There were no significant differences in PHEX expression in response to MET compared to NTL, although there was a progressive decrease in PHEX expression in both groups over 24h.

Conclusions: Thus, MET stimulation of MEPE expression may be an initial step by which MET increases FGF23 production in mouse osteoblasts. By better understanding how MET stimulates FGF23 expression we may gain a directed approach towards interventions for MET, especially in CKD patients, can be devised to not only prevent bone resorption but also lower FGF23.

Funding: Private Foundation Support

TH-PO493

Effect of High-Dose and Flux Hemodialysis on Circulating Markers of Mineral Metabolism in the HEMO Study

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Background: There are limited and somewhat contradictory data in the literature on the effects of high vs low dialysis clearance and high vs low flux circulating markers of mineral metabolism.

Methods: The HEMO Study was a randomized multicenter study of the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Fibroblast growth factor 23 (FGF23, pre-specified primary endpoint for these analyses), serum phosphorus, and 25-hydroxivitamin D (25(OH)D) were measured in stored serum samples. We used multi-state analyses to analyze the dose and flux effects on each mineral metabolism marker while accounting for mortality. We estimated the proportions of patients in 5 ordered states (S) for serum phosphorus, 25(OH)D and FGF23: S1 = deceased (score=0); S2 = alive in highest quartile (score=1); S3 = alive in intermediate quartile (score=2); S4 = alive in lowest quartile (score=3); and S5 = alive in lowest quartile (score=4). The average rank was computed over 3 years of follow-up and compared between the randomized groups.

Results: Randomized patients had high rates of coexisting conditions 45% had diabetes, 40% had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups.

The state distributions for FGF23 each year by dose (KTV) group and by flux group are shown in Figure 1. FGF23 differed significantly between dose groups (p=0.02) but not between flux groups (p=0.17). No significant differences were observed for serum phosphorus or 25(OH)D.

Funding: Private Foundation Support

TH-PO494

Factors for Persistent Low or High FGF-23 Levels in Maintenance Hemodialysis Patients

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Background: The aim of this study was to assess the association between serum fibroblast growth factor-23 (FGF23)-23 and mortality, and to determine the factors for persistent low or high FGF-23 levels, in maintenance HD (MHD) patients.

Methods: We examined serum intact FGF-23, age, dialysis vintage, presence of diabetes, BMI, blood pressure, serum phosphorus, 25(OH)D and FGF23, hs CRP, serum albumin, nPCR, geriatric nutritional risk index (GNRI), serum phosphate, serum calcium, iPTH, active vitamin D dosage, and phosphate binders and/or cinacalcet in 332 MHD patients in September of 2012, 2013 and 2014. Coronary artery calcification score (CACS) was measured in a subgroup (n=173). According to quartile (Q) of FGF-23 in 2012, mortality was assessed by Kaplan-Meyer and adjusted Cox models. Patients with FGF-23 Q1-Q1-Q1 were categorized in Group 1, patients with FGF-23 Q4-Q4-Q4 in Group 3, and the others in Group 2.

Results: Median age and dialysis vintage were 69 years and 66 months, respectively, at baseline. During the 2 years, 71 patients died and 24 patients left our hospital. Baseline FGF-23 levels (pg/ml) were <310 (Q1), 310-1489 (Q2), 1490-5294 (Q3) and >5294 (Q4) (P<0.05), with cumulative survival rates of 65.4%, 78.9%, 85.1% and 80.6%, respectively (P<0.05), and hazard ratios (HRs) for death of 1.0, 0.6, 0.4 and 0.5, respectively, in univariate model. However, there was no significant association between Q of FGF-23 level and mortality in multivariate model. HR for death of CACS was 1.1 (P<0.01), but there were no differences in CACS in patients based on FGF-23 level. Significant associations between CACS and diabetes (OR: 3.5), age (OR: 1.1), serum phosphate (OR: 0.4) and vitamin D dosage (OR: 0.2), and between Group 3 and serum phosphate (OR: 2.0), iPTH (OR: 1.004) and vitamin D dosage (OR: 1.9), were observed (P<0.05).

Conclusions: FGF-23 in the lowest quartile showed the lowest 2-year cumulative survival rate in MHD patients, factors for persistent low FGF-23 levels were diabetes, age, serum phosphate and active vitamin D dosage.

Funding: Private Foundation Support

TH-PO495

Maintenance of Residual Diuresis and Type of Dialysis Can Influence FGF23 Levels

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Background: Bone mineral disorders are common in patients (pts) with end stage renal disease (ESRD). In particular, hyperparathyroidism can be frequently seen in pts undergoing peritoneal dialysis (PD) and hemodialysis (HD). Recently, several studies investigated the role of fibroblast growth factor 23 (FGF23) in regulation of renal phosphate excretion in ESRD pts. However, patients with residual diuresis (RD) seem to better control serum phosphorus levels than those without RD. The aim of our study was to determine if the dialysis modality and the preservation of RD influence serum levels of FGF23.

Methods: We performed a cross-sectional study in two groups of pts: HD and PD. The variables analyzed were creatinine, urea, calcium, phosphate (Phosp), i parathormone (intact PTH) and eFGF23 (C-term). The urinary output collection refers to one week. All p value were sides and statistical significance was set at p<0.05. Statistical analysis was performed by SPSS version 20.

Results: A total of 122 pts were enrolled (58HD,64PD).The mean age of HD pts was 64±15±14,25yrs and of PD pts 62±13,86 yrs. RD was present in 78 pts (65,46%)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Iron Deficiency Is Associated with Elevated FGF23 Levels in Pediatric CKD

Farah Y, 1 Bradley Warady, 1 Susan L. Furth, 2 Harald Jüppner, 3 Isidro B. Salusky, 1 Anthony A. Portale, 4 Myles S. Wolf, 1 Northwestern Univ; 2 Children’s Mercy Hospital; 3 Children’s Hospital of Philadelphia; 4 MGH; 5 UCLA; 6 UCSF.

Background: FGF23 excess contributes to CV disease and death in CKD. Mechanisms of elevated FGF23 levels in CKD are incompletely understood. Iron deficiency is a novel stimulus of FGF23 production. Given high rates of iron deficiency in CKD, we hypothesize that iron deficiency is related to higher FGF23 levels in pediatric CKD and that iron deficiency induced by proteinuria contributes to higher FGF23 levels in glomerular diseases.

Methods: We measured ferritin, TSAT, C-terminal (c) FGF23, CRP, and urine protein/creatinine (p/cr) in 551 children in the CKD Study.

Results: Mean age was 10.2 ± 4.4 yrs; 62% were male; mean eGFR was 53 ± 19 mL/min/1.73m2; mean TSAT was 26 ± 13%, median ferritin was 46 ng/mL (IQR 27-81); median urine p/cr was 0.33 mg/mg (IQR 0.10-1.00); median cFGF23 was 114 RU/mL (IQR 80-185). cFGF23 correlated inversely with ferritin (p = 0.055) and CRP (p = 0.049), proteinuria (p < 0.001), and phosphate (p < 0.001). Grouping proteinuria into low or high grade (p/cr > 3) revealed no differences in ferritin and TSAT, but TIBC was lower (288 vs 310 µg/dL, p = 0.016). cFGF23 levels were significantly elevated in the lowest ferritin quartile, preferentially in early stages of CKD (Figure).

Conclusions: In this study, we observed elevation of cFGF23 and CRP in iron deficiency patients with CKD. This might be because iron-deficiency stimulates FGF23 transcription and its cleavage simultaneously just as reported in non CKD women.

Iron Deficiency and serum FGF23: buffy coat effect

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In multivariate analysis that included proteinuria and CRP, only lower eGFR, glomerular disease, higher phosphate, and lower ferritin were independent predictors of higher cFGF23 levels (p < 0.001 for all). The relationship between proteinuria and cFGF23 was mitigated when ferritin was added to the multivariable model.

Background: FGF23 excess contributes to CV disease and death in CKD. Mechanisms of elevated FGF23 levels in CKD are incompletely understood. Iron deficiency is a novel stimulus of FGF23 production. Given high rates of iron deficiency in CKD, we hypothesize that iron deficiency is related to higher FGF23 levels in pediatric CKD and that iron deficiency induced by proteinuria contributes to higher FGF23 levels in glomerular diseases.

Methods: We measured ferritin, TSAT, C-terminal (c) FGF23, CRP, and urine protein/creatinine (p/cr) in 551 children in the CKD Study.

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Iron Deficiency and serum FGF23: buffy coat effect

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osteocytes but it is unclear whether it could also modulate FGF23 synthesis. Our research objectives were to examine the effect of intravenous iron supplementation on the parameters of mineral metabolism in patients with CKD.

**Methods:** The study included 35 non-dialysis patients with CKD stages 3-5. Each patient received once-daily 100 mg iron solution (Ferric oxide saccharated complex; Vifor, France) for 5 consecutive days. Iron doses were administered in a slow 40-min. intravenous infusion. On day 1 and 3 at baseline and 2 hours after each dose administration, calcium (Ca), phosphorus (P), parathormone (PTH), intact-FGF23 (iFGF23), C-terminal-FGF23 (cFGF23), bonealkaline phosphatase (BAP) were assessed. The measurements were repeated on day 6.

**Results:** Two hours after the iron infusion and on day 6 a significant increase in serum iFGF23 was observed (from 257±44.5 to 326.3±52.9 ng/ml on day 1; p<0.005 and to 451.4±601 on day 6; p<0.005). The concentration of cFGF23 was reduced in parallel only on day 1 (from 43.6±41.0 to 1.5±3.3; p<0.005). Serum phosphorus concentration decreased significantly on day 1 two hours after iron infusion (from 1.75±0.6 to 1.53±0.35 mmol/l; p=0.005). On following days the changes of cFGF23 and phosphorus concentration were not significant. The serum concentrations of Ca, BAP and PTH were unchanged throughout the study.

**Conclusions:** Intravenous iron supplementation may interfere with the mechanisms governing both production and degradation of FGF23 thereby leading to transient hypophosphatemia at the beginning of iron therapy.

**TH-PO500**

The Increase of Fractional Excretion of Phosphorus Induces FGF23 Resistance due to a Decrease in Renal Klotho

**Background:** Phosphate is critically important for biological functions, particularly during growth periods. Phosphate deficiency causes bone diseases such as rickets and osteomalacia. On the other hand, excess intake of dietary phosphate increases secretion of fibroblast growth factor 23 (FGF23) and parathyromide (PTH) to maintain plasma phosphate level. FGF23, is a potent phosphataturic factor, binds to α-klotho / FGF complex in the glomeruli to promote excretion of phosphate into urine. In addition, excess intake of dietary phosphate also decrease in renal α-klotho expression. Downregulation or lack of α-klotho induces a premature aging-like phenotype such as ectopic calcification and osteoporosis resulted from hyperphosphatemia. However, the effects of high phosphate diet on renal α-klotho expression and renal aging are still unknown.

**Methods:** To investigate that, we used C57BL/6 mice aged 3-4 week old under a rapid growth phase. Mice were fed 0.02, 0.3, 0.6, 0.9, 1.2, 1.5 or 1.8% phosphate diets for 7 days beginning just after weaning at 3 week old. Results: As a result, elevation of plasma phosphate and FGF23 levels, and decrease in renal α-klotho expression were observed as the content of dietary phosphate increased. In addition, renal calcification was clearly observed in mice fed 1.5 or 1.8% phosphate diets.

The renal calcification did not observed when the 8 week-old mice were fed with 1.5 or 1.8% phosphate diet for 7 days. These results suggest that the effects of high phosphate diet during growth periods have a much greater adverse effect on renal α-klotho expression and morphology of the kidney as compared to a similar investigation during maturation periods.

**Conclusions:** In conclusion, excessive dietary phosphate intake during growth periods such as just after weaning period decreases in renal α-klotho expression relating to premature aging-like lesions.

**Funding:** Government Support - Non-U.S.

**TH-PO502**

The Secreted Klotho mRNA Transcript Is Continuously Degraded by Nonsense-mediated mRNA Decay And Its Splicing Is Dysregulated After Kidney Damage

**Background:** Klotho is an anti-aging gene of which two mRNA transcripts have been identified: one corresponds to the full 5-exon coding sequence and the other, alternatively spliced, consists of exons 1-3 and 5-30 downstream base pairs, forming a stop codon. The latter mRNA transcript is thought to code for a soluble Klotho protein. While soluble Klotho proteins can be detected in blood, urine, and cerebrospinal fluid, a product of this alternative transcript has never been identified. Nonsense-mediated mRNA decay (NMD) research predicts that the premature stop codon induces continuous degradation during translation.

**Methods:** We first assessed the mRNA transcripts in human kidney and HK-2 cells by RT-PCR and DNA sequencing. We then blocked NMD in HK-2 cells using cycloheximide (CHX) (100 µg/ml) for 2, 4, 6, or 8 h, or using XRN1 siRNA for mRNA degrading enzyme exoribonuclease 1, to assess possible accumulation of the alternative mRNA by RT-PCR and densitometry. Then, we assessed whether splicing was different in normal human kidneys (N=11) and in chronic rejection transplanted (CRT) kidneys (N=4).

**Results:** Expression of both Klotho mRNA transcripts was confirmed in human kidney and in HK-2 cells by RT-PCR and DNA sequencing. CHX-induced inhibition of translation increased the "secreted" membrane-bound Klotho mRNA ratio from 0.14±0.02 to 0.44±0.06 (p<0.001). Preliminary data show that silencing of XRN1 has the same effect. Furthermore, already in normal kidneys, there was a marked, reproducible variation in splicing ratios, ranging from 0.03±0.01 to 0.20±0.02. In CRT kidneys, Klotho mRNA was expectedly down-regulated and splicing was skewed towards the non-functional alternative splice variant.

**Conclusions:** The alternative Klotho mRNA contains a premature stop codon and is a likely NMD substrate. Soluble Klotho would therefore be cleaved Klotho only. Furthermore, in damaged kidneys, splicing of the Klotho gene is dysregulated, which constitutes a new mechanism of Klotho down-regulation.

**Funding:** Government Support - Non-U.S.

**TH-PO503**

Genetic Deletion of NaPi-2c Rescue Phenotype of Klotho Knockout Mice without Improving Severe Hyperphosphatemia

**Background:** SLC34A3/NaPi-2c is one of the renal sodium dependent phosphate (Pi) transporters. Mutation of human NaPi-2c causes hereditary hypophosphatemic rickets with hypercalciuria (HRH1). Thus, NaPi-2c may have an important role on renal Pi reabsorption and bone mineralization in humans. The physiological role of NaPi-2c, however, has not been completely explained yet. NaPi-2c knockour (NaPi-2c/-) mice showed hypercalciuria, but did not show any Pi abnormality. Recently, Hernand N. et al. reported that kidney specific NaPi-2c conditional knockout mice did not show any abnormality. These results suggested that NaPi-2c has minor role in the Pi homeostasis. To discover the role of NaPi-2c in kidney, we examined genetic inactivation of NaPi-2c in klotho knockout (klotho/-) mice.

**Methods:** To obtain the klotho and NaPi-2c double knockout (klotho/-/NaPi-2c/-) mice, we crossed klotho/- mice with NaPi-2c/- mice. Total body weight of each of wild-type, klotho/+, NaPi-2c/-, KLD2 DKO and NaPi-2c/- mice was taken every week. Urine and blood were obtained for biomedical measurements at the several ages of weeks. Tissues were obtained from each mice for histological and calcification analysis.

**Results:** Genetic disruption of NaPi-2c significantly increased body weight and extended the life span of klotho/+, NaPi-2c/-, KLD2 DKO and NaPi-2c/- mice. NaPi-2c/- mice were viable and larger in size than klotho/+, but smaller than wild-type and NaPi-2c/- mice. KLD2 DKO mice showed slightly decreased plasma Pi levels at early hood, but not adult hood. Plasma FGF23 levels were extremely high in KLD2 DKO mice as well as klotho/+. mice. Conclusions: Our finding demonstrated that NaPi-2c genetic deletion rescued the phenotype of klotho/- mice without improving severe hyperphosphatemia.

**Funding:** Government Support - Non-U.S.
TH-PO504
Klotho/FGF23-Independent and ERs Mediated Direct Downregulation of NaPi-IIa by Estrogen in the Mouse Kidney Proximal Tubule
Hassane Amlal, Sulaiman Sheriff, Rose P. Webster. Internal Medicine, Univ of Cincinnati, Cincinnati, OH.

Background: Estrogen treatment is associated with renal wasting of inorganic phosphate (Pi) and hypophosphatemia in rats and humans; however the molecular and signaling mechanisms mediating this effect are still not fully understood.

Methods: To determine the roles of estrogen receptor isoforms (ERα and ERβ) and Klotho/FGF23 pathway in these effects, we studied the effects of estrogen on renal Pi handling in the kidneys of mice with null mutations of ERα or ERβ or Klotho and their wild-type (WT) littermates. Accordingly, Females ERα Knockout (KO), ERβKO and WT mice were placed in metabolic cages and had free access to food and distilled water. After adjustment, mice were injected daily with 17β-estradiol (estrogen) or vehicle for 3 days.

Results: The results indicate that estrogen-treated WT and ERβ KO mice exhibited a significant phosphaturia despite a reduction in food intake. The phosphaturic effect resulted from a significant downregulation of NaPi-IIa with no change in their mRNA expression levels. Interestingly, these effects were abolished in those recieving placebo. Other endpoints were the proportion of participants having 30% reduction in PTH, hand grip strength and fatigue, assessed by a questionnaire, and differences in calcium, phosphate, calcitriol and FGF23.

Conclusions: Suboptimal levels of calcitriol (25D) may accelerate secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD). The aim of this study is to determine if a substantial increase in 25D has beneficial effects on mineral metabolism, muscle strength or fatigue.

TH-PO506
A Double Blind Randomized Trial to Compare the Effect of High-Dose Cholecalciferol versus Placebo on Secondary Hyperparathyroidism in Chronic Kidney Disease Stage 3-4
Per-Anton Westerberg, Gunnar Sterner, Osten Ljunggren, Torbjorn Linde. Medical Sciences, Univ Hospital, Uppsala, Sweden; Nephrology, Skåne Univ Hospital, Malmö, Sweden; Internal Medicine, Ryhov County Hospital, Jönköping, Sweden.

Background: Suboptimal levels of calcitriol (25D) may accelerate secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD). The aim of this study is to determine if a substantial increase in 25D has beneficial effects on mineral metabolism, muscle strength or fatigue.

Methods: We conducted a double blind randomized trial (EudраCT-2011-002586-38) of cholecalciferol 8000IU/day versus placebo in 97 adult CKD-3 patients with mild SHPT and a 25D level below 75 nmol/L. The primary endpoint was the difference in mean change, after 12 weeks, in intact PTH between those treated with cholecalciferol as compared to those receiving placebo. Other endpoints were the proportion of participants having a 30% reduction in PTH, hand grip strength and fatigue, assessed by a questionnaire, and differences in calcium, phosphate, calcitriol and FGF23.

Conclusions: High dose cholecalciferol increases calcitriol and alleviates the development of SHPT in CKD, without causing hypercalcemia or influencing muscle strength or fatigue.

TH-PO505
Effect of Calcitriol on Serum Hepcidin in Individuals with Chronic Kidney Disease
Bhupesh Panwar, Orlando M. Gutierrez. Univ of Alabama.

Background: Anemia is highly prevalent in CKD. Elevated hepcidin levels are an important mediator of disordered iron metabolism, a key mechanism underlying anemia of CKD. Vitamin D was recently shown to reduce hepcidin levels in healthy individuals. We examined whether treatment with calcitriol reduces serum hepcidin in individuals with CKD.

Methods: A double blind randomized trial (RCT) of cholecalciferol 8000IU/day vs. placebo in 97 adult CKD3-4 patients with mild SHPT. Baseline serum hepcidin was 615±242 pmol/L in the placebo group. Serum hepcidin was measured in blood samples taken at baseline, 2, 4, 6 and 8 weeks on treatment.

Results: There were no significant differences in serum hepcidin, iron parameters, or hemoglobin between the 2 groups. There was a significant increase in serum calcium at 6 weeks in the calcitriol arm compared to the placebo.

Conclusions: Calcitriol did not reduce serum hepcidin levels among individuals with stage 3/4 CKD. Future studies are needed to assess if nutritional forms of vitamin D affect hepcidin levels in CKD.

Table 1. Median[IQR] or Mean±SD of outcome parameters over a 6 week follow-up

<table>
<thead>
<tr>
<th>Baseline</th>
<th>3 days</th>
<th>1 week</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>76[46,124]</td>
<td>77[46,122]</td>
<td>73[40,112]</td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saturation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitrol</td>
<td>23.5±1.25</td>
<td>24.1±0.79</td>
<td>24.9±1.58</td>
</tr>
<tr>
<td>Placebo</td>
<td>23.5±0.8</td>
<td>23.6±0.78</td>
<td>22.7±0.7</td>
</tr>
<tr>
<td>Hemoglobin</td>
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<tr>
<td>Calcitrol</td>
<td>12.3±1.7</td>
<td>12.2±1.7</td>
<td>12.2±1.9</td>
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<tr>
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<tr>
<td>Calcium</td>
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</tr>
<tr>
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<td>9.21±0.43</td>
<td>9.28±0.42</td>
<td>9.32±0.48</td>
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<tr>
<td>Placebo</td>
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</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Paricalcitol and Calcitriol Exhibit Differential Effects on Gene Expression in Human Arteries.  

Tzyyushu Li, 1  Lisun Ho, 2 Thomas F. Hiemstra, 2 Daniel Zehnder, 3 Li-Li Hsiou. 1  Renal Div, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2  Chemical Engineering, Massachusetts Inst of Technology, Cambridge, MA; 3  School of Clinical Medicine, Univ of Cambridge, Cambridge, United Kingdom; 4  Univ Hospital Coventry and Warwickshire NHS Trust, Coventry, United Kingdom.

Background: Vitamin D deficiency is common in patients with CKD, and therapeutic use of vitamin D receptor activators (VDARs) may improve cardiovascular outcomes. The molecular targets of the VDARs calcitriol and paricalcitol are incompletely understood.

Methods: We studied gene expression in human arterial explants from healthy individuals and CKD patients after exposure to calcitriol, paricalcitol or vehicle. We selected the differentially expressed genes based on log2 ratio fold changes (∆).

Results: Calcitriol and paricalcitol exhibited differential effects on gene expression. Calcitriol induced expression of Toll-like receptor 4 (TLR4) (a 14.369) and Nuclear Factor of Activated T-cells (NFAT) (∆ 38.51) in healthy arteries. In CKD arteries, Calcitriol selected the leading differentially expressed genes based on log 2 ratio fold changes (∆).

Conclusions: Our data demonstrate differential effects of calcitriol and paricalcitol on gene expression in human arterial explants. This finding may provide important mechanisms in developing therapeutic strategies for the roles of VDARs. Further investigation is needed.

Funding: Private Foundation Support

TH-P0509

Paricalcitol and FGF23 Effects on the Progression of Cardiac Disease in Pediatric Hemodialysis  

Wacharee Seeharanong,1 Chryso P. Katsoufis,2 Arpit Kumar Agarwal,2 Sethuraman Swaminathan,2 Phillip Ruiz,2 Gaston E. Zilleruelo,2 Carolyn L. Abitbol,1 Michael Freundlich.1 1  Pediatric Nephrology, Univ of Miami; 2  Pediatric Cardiology, Univ of Miami; 3  Pathology, Univ of Miami, Miami, FL.

Background: FGF23 induces and Paricalcitol (Pc) attenuates left ventricular hypertrophy (LVH) in uremic animals. In adults CKD, Pc has not yet consistently improved LVH. We hypothesized that in young hemodialysis (HD) patients, Pc improves LVH and function despite FGF23 levels.

Methods: Twenty patients (16±4 years) on HD (31±17 months) on Pc >6 months underwent longitudinal biochemical and echocardiography (Echo1 and Echo2) measurements. LV mass index (LVMi) reflects LV structure and diastolic dysfunction, LVMI is an echocardiographic surrogate of LV systolic function. To assess LV diastolic function, early (E), late (A) diastolic trans-mitral flow velocities were measured with E/A, E/Em and E/Em ratios calculated. Values >2 Z-scores defined diastolic dysfunction. Echo results were reported as heart-age adjusted Z-scores. The ratio of the cumulative average weekly Pc dose to the prevalent logFGF23 level (Pc/logF) was used as a reflection of the patients metabolic status.

Results: Overall Z-LVMi (1.71±1.3 vs. 2.0±1.8) was unchanged; LVH prevalence, from 55% to 45% (Z-LVMI in 35% vs0.01); SF was normal throughout. Abnormal E, Em and E/Em (in 30-61%) all improved by 25% on Echo2. Z-LVMi correlated with LVMI, wall thickness and E/Et (all r <0.5, p<0.05). The urinary excretion of phosphate was greater in the HP group (p<0.05). The ratio of the cumulative average weekly Pc dose to the prevalent logFGF23 level (Pc/logF) was used as a reflection of the opposing hormonal effects.

Conclusions: While serum PTH levels were similar, our data suggested that the effect of Pc appeared to be associated with the difference in the expression of VDR and Klotho in the HD group.

Funding: Private Foundation Support

TH-P0510

A Phase 2A Pharmacokinetic Study of an Oral Vitamin D Compound (2MD) in Patients on Dialysis with Secondary Hyperparathyroidism  

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Background: Dialysis patients frequently receive a vitamin D receptor agonist such as the endogenous hormonal form of the vitamin, calcitriol, or an analog (e.g. paricalcitol) for treatment of secondary hyperparathyroidism. Although effective, these drugs can cause hypercalcemia. 2MD is a new vitamin D analogue that suppresses parathormone (PTH) at doses that do not adversely affect serum calcium and phosphorus.

Methods: We conducted a phase 1, open-label, single-blind, randomized, parallel-group, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of 2MD in 3 doses in patients on dialysis. We evaluated E/Et, NFAT and serum FGF23 and Ca (adjusted for dialysate Ca) over 4 weeks. Results were reported as height-age adjusted Z-scores. The ratio of the cumulative average weekly dose of 2MD orally after each stage of treatment for the next 4 weeks. PK studies were performed after the first and final dose.

Results: All eleven patients completed the study. At 4 weeks, the half-life (t1/2) of 2MD was 50.9 ± 25.3h, time to maximum plasma concentration (tmax) was 4.0 ± 2.4h and concentration maximum (Cmax) was 3.4 ± 0.8966ng/ml, while the area under the curve (AUC [0.96h]) was 148.0 ± 38.776ng/ml. Similar results were observed after a single dose. Mean PTH was suppressed 32% and calcium and phosphorus did not change significantly.

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

Underlines represent presenting author.
this model. Both VDRMs (CAL: 13.4, P<0.05 vs UC, and VS: 105: 6.0, P<0.05 vs UC) significantly increased in TNFα levels. A 25(OH)D level significantly increased in the UC (P<0.05 vs NC), but not altered by the VDRMs. No statistical significance was observed in serum calcium and phosphorus among all 4 groups. The mRNA expression of PCNA in the aortic tissue was significantly increased in the UC (15.8- fold) compared with the NC (P<0.05), which was significantly suppressed by the VDRMs (CAL: 9.2- fold, P<0.05 vs UC, and VS: 105: 5.0-fold, P<0.05 vs UC). A similar observation was made in the Nox4 mRNA levels (7.2-fold in UC, 1.3-fold in CAL, and 1.8-fold in VS:105).

Conclusions: These results demonstrate that VS-105 has a suppressive effect on various inflammatory mediators. Further study with a preclinical state of CS nephropathy rats in which oxidative stress is involved, suggesting that VS-105 exhibits anti-inflammatory pleiotropic effects.

Funding: Government Support - Non-U.S.

TH-PO513
Differential Effects of Ergocalciferol and Cholecalciferol Therapies in Chronic Kidney Disease Patients with Vitamin D deficiency
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Background: Nutritional vitamin D deficiency is common in patients with chronic kidney disease (CKD) and may contribute to a variety of comorbidities. Prospective studies assessing the comparative efficacy of cholecalciferol and ergocalciferol for correction of 25(OH)D deficiency in CKD patients are lacking.

Methods: We conducted a prospective, randomized, double-blinded trial to assess the relative efficacy of ergocalciferol versus cholecalciferol, 50,000 IU weekly for 12 weeks, to raise serum 25(OH)D levels in vitamin D-insufficient CKD patients (n = 41). Serum 25(OH)D concentrations were assessed at baseline (week 0), 4 weeks (week 4), 6 weeks (week 6), 8 weeks (week 8), 12 weeks (week 12), and 6 months (week 24) post-therapy (week 12), and six weeks following discontinuation of therapy (week 18).

The primary outcome was the absolute change in 25(OH)D from baseline to 12 weeks. Secondary outcomes included change in 25(OH)D from weeks 12 to 18, as well as changes in PTH and 1,25(OH)2D. The dose of cholecalciferol was to 35 mcg/day for patients with stage III-IV and serum 25-OHD<30 ng/mL. The patients were randomized into two groups: conventional-dose ergocalciferol after 12 weeks of treatment. The high-dose treatment might be needed to increase serum 25-OHD levels and might improve bone and mineral homeostasis. In the high-dose-group treated with double dosage of ergocalciferol from the recommendation.

Conclusions: The conventional-group treated with ergocalciferol as recommended by K/DOQI guidelines or the high-dose group might increase serum 25(OH)D levels significantly and may be beneficial in the treatment of vitamin D deficiency in patients with chronic kidney disease (CKD). Further studies are needed to validate these findings.

Funding: NIDDK Support, Private Foundation Support

TH-PO515
Effectiveness of High Dose Ergocalciferol versus Conventional Dose Ergocalciferol on 25-Hydroxyvitamin D Level in Chronic Kidney Disease Patients with Vitamin D Deficiency
Bancha Satrapiwut,1 Siwimon Aroonporn,1 Panhubpa Choochivit,1 Uppatham Supasynd,1 1 Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand; 2 Phramongkutklao Hospital.

Background: Patients with chronic kidney disease (CKD) have an exceptionally high prevalence of vitamin D deficiency. Serum 25(OH)D is important biomarker associated with risk of mortality and mineral and bone disorders in CKD patients. There was limitation with evidence of dosage for ergocalciferol supplement in CKD population.

Methods: This was an open labeled, randomized, controlled study in CKD patients with stage III-IV and serum 25-OHD<30 ng/mL. The patients were randomized into two groups: conventional-group treated with ergocalciferol as recommended by KDOQI guidelines or high-dose-group treated with double dosage of ergocalciferol from the recommendation. Serum testing including 25-OHD, intact PTH, phosphate, and calcium were performed at baseline and 12 week post therapy.

Results: Sixty-three patients with average aged 69.23±11.62 years were included. Characteristics of the two groups were similar at baseline. At the end of the 12-week, the mean 25-OHD level significantly increased from 18.98±7.23 to 27.95±10.06 ng/mL in the conventional-group (p<0.001) and increased from 18.15±7.44 to 32.08±9.04 ng/mL in the high-dose-group (p=0.001). There was also a significantly increase 25-OHD levels in high-dose-group compared with conventional-group (13.64±9.87± vs 8.52±6.77 ng/mL, p< 0.03). Moreover, there was a significantly greater decrease in serum PTH level in the high-dose-group than in the conventional-group (−16.75±26.42 vs. −0.25±26.76 ng/mL, p= 0.03). Serum calcium and phosphate were not significantly different between the groups. There was no adverse effects associated with the treatment.

Conclusions: The study demonstrated that oral high-dose ergocalciferol had higher efficacy for increasing 25-OH and decreasing PTH level in patients with CKD than conventional-dose-ergocalciferol after 12 weeks of treatment. The high-dose treatment might have potential effects on improved the bone and mineral disorders in patients with CKD.

TH-PO517
Treatment with Cinacalcet Increases Plasma Sclerostin Concentration in Hemodialyzed Patients with Chronic Kidney Disease and Secondary Hyperparathyroidism
Andrzej Wieck, Piotr Kuczer, Marcin Adamczak. Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.

Background: Sclerostin (Scl) is a paracrine acting factor which is expressed in the osteocytes and articular chondrocytes. Results of recent clinical studies suggest that Scl may decrease the osteoblast-related bone formation through the inhibition of the Wnt/beta-catenin pathway. The aim of this prospective, single-arm, open-label clinical study was to assess the influence of six-month cinacalcet treatment on plasma Scl concentration in hemodialysed patients with secondary hyperparathyroidism (shPTH).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Methods: In 45 hemodialysed patients with shPT (PTH: 300 pg/ml) plasma Sc as well as serum PTH, calcium and phosphate concentrations were assessed before the first dose of cinacalcet and after 3 and 6 months of treatment. Repeated measures ANOVA with Bonferroni correction was used in the statistical analyses. The results are shown as means and 95% confidence index.

Results: Serum PTH concentration decreased significantly after 3 and 6 month of treatment from 1173 (905-1441) pg/ml to 859 (584-1134) pg/ml and to 700 (432-767) pg/ml; p for trend <0.0001, respectively. Mean serum calcium and phosphate concentrations remained stable during the treatment period. Plasma Sc concentration increased after 3 and 6 months of treatment from 1.39 (1.20-1.58) mg/ml to 1.47 (1.27-1.67) mg/ml and to 1.55 (1.32-1.79) mg/ml; p for trend = 0.04, respectively. There were no significant correlations between the magnitude of the plasma sclerostin increase and the decrease of serum PTH concentration after 3 or 6 months of treatment (r=0.006;p=0.97 and r=0.004;p=0.98), respectively.

Conclusions: In hemodialysed patients with secondary hyperparathyroidism treatment with cinacalcet increases plasma sclerostin concentration which seems to be independent from the concomitant decrease of parathormone concentration.

Funding: Government Support - Non-U.S.

TH-PO518

The Effect of Cinacalcet Persistence on Risk of All-Cause Mortality and Heart Failure

Diane Reams,1 Paul Dlužničkova,2 Abhijit V. Kshirsagar,3 Brian D. Bradbury,1 Limor Walsh,1 M. Alan Brookhart,1 UNCG Gillings School of Global Public Health, Chapel Hill, NC;4 UNCG Kidney Center, Chapel Hill, NC;5 Amgen, Inc., Thousand Oaks, CA.

Background: Cinacalcet (Sensipar®) discontinuation occurs frequently for medical and non-medical reasons, such as parathyroid hormone levels below 150 pg/ml and medication cost. However, the clinical impact of discontinuing calcimimetic therapy is not well studied. We compared the risk of mortality and congestive heart failure (CHF) hospitalization between individuals with persistent cinacalcet use and patients who discontinued therapy for pre-defined non-medical indications.

Methods: Using data from a large dialysis provider merged with data from the USRDS, we identified new users of cinacalcet (2007-2011) from Part D prescription claims. Cinacalcet discontinuation was assessed in 30-day intervals and classified as either for medical or non-medical reasons. CHF hospitalizations were defined as ICD-9 claims. Cinacalcet discontinuation was assessed in 30-day intervals and classified as either for medical or non-medical reasons. CHF hospitalizations were estimated at pre-specified follow-up times by comparing crude and (IPCW) estimators. The risk differences (RD) and 95% CI’s for mortality and CHF hospitalizations were estimated at pre-specified follow-up times by comparing crude and IPCW cumulative risk functions.

Results: We identified 21,827 cinacalcet initiators who contributed 340,622 30-day follow-up intervals. At 12 months, 3,246 initiators (14.9%) had discontinued for medical indications and 12,077 initiators (55.3%) had discontinued for non-medical indications. We observed RDs for all-cause mortality at 12 months and 24 months, RD = -0.03 (95% CI -0.02, -0.03) and -0.04 (95% CI -0.03, -0.05), respectively. For CHF hospitalizations at 12 months and 24 months, RD = -0.00 (95% CI 0.00, -0.00) and -0.00 (95% CI 0.01, -0.01), respectively.

Conclusions: Our results find that approximately 3 extra deaths per 100 persons occur with discontinuation due to non-medical reasons during the first year of treatment. Reduction in risk for CHF hospitalization was evident when a broader definition of hospitalization was used; but no effect was seen with a more specific definition.


TH-PO519

A Bayesian Meta-Analysis of Randomized and Observational Studies on Cinacalcet Use and Mortality in Secondary Hyperparathyroidism

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Background: Conventional meta-analyses of therapeutic effects focus on randomized controlled trials (RCTs) and exclude valuable information captured in observational studies. We conducted a meta-analysis of the effect of cinacalcet in treating secondary hyperparathyroidism (shPT) in patients with end stage renal disease (ESRD) using methodology that allows for incorporation of non-RCT evidence.

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (2000-February 2014) for RCTs and observational studies in which cinacalcet was compared to placebo or standard of care using all-cause mortality as an endpoint. A high Grading of Recommendations Assessment, Development and Evaluation (GRADE) score was used as an entry criterion. We applied a Bayesian approach where the meta-analysis of RCTs.

Results: A total of 616 abstracts were identified. High quality studies meeting inclusion criteria included 2 RCTs and 2 observational. There was insufficient data to estimate between-study variance under a random effects model. The fixed effect hazard ratio estimate (95% credible interval) for the effect of cinacalcet on mortality was 0.83 (0.78, 0.89).

Conclusions: This Bayesian meta-analysis of high quality studies indicates potential beneficial effects of cinacalcet on mortality in ESRD patients with shPT.

TH-PO520

WELCOME – Web-Based Evaluation of Clinical Benefit of Cinacalcet in End-Stage Renal Disease in Central and Eastern Europe

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Background: Cinacalcet (MIM) is approved for treatment of secondary hyperparathyroidism (shPT) in ESRD. Study objective: to describe KDOQI target achievement and treatment patterns before release of KDOQI guidelines (BGR; cut-off 08/2009) and thereafter (AGR).

Methods: Design: multicenter, non-interventional, observational study of CEE. Dialysis patients (pts) starting MIM £1 month prior enrollment (BL) were eligible. Primary endpoint: % achieving PTH ≤300 pg/ml after 6 months. Secondary endpoints: % at KDOQI target for Ca or P at BL and 6 months; MIM dose; vitamin D sterol (ViD) and phosphate binder (PB) use; adverse drug reactions (ADR). The 2nd interim analysis is reported on 12 cohorts enrolling between 01/2007-12/2012. 4 of 6 countries enrolled pts BGR (Figure).

Results: 2571 pts were enrolled, 2172 (84.5%) completed 144 days of MIM.

Conclusions: Average median (IQR) MIM dose was 30 (30-42); BGR and 30 (30-43) mg/day (AGR). Substantial differences in PTH were observed between countries.

Funding: Amgen, Inc., Thousand Oaks, CA; Abbott, Abbott Park, IL; AstraZeneca, London, United Kingdom; Bayer HealthCare Pharma, Leverkusen, Germany; Bristol-Myers Squibb, Princeton, NJ; Merck & Co, Inc., Whitehouse Station, NJ; Novo Nordisk, Bagsvaerd, Denmark; Pfizer, New York, NY; and others.
Background: A successful kidney transplant (KTx) improves most of the mineral disturbances produced by CKD, but some disorders may persist for several years, such as hypercalcemia, elevated PTH and low phosphorus. Previous studies have shown the negative impact of persistent hyperparathyroidism (PHPT) on one year graft function. However, the long term effects of PHPT on renal function are poorly known. Based on that, we aimed to analyze the impact of PHPT on long term graft outcome.

Methods: Retrospective analysis of the isolated adult KTx that occurred between 01/2005 and 12/2014 at the Hospital das Clinicas - USP. Clinical and laboratory data were collected from the charts. Graft failure was defined as return to dialysis. PHPT was considered when, one-year after KTx, ionized calcium was > 5.3 mg/dl or PTH > 100 pg/ml.

Results: From the total of 1708 KTx occurred in this period, we analyzed 1102 patients that, one year after KTx had an eGFR= 30 ml/min and available data for analysis. Of those, 28% (318) had hypercalcemia and 32% (356) had an elevated PTH. PHPT was present in 47% of the patients. The mean follow up time was 1689 days. Graft failure was observed in 47 patients (33 in PHPT and 14 in non-PHPT group, HR = 1.5; p<0.05). Cox-regression analysis showed that graft failure was dependent on PHPT (β=2.3; 1.3-4.1; p= 0.007) even after adjustment for age at KTx, donor age, donor type, PTX and eGFR at 1 year after KTx, as shown in Figure.

Conclusions: Individuals with PHPT one year after KTx, even those with slightly elevated calcium or PTH, have an increased risk of long term graft failure. Our results call our attention for a better management of CKD-MBD before KTx and during the first year of follow-up.

TH-PO523

Chronic Kidney Disease Caused Hypermethylations of CaSR and VDR Genes in Parathyroid Glands

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Background: The stability of mineral homeostasis is the most important for the health of the organism. Secondary hyperparathyroidism (SHPT), a common disorder in patients with chronic kidney disease (CKD), occurs during early course of progressive renal insufficiency. It is well known that the reduction of calcium sensing receptor (CaSR) and vitamin D receptor (VDR) occurs slowly and progressively, however the mechanism is largely unknown. Upstream transcription factors of CaSR and VDR are not clear except Gcm2 cells missing 2 (Gcm2), it has affected the CaSR gene directly and transactivates by Gcm2 response elements in the CaSR promoters. In recent years there are reports about epigenetic studies in the field of various diseases including CKD. However, there are few reports related to mineral homeostasis. Here we investigated altered expressions of CaSR, VDR in CKD rats’ parathyroid glands. We then demonstrate that the pathogenic change of SHPT, the reductions of CaSR and VDR expressions proceed from hypermethylations of CaSR and VDR genes.

Methods: Taqman probe (ABI) were used for quantitative real-time PCR. DNA methylation analysis was performed using a restriction digestion and quantitative PCR (qAMP), a combination of methyl-binding protein (MBP) and quantitative PCR (MBP-qPCR). CKD was induced by two-step 5/6 nephrectomy.

Results: The expression level of Gcm2 was not significant both in CKD rats and controls. We then found hypermethylations of CaSR and VDR in CKD rats.

Number: sham 3, CKD 3 * P<0.05

MBP-qPCR

CaSR

qAMP

CaSR

TH-PO524

Proteomic Comparative Analysis of Parathyroid Oxyphil Cell and Chief Cell Nodules of Uremic Secondary Hyperparathyroidism Patients

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Background: Secondary hyperparathyroidism (SHPT) is the common abnormality in CKD patients. Hyperplasia of the parathyroid gland (PG) was considered to be an important processes in SHPT pathophysiology. Physiologically, PG mainly composed of chief cells (CC, 95-99%) and oxyphil cells (OC, 1-5%). Our previous study showed that OC in PG were significantly increased in uremic SHPT patients and closely related to oral calcitriol dose.
and treatment duration. In order to investigate OC proliferation and vitamin D metabolism, we conducted proteomic analysis to compare differences between PG OC and CC nodules from SHPT patients.

Methods: Two pairs of PG OC and CC nodules were selected to conduct proteomic (liquid chromatography tandem mass spectrometry). The protein expression were quantified and compared by more than 2-fold between two groups. By using bioinformatic analysis, the protein expression profiles were sorted to several terms (cellular component, molecular function and biological process). Vitamin D metabolism were further analyzed in both cell type groups.

Results: 14691 unique peptides were identified and 2675 proteins were quantified. A total of 174 proteins (6.5%) were more than 2-folds up/down expressed in OC nodules compared to CC nodules (40 increased and 134 decreased in OC nodules). Bioinformatics analysis showed that in cell components, membrane structure including mitochondrial (47.80%) using most significantly differences. In molecular function, protein with binding capacity (38.46%) were the major differences. In biological processes, protein and energy metabolism (33.92%), cell replication and cycle regulatory (10.14%) were significantly differences. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules, among which, the decreasing of vitamin D binding protein in OC nodules were the most significantly (3.82 times of CC nodules).

Conclusions: Protein, energy metabolism, cell stress and cell cycle regulation are significant differences in the OC from CC nodules. Vitamin D transport and metabolic regulation proteins were less expressed in OC than CC nodules.

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TH-PO525
Clinical Outcomes in Japanese Chronic Kidney Disease Patients Aged Over 65 Years: A Report from the Gourny Study
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Background: Japan will become a full-aged aged society. Aging is a risk factor for progression of chronic kidney disease (CKD) and CKD is common in elderly population. However the information of clinical feature of elder CKD is limited.

Methods: We prospectively followed up 1,750 elderly outpatients over 65 years old under the care of nephrologists. Inclusion criteria was the basal age over 65 years, and estimated glomerular filtration rate <90 ml/min and/or proteinuria. Survival, censored for RRT, was recorded for a follow-up time of 5 years. Patients were divided into 3 age groups, 65-74, 75-85 and over 85 years old, and stratified by CKD stages. The effects on outcomes were evaluated, and assessed in association with body mass index (BMI).

Results: Among 1,750 patients, the median age 74 (min 65- max98) years and males 49.8%, and 118 died and 200 patients started RRT during a median follow-up of 4.60 (quartile 1.84 – 5.00) years. The ESKD incidence did not differ among age groups. While the risk for survival increased in the higher aged groups (Log-Rank c =62.93, P <0.0001), and the incidence rate was higher than that of ESKD in the over 85 years group (164.7 vs. ESKD 126.9 per 1,000 persons per year). When patients were divided by CKD stages, patients with G5 progressed mainly ESKD in all groups, on the other hand, the context of all-cause mortality increased even in G3 and G4 in the higher aged groups compared to ESKD. In competing models, the survival risk before developing ESKD associated significantly with high age, smoking, low BMI, low pulse pressure and history of cardiovascular disease, but did not with diabetes, renal function, proteinuria and hemoglobin level. A high BMI, which decreased significantly in the higher aged groups (P = 0.043), predicted a better survival in patients aged 65-85 years old but no clear effects in patients under 75 years old.

Conclusions: The content of clinical outcomes were different among generations in elder CKD especially in CKD G3-4 in patients over 85 years increased the survival risk before developing ESKD, and the lower BMI associated the higher risk.

TH-PO526
Undocumented Immigrant and Uninsured Status Are Independent Risk Factors for Chronic Kidney Disease Progression
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Background: Being uninsured is a risk factor for chronic kidney disease (CKD) progression to end stage renal disease (ESRD). Undocumented immigrants (UI) belong to a vulnerable group in terms of healthcare. Little is known about the association of UI status and CKD progression.

Methods: Records of adult patients admitted to Elmhurst Hospital Center from 2009 to 2014 with CKD stage 4 or 5 as diagnosis or comorbidity were analyzed. ESRD patients were excluded. Covariates analyzed included sex, age, documentation (Social Security Number) and insurance status. Data was analyzed using STATA; Pearson’s Chi Squared test was used for bivariate analyses.

Results: Of 703 patients analyzed: 81% had insurance (n=569), 19% were uninsured (n=134), 84% were documented (DOC, n=588), and 16% were UI (n=115). Of the DOC, 89% had insurance (n= 525) vs. 38% (n=44) of UI (p<0.005) and were older than UI (71±13 vs. 59±15, p<0.005). 21% of CKD patients progressed to ESRD (n=151); 20% of DO compared to 30% of UI (p<0.05). Analyzed by insurance status, 18% of the insured developed ESRD compared to 36% of the uninsured (p<0.0001). On bivariate level, UI was associated with progression (p<0.05). On multivariate level, documentation status lost significance, but insurance status remains significant for ESRD progression.

Conclusions: Documentation and insurance status are associated with ESRD progression. Once controlling for demographic variables, documentation status is no longer significant, but insurance status remains significant for progression.

Table: Multivariable linear mixed effects regression for the association between patient and disease characteristics with eGFR following surgery. Estimates presented are for the fixed effect of the factor of interest.

<table>
<thead>
<tr>
<th>Age</th>
<th>Estimate</th>
<th>Std.Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-79</td>
<td>-0.309</td>
<td>0.045</td>
<td>0.000</td>
</tr>
<tr>
<td>80-89</td>
<td>-0.203</td>
<td>0.086</td>
<td>0.052</td>
</tr>
<tr>
<td>Pre-op GFR</td>
<td>0.744</td>
<td>0.030</td>
<td>0.000</td>
</tr>
<tr>
<td>HTN</td>
<td>-0.297</td>
<td>1.026</td>
<td>0.773</td>
</tr>
<tr>
<td>Radical procedure</td>
<td>-9.590</td>
<td>1.770</td>
<td>0.000</td>
</tr>
<tr>
<td>Current smoker</td>
<td>-0.063</td>
<td>1.029</td>
<td>0.951</td>
</tr>
<tr>
<td>Months followup</td>
<td>0.120</td>
<td>0.018</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Conclusions: Independent predictors of post-operative decline in renal function include advanced age, lower pre-operative eGFR and RN. A significant number of subjects had recovery in renal function over time following surgery which continued past the 12 month mark. These findings suggest that patients undergoing nephrectomy can experience long-term improvement in renal function. This improvement is greater among younger patients with higher pre-operative eGFR undergoing PN.

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TH-PO528

A Longitudinal Analysis of Chronic Kidney Disease and Related Comorbidities Among Human Immunodeficiency Virus (HIV) Patients
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Background: Patients with HIV infection can present with or develop multiple comorbidities including risk factors for chronic kidney disease (CKD). This study examined CKD and comorbid conditions in HIV patients in the US.

Methods: Adults diagnosed with HIV (ICD-9 code: 042.xx, 795.71, V08) in 2007-2013 were selected from MarketScan Commercial, Medicare, and Medicaid Databases. Patients were continuously enrolled for ≥ 365 days in 2007-2013 and stratified by the presence of CKD based on diagnosis codes. Comorbidities, prevalence (per 1,000 patients), and incidence (per 1,000 patient-years) of CKD in 2007-2013 were assessed.

Results: A total of 31,229 HIV patients (mean age: 42.8; male: 77.9%; mean Deyo-Charlson comorbidity index (CCI): 6.0) were selected from Commercial data, 1,541 (mean age: 57.6; male: 47.4%; CCI: 7.0) from Medicare. CKD prevalence and incidence were, respectively, 48.6 and 13.1 in Commercial, 242.1 and 61.1 in Medicare, and 114.3 and 28.4 in Medicaid. Prevalence and incidence increased over time. During 2007-2013, end-stage renal disease (ESRD)/dialysis patients accounted for 1.8% of Commercial, 7.7% of Medicare and 4.8% of Medicaid patients. Common CKD risk factors included hypertension (Commercial: 32.5%; Medicare: 77.0%; Medicaid: 55.5%), hyperlipidemia (30.6%, 52.7%, 33.8%), diabetes (11.2%, 36.9%, 25.1%), cardiovascular disease (6.4%, 34.4%, 15.5%), and obesity/overweight (7.0%, 7.5%, 16.9%). Annual incremental healthcare costs in 2013 were higher in CKD patients than non-CKD patients (Commercial: $16,406; Medicare: $6,879; Medicaid: $5,663).

Conclusions: We observed an increase in CKD prevalence and incidence over time in HIV-infected patients. Because of the potential effects of ART treatment on CKD observed in published data, understanding CKD risk factors of HIV patients will help optimize care of patients, including choice of antiviral regimens and screening and treating of these risk factors.

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TH-PO529

Association of Short Sleep Duration and Rapid Decline in Renal Function
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Background: The kidney, like all other organs in the human body, is influenced by circadian rhythms, allowing renal function to be entrained to the sleep-wake cycle. Coordination of this periodicity in the kidney permits anticipation of the metabolic and physiological demands of the kidney throughout a 24-hour cycle. Unsurprisingly, disruption of the sleep-wake cycle may lead to disruption of renal physiology. Although sleep disruption has been studied extensively in cardiovascular and metabolic disease, its association with chronic kidney disease has not been shown.

Methods: In a prospective cohort study of 4238 participants from the Nurses’ Health Study with renal function measured on at least two occasions, we analyzed the association of self-reported sleep duration with decline in renal function over an 11-year period.

Results: Individuals who reported shorter sleep duration were more likely to experience a rapid decline in estimated glomerular filtration rate (>25% decline from 1989 to 2000). Compared with sleeping 7-8 hours per night, the adjusted odds ratios for a rapid decline in renal function were 1.2 ml/min/1.73m²/year, 1.65 (95% CI, 1.06-2.55) for ≤5 hours sleep per night, 1.31 (95% CI, 0.81-2.15) for 6 hours sleep per night, and 1.78 (95% CI, 0.481-6.25) for ≥9 hours sleep per night. Similarly, adjusted annualized decline in estimated glomerular filtration rate was 1.2 ml/min/1.73m²/year, 0.9 ml/min/1.73m²/year, 0.8 ml/min/1.73m²/year, and 0.8/ml/min/1.73m²/year for individuals sleeping ≤5 hours per night, 6 hours per night, 7-8 hours per night, and ≥9 hours per night, respectively (p-trend = 0.02).

Conclusions: Shorter sleep duration is prospectively and independently associated with faster decline in renal function.

Funding: NIDDK Support

TH-PO530

Impairment of Endogenous Nighttime Melatonin Secretion Relates to Intrarenal Renin-Angiotensin System Activation and Renal Damage in Patients with Chronic Kidney Disease
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Background: Activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of chronic kidney disease (CKD) and hypertension. Recently, we have demonstrated that the circadian rhythm of intrarenal RAS activation leads to renal damage and hypertension. Melatonin is considered as a major hormone regulating the circadian rhythm and nocturnal melatonin concentrations are reduced in patients with CKD. However, it has not known whether the impairment of endogenous melatonin secretion is related to BP, intrarenal RAS or renal damage in patients with CKD.

Methods: We recruited 53 patients with CKD stage 1-5 and 24-hour ambulatory BP monitoring (ABPM) and urine collection divided into daytime and nighttime were conducted.

We investigated the relationship among urinary 6-sulfatoxymelatonin (U-aMT6s), that is the major melatonin metabolite, BP, renal function, urinary angiotensinogen (U-AGT), and urinary protein (U-P) in daytime and nighttime, respectively.

Results: The nighttime U-aMT6s levels were decreased according to the progression of CKD stage and those in CKD stage 5 was significantly decreased compared with those in other CKD stages. The U-aMT6s levels were significantly and negatively correlated with the clinical parameters such as renal function (serum creatinine), systolic BP, U-AGT and U-P in both daytime and nighttime. Multiple regression analyses for U-aMT6s levels were performed using age, sex, serum creatinine and each parameter (systolic BP, U-AGT or U-P) in daytime and nighttime, respectively. U-aMT6s levels tended to correlate with systolic BP (β=0.22, p=0.11), and were significantly associated with U-AGT (β=0.31, p=0.040) and U-P (β=0.26, p=0.041) in nighttime. On the other hand, U-aMT6s had no associations with the clinical parameters in daytime.

Conclusions: Impairment of nighttime melatonin secretion may be associated with nighttime intrarenal RAS activation and renal damage in patients with CKD.
TH-PO532  
Prognostic Implications of Anemia in Patients with Chronic Kidney Disease Undergoing Elective Percutaneous Coronary Intervention  
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Background: Little is known about the prognostic implications of anemia in patients undergoing elective percutaneous coronary intervention (PCI), especially when they have coexisting chronic kidney disease (CKD).  

Methods: We identified 2792 patients with CKD who underwent elective PCI from the CREDO-Kyoto registry cohort-2. The primary outcome was 3-year major adverse cardiac events (MACE); composite of all cause death, heart failure hospitalization, and myocardial infarction.  

Results: In total, 738 patients (26.4%) had mild anemia (hemoglobin <11.0–11.9 g/dL for women and 11.0–12.9 g/dL for men), and 740 patients (17.9%) had moderate-to-severe anemia (hemoglobin <11.0 g/dL both for women and for men). Compared to the no-anemia group, cumulative incidence of MACE was significantly higher in the mild and moderate-to-severe anemia groups (12.2%, 23.5%, and 37.4%, respectively). The adjusted hazard ratios of mild and moderate-to-severe anemia versus no-anemia for MACE were 1.46 (95% confidence interval: 1.13–1.90) and 1.76 (95% confidence interval: 1.33–2.34), respectively. In addition, the risk for MACE showed an accretive increment with exacerbation in either the renal function or anemia (interaction p < 0.001).  

Conclusions: Even mild anemia was associated with significantly worse 3-year clinical outcomes in CKD patients who underwent elective PCI. Anemia and reduced renal function independently and additively increased the risk for MACE in these patients.  

TH-PO533  
Pathological Classification of Diabetic Kidney Disease in Prognosticating Time to End-Stage Renal Death or Disease  
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Background: We performed a retrospective, longitudinal study of patients with diabetic kidney disease (DKD) undergoing renal biopsy to ascertain the prognostic value of histopathologic features when combined with clinical information.  

Methods: Specimen from clinical native kidney biopsies performed in 1998-2006 containing diabetic glomerulosclerosis in the final diagnoses were analyzed according to the Renal Pathology Society classification system for DKD. Clinical data were extracted from medical records from time of biopsy until the composite outcome of ESRD or death. Multivariate Cox proportional-hazards regression was used to estimate hazard ratios (HR) of the composite outcome according to glomerular class or severity of interstitial fibrosis. Covariates included age, gender, diabetes duration, blood pressure, eGFR and urine protein at the time of biopsy.  

Results: Baseline characteristics according to glomerular class are displayed below.  


The risk for ESRD/death for glomerular classes 2a/b and 3 versus class 4 was HR=0.12 (0.04-0.42) and HR=0.17 (0.06-0.51), respectively. Analysis of interstitial fibrosis (IF) severity 0/1 versus 3 yielded a HR=0.19 (0.06, 0.63). The HR for IF 2 versus 3 was not significant (p=0.09). The only statistically significant clinical covariate in the analyses was eGFR. HR=0.96 (0.93, 0.99) and HR=0.94 (0.91, 0.97), respectively.  

Conclusions: Kidney biopsy significantly improves the prognostication of ESRD or death in patients with diabetic glomerulosclerosis.  

Funding: Private Foundation Support

TH-PO534  
Progression of Chronic Kidney Disease Stage 3 Over 5 Years in a Prospective Primary Care Cohort Study  
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Background: CKD stage 3 is commonly diagnosed in primary care. Previous studies indicate that it runs a variable course with only a minority progressing to ESRD. The Renal Risk in Derby study aims to evaluate progression of CKD in a cohort of people with CKD 3 recruited prospectively from primary care in Derbyshire, UK.  

Methods: 1741 participants were recruited from local primary care practices. All had eGFR 59-30/ml/min on 2 occasions prior to recruitment. At baseline, year 1 and year 5 visits, participants underwent clinical assessment, urine and serum biochemistry. Progression of CKD was defined using KDIGO criteria (25% loss of GFR and an increase in GFR category, or an increase in albuminuria category).  

Results: 299 (17.2%) participants died prior to the end of year 5 follow-up. Only 4 participants (0.2%) progressed to ESRD. 1064 participants attended for year 5 visits or submitted blood and urine samples. Mean age was 71 years at baseline. Mean eGFR was 55.3/ml/min at baseline and 53.8/ml/min at year 5 (p=0.001). Progression occurred in 263 participants (24.6%). Binomial logistic regression identified male gender (HR=1.55), baseline urinary albuminuria (HR=1.33), diabetes (HR=1.57), haemoglobin (HR=0.81) and the change in GFR at year 1 (HR=0.95) as independent determinants of progression at 5 years. Progression in eGFR and albuminuria categories occurred largely independently.  

Funding: 1NIDDK Support  

TH-PO535  
Change in Albuminuria and Risk of ESRD in a Large Health System  
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Background: Albuminuria is used in chronic kidney disease (CKD) staging but it is uncertain how change in albuminuria is associated with ESRD risk in primary care and other generalizable settings.  

Methods: We included Geisinger Health System participants with multiple albuminuria measurements within a 2-year baseline period, using Cox proportional hazards regression to estimate the association of ESRD with log change in albuminuria (per 2-fold rise in albumin to creatinine ratio, ACR). We tested risk for non-linearity and also analyzed 1- and 3-year change in ACR.  

Results: Our data confirm that the 5-year risk of ESRD is low in CKD 3 but progression occurred in 24.6% of participants. Change in eGFR over 1 year was an independent predictor of progression over 5 years indicating that annual monitoring is beneficial for assessing prognosis.  

Funding: Private Foundation Support
Association Between Vascular Access Creation and Regression of eGFR Decline in Late-Stage CKD Patients Transferring to ESRD

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Background: Arterio-venous dialysis access (AVF) creation may be associated with slowing of the decline in eGFR. It is unclear if this is due to physiological benefits of a mature access vs. other confounding factors in late CKD. We hypothesized that the beneficial change in the eGFR would only be seen with a mature AVF.

Methods: From 52,172 U.S. veterans who transitioned to dialysis between 2007-2011, we identified 3,220 who had an AVF created prior to dialysis start, and had at least 3 outpatient eGFR measurements both before the AVF creation and between AVF creation and the initiation of dialysis. We estimated crude and adjusted slopes of eGFR vs. time in multilevel mixed effects models with random intercepts and slopes. Pre- and post-AVF eGFR slopes were compared both overall, and in patients stratified by AVF maturation.

Results: Mean (SD) age was 66.3 (10.8) years, and patients were 98% male, 35% black, and 76% diabetic. Median (IQR) eGFR slope was -5.2 (-8.3 to -3.2) ml/min/1.73m²/year, and 71% had a mature AVF at dialysis start. Compared with the eGFR slopes before AVF, a significant improvement was observed post-AVF (-5.5 [8.9 to -3.4] vs. -4.0 [4.6 to -3.2], P<0.001). This association was present to a similar extent in both patients with matured and un-matured AVF (Figure). Results were unchanged in adjusted models.

Conclusions: Regardless of maturation, the creation of AVF is associated with improved eGFR slopes. Clarifying the mechanism behind this warrants additional studies.

Funding: NIDDK Support, Veterans Administration Support

Telomerase Activity in Patients with Stage 2-5 Chronic Kidney Disease

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Background: The relationship between telomerase activity and stages and progression of Chronic Kidney Disease (CKD) is unknown. The aim of this study is to investigate the association between telomerase activity and stages of CKD.

Methods: A total of 120 patients (30 patients from each stages of 2-5) and 30 healthy volunteers applying to the clinic for their routine examinations were enrolled in the study. The individuals from patient and control groups were matched in terms of age and gender. PBMC telomerase activity was measured by telomeric repeat amplification protocol.

Results: PBMC telomerase activity was different significantly between the groups (p < 0.001). Telomerase activity was found to be lowest in healthy controls (0.15 ± 0.02), and highest in patients with stage 5 CKD (0.23 ± 0.04). Telomerase activity was similar between patients with stage 2, 3, and 4 CKD (p > 0.05). There was positive correlation between telomerase activity and CKD stage (r = 0.412, p < 0.001), serum creatinine (r = 0.404, p < 0.001), potassium (r = 0.207, p = 0.023), and intact parathyroid hormone (r = 0.245, p = 0.007) levels and negative correlation between telomerase activity and estimated glomerular filtration rate (eGFR) (r = 0.407, p < 0.001), serum sodium (r = 0.179, p = 0.05), calcium (r = 0.357, p < 0.001), LDL-cholesterol (r = 0.218, p = 0.017), hemoglobin (r = 0.186, p = 0.042), trombocyte (r = 0.252, p = 0.006), and body mass index (BMI) (r = 0.240, p = 0.008) values. In linear regression analyses, eGFR and BMI were found to be independent predictors of high telomerase activity in CKD group. (Model 1: R² = 0.151, for eGFR β = -0.001, BMI β = 0.004; Model 2: R² = 0.195, for eGFR β = -0.001, P = 0.010; for BMI β = -0.002, p = 0.012).

Conclusions: PBMC telomerase activity is significantly higher in patients with CKD compared to healthy controls. Telomerase activity increases as the CKD stage proceeds, particularly in stage 5. The increase in PBMC telomerase activity is associated with eGFR and BMI.

Funding: NIDDK Support, Veterans Administration Support
TH-PO540

Left Ventricular Global Longitudinal Strain as Early Detection of Subclinical Myocardial Dysfunction in Chronic Kidney Disease Patients

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Background: CV mortality is increased in patients with chronic kidney disease (CKD). Little is known regarding the natural longitudinal changes in cardiac structure and function. Global longitudinal strain (GLS) measures myocardial deformation in addition to left ventricular twist. The aim of our cross sectional study is to assess the grade of myocardial dysfunction in CKD stage 1-5D without previous CV events & normal left ventricular ejection fraction (LVEF).

Methods: 161 pts.38% f,74% DM.Age 67.3±8yo,not previous CV events and LVEF>55%.All received ACEI/ARB,CBHx& diuretics.Echocardiogram was performed using Vivid 9 (GE Vimed Ultrasound Horton, Norway).Parameters derived;GLS, left Atrial volume index (LAVI),E,e/A & LVEF as recommendations of American Society of Echocardiography.Body composition analysis was performed by BIA and serum biomarkers of inflammation,anaemia,mineral bone disease,renal function (GFR-EPI) and ejection fraction (LVEF).

Results: Of the 629 included, mean age was 75 years at baseline, mean eGFR was 51 ml/min/1.73 m². LAVI 40.6 ± 29.8 ml/m². 161 pts. 38% F, 47% DM, Age 67.37 ± 19.8 yr, not previous CV events and 60% LA VI > 24 ml/m². GLS correlates negatively significantly correlation to GLS (r: -0.28, P<0.001). GLS decreased with CKD stage (-0.1 (-0.3, 0.1) mmHg per level increase in CKD stage (P<0.001) and a greater UACR correlated with decreased GLS (P=0.004) in unadjusted linear regression. The difference between brachial and invasive systolic BP increased with 3.1(95% CI 3.0; 3.3) mmHg per mmHg increase in diastolic BP (P<0.001). Conclusion: Our data show that central BP increases more than brachial BP with increasing CKD stage. The differences were significantly associated with increased arterial stiffness. In the future, GLS might be a useful parameter for the evaluation of aortic stiffness.

TH-PO541

Aortic Stiffness and Change in GFR and Albuminuria in Older People

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Background: Higher aortic stiffness (AS) has a direct effect on microvascular structure and function, and may be an underlying mechanism for progression of CKD in older people.

Methods: Our study included community dwelling Icelandic elderly adults. Linear and logistic regression were used to assess the association between AS measures (carotid-femoral pulse wave velocity [CFPWV], carotid pulse pressure [CPP] and augmentation index [AI]) with the change in creatinine-creatinine C based estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (ACR) by two measurements 5 years apart. Rapid eGFR decline was defined as a decrease of ≥ 3 ml/min/1.73 m² yr. The difference between brachial and invasive systolic BP was not statistically significant with increased arterial stiffness.

Results: Of the 629 included, mean age was 75 years at baseline, mean eGFR was 72 ml/min/1.73 m² and median ACR was 2.9 mg/g. The table shows associations of AS parameters to change in eGFR. No significant associations were observed between AS parameters and change in ACR.

Conclusions: AS is associated with rapid decline in kidney function in older age beyond traditional cardiovascular risks.

TH-PO542

Central Aortic Blood Pressure in Patients with Chronic Kidney Disease

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Background: Central blood pressure (BP) has been suggested as a better predictor cardiovascular outcome than the brachial BP. However, in patients with chronic kidney disease (CKD) the relationship between aortic BP and brachial BP remains to be elucidated. This study compared invasive measurements of central aortic BP with brachial artery BP and the accuracy of estimated central BP obtained non-invasively by radial artery tonometry.

Methods: A cohort of 83 with stage 3-5 CKD and 41 patients without signs of renal disease undergoing planned coronary angiography for evaluation of ischemic heart disease were included. BP was sequentially measured at the brachial artery with an oscillometric BP device; in the ascending aorta using an invasive catheter; and by radial artery tonometry using the SphygmoCor device for the estimation of the central BP. Arterial stiffness was assessed by pulse wave velocity (PWV).

Results: The difference between estimated central and invasive systemic BP increased with 3.6(95% CI 1.8; 5.3) mmHg per level increase in central BP stage (P=0.001) and 0.195(95% CI 0.05;0.18) mmHg per decrease in eGFR (P=0.001) in unadjusted linear regression. The difference between brachial and invasive systemic BP increased with 3.1(95% CI 3.0; 3.4) mmHg per level increase in central BP stage (P=0.001) and 0.195(95% CI 0.03; 0.16) mmHg per decrease in eGFR (P=0.003) in unadjusted linear regression. Multivariate adjustment did not change the results. The difference between brachial and invasive systemic BP was significantly associated with PWV (P=0.01).

Conclusions: Our data shows, that central BP increases more than brachial BP with increasing CKD stage. The differences were significantly associated with increased arterial stiffness. As brachial BP is used for calibration of the tonometry based SphygmoCor device, central BP might be increasing underestimating true central BP stage increases. Thus, in advanced kidney disease the utility of non-invasively obtained central BP seems questionable.

TH-PO543

Correlation of Pulse Pressure to Renal Functional Parameters in a Cross Sectional Study of General Population – The Texas Kidney Study

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Background: Chronic kidney disease (CKD) presents an increasing economic burden. Diabetes and hypertension remain the major risk factors for development and cardiovascular complications the leading cause of mortality among patients with CKD. Pulse pressure has been noted to be an important and independent factor for cardiovascular mortality. Effect of pulse pressure (PP) on renal function in the general population has not been well studied. In this study, we examined the relation of pulse pressure to kidney function in a random, cross-sectional study of unselected population in Texas.

Methods: A cohort of 1606 subjects was recruited from the general population using random digit dialing. Detailed history and physical examination were performed and blood and urine samples were taken for renal function assessment. Estimated glomerular filtration rate (eGFR) was derived using both the 4 variable MDRD formula. Subjects were divided into normal PP group (PP<40), wide PP group (PP>45) and were further subdivided in different age categories (age <50 and age ≥50) and those with and without systolic hypertension. Correlation of PP to eGFR and logarithmically transformed urine albumin to creatinine ratio (UACR) were analyzed.

Results: A total of 1576 subjects completed the study. There were 976 subjects with normal PP and 603 with wide PP. Among subjects with age ≥50, wide PP was associated with higher UACR (p<0.001), but not with eGFR (p=0.09). In patients without systolic hypertension, the group with wide PP compared to normal PP, had a significantly lower eGFR (p=0.001) and a greater UACR (p=0.05). In patients with systolic hypertension, no significant differences in these parameters were seen between the PP groups (p=0.234).

Conclusions: In patients without systolic hypertension, wide PP is a predictor of worse kidney function in terms of eGFR and UACR. This could be attributed to underlying heart disease, severe anemia, thyroid disorders and other factors that lower diastolic blood pressure. Hemodynamic significance of wide pulse pressure on renal functional parameters needs further exploration.

Funding: Other U.S. Government Support

TH-PO544

TNFα Receptor Type 2 Is Not Associated with an Accelerated Age-Related GFR Decline in the General Middle-Aged Non- Diabetic Population

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Background: TNF-α is an inflammatory cytokine that mediates renal injury in animal studies. Soluble TNFα receptor type 2 (sTNFR2) is a receptor antagonist that has been shown to act as an independent predictor for kidney function decline in persons with diabetes. However, few studies have investigated the effect of sTNFR2 on chronic kidney disease (CKD) risk in the general population. Previous studies have mainly used...
estimated GFR which is inaccurate in the near normal range of GFR and biased by non-GFR determinants. We investigated whether sTNFR2 is a risk-factor for GFR decline in the general population using measured GFR.

Methods: We measured GFR by ioHx clearance in a cohort of the general population aged 50-62 years without diabetes, kidney- or cardiovascular disease at baseline. Of the 1594 subjects investigated at baseline, 1299 (81%) had a second measurement after a median observation of 5.6 years in the Renal Iohexol-clearance Survey Follow-up study (RENIS-FU). Baseline sTNFR2 levels were measured by ELISA.

Results: In a linear mixed regression model adjusted for time-dependent variables including sex, weight, height, smoking, use of NSAIDs, HbA1c and albumin-creatinine ratio, one standard deviation (SD) increase in baseline sTNFR2 was associated with a slower GFR decline of 0.10 ml/min/year (95% CI: -0.01 to 0.19). There was a strong negative association between the baseline values of sTNFR2 and GFR; one SD increase in sTNFR2 was associated with lower GFR (β=−3.63 ml/min, 95% CI: -6.87 to -4.40).

Conclusions: Increased sTNFR2 is not a risk-factor for accelerated decline in GFR in the general middle-aged population. The negative baseline association between sTNFR2 and GFR is probably due to renal clearance of sTNFR2. A longer follow-up time may be necessary to fully evaluate whether sTNFR2 influences age-related GFR decline in the general population.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim

TH-PO545

Abstract Withdrawn

TH-PO546

Diagnosis of Non-Adherence and Renal, and Cardiovascular Outcomes in Newly Treated Hypertensive U.S. Veterans Ahmed Zeen Alabedeen Alrifai, 1 Kamyar Kalantar-Zadeh, 3 Csaba P. Kovesdy, 1 Elvira Gosmanova, 1 Miklos Zsolt Molnar, 1 Ahmed Zeen Alabedeen Alrifai, 1 Jun Ling Lu, 1 Elani Strieja, 2 William C. Cushman, 1 Kamyar Kalantar-Zadeh, 3 Csaba P. Kovesdy 1, 1

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Background: Adherence is paramount in treating hypertension, yet no gold standard method is available for non-adherence screening delineating high-risk patients. An ICD-9-CM diagnostic code (V15.81) has been available for many years; however, its utility is poorly studied.

Methods: We examined the association between V15.81 code assigned prior to HTN diagnosis, with renal (incident CKD and ESRD) and cardiovascular (incident coronary heart disease-CHD and stroke) outcomes in 312,489 incident hypertensive individuals identified from a historical prospective cohort. Baseline mean age was 53.8 years, patients were 91% males and 20% African Americans; 10,401 patients had a V15.81 code. We used crude and Cox models adjusted for baseline demographic characteristics, eGFR, BMI, blood pressure, and co-morbidities.

Results: During a median follow up of 7.9 years, event rates were: for incident CKD 7.1 (7.0-7.2)/1000 patient-years, for ESRD 0.15 (0.13-0.16)/1000 PY, for CHD 4.6 (4.5-4.7)/1000 PY, and stroke 4.0 (3.6-4.3)/1000 PY. The presence of a V15.81 code was associated with a higher risk of all renal and cardiovascular outcomes in unadjusted and adjusted analyses including 2 fold higher risk of ESRD and 70% higher stroke risk.

Conclusions: A diagnosis of non-adherence based on the assignment of a V15.81 code prior to the diagnosis and treatment of hypertension was associated with increased adverse renal and CV outcomes in incident hypertensive US veterans. Further research is warranted to examine interventions targeting modifiable patient characteristics linked to non-adherence with the aim to improve outcomes in hypertensive individuals.

Funding: NIDDK Support, Veterans Administration Support

TH-PO547

Soluble Klotho Negatively Correlates with Low-Grade Inflammation in Chronic Kidney Disease Patients: A Prospective Study

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Background: Circulating soluble Klotho (sKLOTHO) is a multifunctional protein, possessing anti-aging properties, recently associated with beneficial modulation of phosphate metabolism, cardiovascular protection and lower oxidative stress. In chronic kidney disease (CKD), sKLOTHO concentrations decrease along with the decrease of kidney function. Our aim was to study the relationship of low-grade inflammation observed in CKD patients with sKLOTHO concentrations.

Methods: The studied group consisted of 90 predialysis CKD patients (13 stage 1, 4 stage 2, 13 stage 3a, 19 stage 3b, 32 stage 4 and 9 stage 5), 52 male and 38 female, age 60+/−11. Serum concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) were measured to assess inflammation. Soluble KLOTHO concentrations were measured in sera of patients using ELISA method.

Results: Median sKLOTHO concentrations in the whole group of patients were 822 (IQR: 475-1078) pg/ml and was highest in patients with stage 1-2 CKD [1078 (990-1832) vs 794 (469-1034) pg/ml; p=0.002]. Median CRP concentrations were 2.13 (IQR: 0.80-4.97) mg/l. In the whole studied group, log(CRP) and log(IL-6) concentrations negatively correlated with log(sKLOTHO) (R=−0.33; p=0.002 and R=−0.25; p=0.014, respectively). Such correlations were observed throughout CKD stages, even in patients with CKD stage ≥ 2 (R=−0.66; p=0.005 and R=−0.75; p=0.001). In the whole group, CRP above the median value was associated with significantly lower sKLOTHO [713 (412-1031) vs 979 (574-1823) pg/ml; p=0.042]. In multiple analysis, log(CRP), but not log(IL-6) was a significant predictor of log(sKLOTHO) concentrations (beta=−0.22/−0.10; p=0.045), independently of age and CKD stage.

Conclusions: In CKD patients chronic low-grade inflammation may be one of the factors lowering sKLOTHO concentrations. It is important to carefully diagnose and treat any inflammatory states in those patients, starting at early stages of CKD.

Funding: Government Support - Non-U.S.

TH-PO548

Inflammomasome Activation by Lipopolysaccharide (LPS) and Angiotensin II (Ang II) in CKD

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Background: Inflammomasome dependent cytokines, such as IL-1β play a role in CKD, but their regulation during renal injury is not clearly elucidated. In this study we analyzed the ontogeny of inflammasome markers during the development of CKD in rats. Earlier studies have shown that changes in gut microbiota releases LPS in the circulation of CKD animals. LPS plays a major role in inflammasome activation. In this study we explored if LPS plays a role to activate inflammasome in CKD.

Methods: CKD was generated in Sprague Dawley rats by 5/6 nephrectomy (Nx). Rats were sacrificed at 2, 4, 8 and 12 weeks after Nx (n=5/group). The controls were sham operated rats sacrificed on the 12th week. A group of Nx rats received 10 mg/kg losartan from 4 to 8 weeks. Kidney cytokines were taken to measure inflammasome markers (NFκB, ASC, caspase 1 and 1L-1β) by western blot. Serum LPS was measured by LAL assay. Ang II levels in the kidney were measured by ELISA. Rat mesangial cells were treated with Ang II and LPS to investigate inflammasome activation.

Results: Serum creatinine and urea significantly went up from 2 weeks onwards and glomerulosclerosis was seen from 4 weeks onward. Kidney LPS levels increased longitudinally from 2 weeks and plateaued at 8 weeks. Significant increase in caspase 1 and IL-1β were seen only at 8 and 12 weeks, whereas ASC increased from 4 weeks. However, pNFκB was significantly activated from 2 weeks onward. Serum LPS significantly increased from 4 weeks onward. Losartan significantly decreased all the inflammasome markers. Mesangial cells were treated with LPS and/or Ang II to investigate inflammasome activation. 50 ng/ml LPS and 10-4M and 10-5M Ang II did not affect inflammasome activation. When 50 ng/ml LPS and Ang II (10−5 M) were combined significant increase in all the inflammasome markers was observed and this was blocked by losartan.

Conclusions: Appearance of LPS at 4 weeks is probably due to increased intestinal permeability associated with CKD. Neither LPS or AngII alone could activate inflammasome. By blocking AT1 receptor we could reduce inflammasome activity. This suggest that Ang II is required for LPS mediated inflammasome activation in CKD.

TH-PO549

Plasma Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Cardiovascular Events and All-Cause Mortality in Patients with Chronic Kidney Disease

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Background: Elevated neutrophil gelatinase-associated lipocalin (NGAL) levels have recently been reported in patients with heart failure, coronary heart disease, or stroke. Here, we aimed to assess the usefulness of plasma NGAL (pNGAL) as a predictor of cardiovascular (CV) events and mortality in patients with chronic kidney disease (CKD).
**Methods:** In this prospective cohort study, the pNGAL level was measured in 371 ambulatory patients with CKD not on dialysis with an estimated glomerular filtration rate < 60 mL/min/1.73 m². CV events were defined as CVD death, acute coronary syndrome, hospitalization for worsening heart failure, stroke, or aortic dissection.

**Results:** During a median follow-up period of 58 months, 84 CV events (22.6%) and 32 deaths (8.6%) occurred. Cox univariate multivariate analysis of all significant variables (p < 0.05) on univariate analysis, pNGAL, B-type natriuretic peptide (BNP), the urinary albumin creatinine ratio, and a history of previous CV diseases were significant predictors of CV events, while pNGAL, BNP, hemoglobin, and age were significant predictors of mortality. Considering both pNGAL and BNP, we stratified patients into four groups, with the median level of each marker as cutoff values (109.7 ng/mL for pNGAL and 42 pg/mL for BNP). Five-year CV event-free survival rates were 94.6%, 80.3%, 68.3%, and 59.4% in the four groups above, respectively (p = 0.0001).

**Conclusions:** Elevated pNGAL could predict future CV events and mortality in patients with CKD, while the combination analysis of pNGAL and BNP was useful in stratifying CV event risk.

**TH-PO551**

**Clinical Significance of Urinary Liver-Type Fatty Acid Binding Protein as a Predictor of End Stage Renal Disease and Cardiovascular Disease in Patients with Chronic Kidney Disease**

**Background:** To improve outcomes in patients with chronic kidney disease (CKD), it is important to identify prognostic factors for end-stage renal disease (ESRD) as well as cardiovascular disease (CVD). This study assessed urinary concentrations of albumin, N-acetyl-b-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP), as predictors of ESRD and CVD.

**Methods:** A prospective, observational, multicenter study, comprising 244 Japanese outpatients with CKD who had a follow-up period of at least 3 months. The primary endpoint was the first onset of a nonfatal or fatal CVD event and progression to ESRD.

**Results:** During the study period, 6 patients in the L group (n=55) and 21 patients in the H group (n=49) started dialysis (p = 0.0005). The dialysis-free survival rates at 60 months in groups L and H were 87.4% and 52.2%, respectively (p < 0.0005). Cox multivariate analysis identified low ADPN (HR, 0.35; p < 0.05), age (HR, 0.9; p < 0.05) and eGFR 30 - 60 mL/min/1.73 m² (HR, 0.07; p = 0.00005) as independent risk factors for end stage kidney disease.

**Conclusions:** High serum adiponectin levels might predict end stage kidney disease in Japanese patients with moderate-to-severe chronic kidney disease.

**TH-PO552**

**The Association Between Direct Measures of Body Fat, Incident Chronic Kidney Disease and Kidney Function Decline: The Health Aging Body and Composition Study**

**Background:** We evaluated and compared the association of CT and anthropometric measures of obesity with kidney outcomes in the Health ABC Study. We hypothesized that CT measures, particularly of visceral fat, would confer the highest risk for kidney outcomes in comparison with other measures.

**Methods:** CT measures included visceral abdominal fat (VAT) and subcutaneous adipose tissue (SAT), anthropometric measures included waist circumference (WC) and body mass index (BMI). Kidney outcomes included incident CKD (follow-up eGFR <60 mL/min/1.73m²) and kidney function decline (30% decrease in eGFR, in follow up either year 3 or 10). Multivariable logistic regression models were used to evaluate the association with outcomes.

**Results:** 2489 individuals were included. Mean age was 74±3, 49% were male, 39% were black and 15% were diabetic. In continuous models SAT, VAT and WC were associated with kidney function decline. VAT, BMI and WC were also all associated with incident CKD, but SAT did not reach statistical significance.

**Conclusions:** Anthropometric measures of body fat appear to provide as reliable estimates of kidney decline risk as direct measures in elders.

**Funding:** NIDDK Support

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

**Underline represents presenting author.**

213A
**TH-PO553**

**Gender Dependent Association Between Metabolic Syndrome and Arterial Stiffness in Patients with Chronic Kidney Disease: Findings from the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) Study**

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**Background:** We investigated the relationships of metabolic syndrome (MS) to arterial stiffness in chronic kidney disease (CKD) patients across a wide range of renal function from early CKD to predialysis.

**Methods:** Risk factors for MS and brachial-ankle pulse wave velocity (baPWV) as measures of arterial stiffness were assessed in 1,256 CKD patients from the KNOW-CKD study. MS was defined by modified National Cholesterol Education Program Adult Treatment Panel III guidelines. Multivariate logistic regression was used to test the association between MS and cardiovascular risk factors, measures of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), and arterial stiffness.

**Results:** Higher arterial stiffness levels were associated with older age, lower estimate glomerular filtration rate, diabetes, and hypertension. Arterial stiffness was not associated with measures of CKD-MBD including total calcium, intact parathyroid hormone, alkaline phosphatase, and albumin. MS was an important determinant of arterial stiffness in CKD patients after adjustment for demographics, cardiovascular risk factors, and CKD-MBD measures, and medication. Systolic blood pressure (SBP) and fasting plasma glucose were the major determinant of arterial stiffness. In sub-analysis by gender, women had more stronger association between arterial stiffness and MS than men. SBP, waist circumference, and triglyceride were independent determinants of arterial stiffness in women, whereas only SBP predicted arterial stiffness in men.

**Conclusions:** The presence of MS and its risk factors were associated with increased arterial stiffness and that these relationships were independent of renal function, CKD-MBD measures, and cardiovascular risk factors in CKD patients. Women had more stronger association between arterial stiffness and MS than men and the association between risk factors for MS and arterial stiffness may differ between men and women in CKD patients.

**Funding:** Government Support - Non-U.S.

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**TH-PO554**

**Body Mass Index (BMI) Has a U-Shaped Association with Chronic Kidney Disease (CKD) Progression in Children with Glomerular Diseases**

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**Background:** In adult patients, BMI has a U-shaped association with disease progression in CKD stages II to IV. Data in children have not been reported. We investigated BMI association with disease progression in the Children in CKD (Cohort).

**Methods:** Children with CKD stages II to IV had annual measurements of glomerular filtration rate (GFR), either directly by iothalamate clearance or estimated using a GFR data-derived equation. Stratifying by CKD diagnosis, glomerular (G) and non-glomerular (NG) diseases, GFR decline rate during follow-up was modeled on baseline BMIz-score for height-age and sex using joint shared-parameter models to account for informative censoring associated with renal replacement therapy (RRT). GFR was log-transformed for height-age and sex using joint shared-parameter models to account for informative censoring associated with renal replacement therapy (RRT). GFR was log-transformed for height-age and sex using joint shared-parameter models to account for informative censoring associated with renal replacement therapy (RRT).

**Results:** 866 children with median age 11 [8.15] yrs and median GFR 52 [38, 71] ml/min/1.73m² at baseline were followed for a median of 4.6 [2.0, 6.9] yrs; 131 children initiated RRT or died (n=2) during follow-up. In 276 children with G diagnoses, expected GFR decline rate exhibited a quadratic relationship with baseline BMIz modeled continuously; R²=0.56. Adjusting for sex, age, black race and proteinuria did not change this relationship qualitatively. In contrast, in 590 children with NG diagnoses, BMIz was not associated with expected GFR decline rate, which was 4.5%/yr.

**Conclusions:** BMIz has a U-shaped association with disease progression in children with CKD stages II to IV with G but not with NG diagnoses. Weight management in CKD children to avoid extremes in BMIz may improve CKD outcomes and await clinical trials confirmation.

**Funding:** NIDDK Support

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**TH-PO555**

**Combination of Low Body Mass Index and Serum Albumin Level Leads to Chronic Kidney Disease Progression: The Chronic Kidney Disease–Research of Outcomes in Treatment and Epidemiology Study**

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**Background:** The relationship between nutritional deficiency and chronic kidney disease (CKD) progression is unknown. In the present prospective cohort study, we evaluated the hypothesis that a combination of low body mass index (BMI) and serum albumin level leads to rapid CKD progression.

**Methods:** The study cohort comprised 728 predialysis patients with CKD (stages 2–5) enrolled from 2010 to 2011. Patients were categorized into 4 groups according to their serum albumin levels and BMI: group 1, low serum albumin level (<4 g/dL) and low BMI (≤23.5 kg/m²); group 2, high serum albumin level (≥4 g/dL) and low BMI; group 3, low serum albumin level and high BMI (≥23.5 kg/m²); and group 4, high serum albumin level and high BMI. The primary outcome was a 30% decline in estimated glomerular filtration rate (eGFR) or start of dialysis within 2 years. The secondary outcome was an annual GFR decline (mL/min/1.73 m²/year).

**Results:** Logistic regression analysis adjusted for baseline characteristics (reference, group 4) showed that only group 1 was associated with a high risk of CKD progression; adjusted odds ratio (aOR) 3.07 [95% confidence interval (CI) 1.51, 6.24]; group 2, aOR 1.81 [95% CI 0.89, 3.70]; group 3, aOR 1.97 [95% CI 0.96, 4.03]. A multivariate general linear regression analysis adjusted for baseline characteristics showed a significant difference in annual eGFR decline between groups 1 and 4 (β = 3.04, P < 0.001).

**Conclusions:** This study suggests that combined effects of low body mass index and serum albumin level lead to CKD progression.

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**TH-PO556**

**Weight Reduction Has an Additive Effect on the Anti-Albuminuric Effect of Angiotensin II Type 1 Receptor Blocker in Hypertensive Patients with Chronic Kidney Disease**

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**Background:** We searched the additive anti-proteinuric effect of weight reduction in addition to medication of an angiotensin II type 1 receptor blocker (ARB) for hypertensive chronic kidney disease (CKD) patients with mild overweight.

**Methods:** This study is a sub-analysis of data from an open-label, case-controlled, randomized clinical trial including 245 hypertensive CKD patients completed the trial (NCT01552954). We were able to calculate the ratios of estimated daily excretion of sodium (eUna), albumin (eUalb), and urea nitrogen (eUUN) in 227 participants during 16 week-trial period with medication of Olmesartan 40 mg a day. The primary outcome of the study was a decrement of eUalb ≥ 25% during 16 weeks. We grouped the participants according to the ratio of weight (WtRatio) during 16 weeks.

**Results:** The baseline mean values of BMI, GFR, and eUalb were 25.4 ± 3.8 kg/m², 67.0 ± 23.9 ml/min/1.73 m² and 1.0 ± 0.7 g/dL, respectively. The proportion of patients that achieved a decrement of eUalb ≥ 25% during 16 weeks with an ARB medication was 93.0% (53/57) in group 1 with a decrement of weight ≥ 1.5%, 83.3% (25/30) in group 2 with weight between -1.4% and -0.1%, and 70.6% (96/136) in group 3 with WtRatio ≥ 0.5% (p = 0.002). The probability of a decrease in albuminuria was 7.405-fold (95% CI: 2.168-25.293, p=0.001) higher in group 1 compared to group 3, as observed in multiple logistic regression analysis as well. The decrement of eUalb was the highest in group 1 (−59.4 ± 47.1%) compared to group 2 (-38.4 ± 70.1%) or group 3 (-26.2 ± 168.4%) (P=0.005).

**Conclusions:** A weight reduction that is part of the medication of an ARB is independent from the change in urinary excretion rate of sodium or urea nitrogen calculated using 24-hour urine collection.

**Key:** The combination of low body mass index and serum albumin level leads to rapid CKD progression.

**Funding:** Pharmaceutical Company Support - Daichi-Sancho Korea and Daesong Pharm.

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**TH-PO557**

**Can Exercise-Induced Proteinuria Predict the Onset of Chronic Kidney Disease?**

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**Background:** Post-exercise proteinuria (PeP) shares characteristics with proteinuria of chronic kidney disease (CKD) including its cause (increased intraglomerular pressures) and its consequences (albuminuria and reduction in glomerular filtration rate). The aim of this study was to perform a systematic review to determine if PeP could predict the onset or progression of CKD.

**Methods:** A systematic review of articles published in Ovid Medline(R), Ovid Medline in process, AMED, EMBASE, Pubmed, Cochrane Library and Web of Science between 1946 and 2014 was conducted. Eligible studies included randomized controlled trials

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

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and prospective observational cohorts whose participants had or were at-risk of CKD and performed an exercise test to elicite PeP. Search terms included: exercise, proteinuria, albuminuria, chronic kidney disease and nephropathy. Primary outcomes examined were biomarkers of CKD (e.g. rise in blood creatinine) during a follow-up period of at least three months.

Results: Five studies (n=351) met inclusion criteria. Full meta-analysis was not possible and PeP measurements varied markedly between studies. Therefore, narrative synthesis was performed. When combining results of the primary outcome in four similar studies (n=318), the presence of PeP was highly associated with elevated resting proteinuria at follow-up (r² test, P < 0.0001) and significant odds ratio (OR) of developing CKD, following a positive exercise test vs. not developing CKD were noted for each of these four studies (OR 2.3 to 2.5). However, interventions induced potential bias with notable differences in type of exercise routines between studies. Also, primary outcomes did not factor in confounding variables (e.g. use of angiotensin receptor antagonists). Finally, findings are only generalisable to a young type 1 diabetes at risk of CKD.

Conclusions: Despite the limited number of studies in the literature and their shortcomings, PeP shows promise as a predictor for CKD progression. However, there is a need to define the most appropriate exercise test for this purpose.

Funding: Private Foundation Support

TH-PO558
Ketanomol Supplementation Decreases Dialysis and Mortality Risk in Patients with Advanced Chronic Kidney Disease
Che-Huang Wu,1 Vincent Wu,2 Tai-Tai Tsai,3 Chi-Hsiung Lui,1 National Taiwan Univ Hospital, Taiwan

Background: The benefit of alpha-ketanomol (KA) supplementation for advanced chronic kidney disease (CKD) patients that followed low-protein diet (LDP) remains undetermined.

Methods: We extracted longitudinal data for all advanced CKD patients in the Taiwan National Health Insurance from January 1, 2000 through December 31, 2010. A total of 1113 patients with advanced CKD treated with LDP (n=835), who started KA supplementation, were enrolled in this study. We analyzed the risks of end stage renal disease and all-cause mortality using Cox proportional hazard models with influential drugs as time-dependent variables.

Results: A total of 1113 events of initiating long-term dialysis and 1228 events of death were observed. Using Cox proportional hazard models with influential drugs as time-dependent variables, KA supplementation was associated with a lower risk for long-term dialysis (table 1) (HR, 0.54 [95% CI 0.47 - 0.62]) and the composite outcome of long-term dialysis or death (HR, 0.49 [95% CI 0.43 - 0.55]) when daily dosage was more than 5.5 tablets. The beneficial effect was consistent in subgroup analysis.

Conclusions: Among advanced CKD patients that followed LDP, KA supplementation at an appropriate dosage may substantially reduce the risk of initiating long-term dialysis or of developing the composite outcome. KA supplementation represents an additional therapeutic strategy to slow the progression of CKD. The promising results in terms of mortality and commencing chronic dialysis need confirmation with different study designs.

Funding: National Taiwan University Hospital, Taipei, Taiwan.

TH-PO561
Serum Phosphorus Individually Predicts Risk of ESRD in an Urban CKD Clinic

Background: Serum phosphorus (PO4) levels have been positively associated with adverse outcomes in chronic kidney disease (CKD) populations, albeit in cross sectional studies of largely Caucasian cohorts. Given differences in vitamin D and PTH homeostasis in African-Americans (AA) and dietary fluctuation, we tested the hypothesis that PO4 measured over time (as is done in clinical practice) will be associated with the risk of dialysis initiation in our urban, predominantly AA CKD population.

Methods: A retrospective cohort of 754 adult patients with CKD (GFR < 60 ml/min at baseline) visiting the nephrology clinic at a large urban county hospital from 2007-10 were followed until death or May 2012. A Cox proportional hazards model adjusted for demographics, comorbidities, medications, and laboratory values was used to study the association of time varying PO4, with the end point of time to dialysis initiation (days to event from index date). Death before dialysis was a censoring event (n=100; 13.2%).

Results: Of 754 patients, 54% were female, 60% were AA and 57% had diabetes mellitus. The mean age was 58.6 ± 13.6 years (mean ± SD), mean eGFR at the start of follow-up period was 33.4 ± 14.9 ml/min/1.73m2. The median PO4 level was 3.9 mg/dl (IQR: 3.3-4.3). PO4 was measured ≥2 times in 437 (58%) patients. During a median follow up of 714 days, 117 (15.5%) patients were initiated on dialysis. When fully evaluated in a multivariable model, the time varying PO4 remained a significant in predicting time to dialysis initiation (HR 1.44, 95%CI 1.07-1.93).

Funding: Pharmaceutical Company Support - Dialysis Clinic, Inc.

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history of cardiovascular disease, eGFR, fasting status, phosphorus-altering medications (oestrogen, testosterone, calcium supplements, and other phosphorus-binding medications), time of day (morning, afternoon, evening), and renal risk factors.

Results: Overall, 25% were fasting lab values and 70% were drawn in the morning (8-12am). Elevated serum phosphorus was associated with increased risk of kidney failure. The highest quartile of serum phosphorus (≥3.8 mg/dL) was associated with a hazard ratio of 1.99 (95% CI: 1.65-2.41) compared to the lowest quartile of serum phosphorus. The relationship between serum phosphorus and risk of kidney failure was similar by gender, baseline eGFR, and time of day of measurement. Associations between serum phosphorus and kidney function were ≥30% similar.

Conclusions: Elevated serum phosphorus is associated with increased risk of kidney failure. Future studies are needed to determine whether lowering phosphorus levels can delay progression to ESRD.

Funding: Private Foundation Support

TH-PO562

Serum Calcification Propensity Signifies Myocardial Injury and Myocardial Structural and Functional Abnormalities in Chronic Kidney Disease

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Background: A recent novel blood test measuring the maturation time of calciprotein particles or serum calcification propensity (T50) has been shown to predict all-cause mortality in CKD subjects. This study aims to elucidate the mechanisms that explain this association.

Methods: We prospectively recruited 300 stages 3–5 non-dialysis CKD patients (age:60±10yrs, 56%men) & 100 healthy control subjects. Echocardiography with tissue Doppler Imaging & plain cardiac multislice computed tomography were done to evaluate cardiac dimensions, function & coronary artery calcium scores. Their associations with T50 were investigated.

Results: T50 was significantly lower in CKD patients vs control subjects (P<0.001). A significant increase in age (P<0.05), serum phosphate (P<0.001), intact parathyroid hormone (P<0.001), C-reactive protein (P<0.031), spot urine protein to creatinine ratio (P<0.001) as well as a decrease in serum albumin (P<0.001) & eGFR (P<0.001) were observed across the three tertiles of decreasing T50 in CKD. Adjusting for age & gender, T50 showed significant inverse associations with left ventricular (LV) mass index (P<0.001), left atrial volume index (P<0.01), early diastolic mitral annular velocity (Em) (P=0.004) & the ratio of early to late diastolic flow velocity (E) to Em (P>0.001) but not systolic functional parameters. Serum T50 retained significant association with cardiac troponin T (P=0.027) in the model adjusting for age, gender, eGFR & LV mass index. T50 however showed no direct correlation with coronary artery calcium scores.

Conclusions: Low T50 may predict adverse outcomes in CKD via its close associations with myocardial injury, myocardial structural & diastolic functional abnormalities. These data suggest T50 may more be a biomarker reflecting myocardial disease rather than calcification of the coronary arteries.

Funding: Pharmaceutical Company Support - Sanofi

TH-PO563

Loss of AT-1 Receptor Regulation in CKD: Role of β-Arrestin2

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Background: Angiotensin II (A-II) is known to play a major role in renal failure. Studies have shown that A-II down regulates AT-1 receptors via β-arrestin2. In CKD A-II levels increase significantly and mediates it action via ERK signaling. Increased A-II levels increase significantly and mediates it action via ERK signaling. Increased A-II concentration of the control animals was 303±19.86 mg/dL) and after treatment (77.83±18.99 mg/dL), and the lowest in patients with pre-dialysis therapy (58.06±20.38 mg/dL). The average concentration of S1P in the plasma were measured using the RP-HPLC. Obtained results were statistically analysed using STATISTICA PL v.10.1.

Methods: The highest average concentration of S1P has been obtained in patients on peritoneal dialysis (83.83±18.99 mg/dL), and the lowest in patients with pre-dialysis therapy (58.06±20.38 mg/dL). The average concentration of S1P in patients before hemodialysis (71.52±19.86 mg/dL) and after treatment (77.83±22.46 mg/dL) were similar. Significant differences in concentration of S1P were found between patients with peritoneal dialysis and pre-dialysis patients (p = 0.0002) and between patients after hemodialysis and pre-dialysis (p = 0.003).

Conclusions: Observed higher concentrations of S1P in hemodialysis patients and peritoneal dialysis in comparison to patients treated conservatively. Indicate that activation of different lipid sources may be caused by the activation of the coagulation system and increased oxidative stress.

Acknowledgments: This study was supported by a grant awarded by the Polish National Science Center (2011/01/B/NSZ/04235) and as part of a doctoral scholarship ETIUDA by the Polish National Science Center (DEC-2013/08/T/NSZ/00716).

TH-PO564

Sphingosine 1-Phosphate Changes in Patients with Chronic Kidney Disease on Hemodialysis and Peritoneal Dialysis

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Background: Sphingosine-1-phosphate is involved in the development and pathogenesis of renal function and physiology of many renal diseases including chronic kidney disease. Changes in concentrations of sphingosine-1-phosphate may affect the renal function and appear to be potential indicators of renal damage and renal graft function. This study was the associations of the bioclinical parameters and quantitative analysis of the concentrations of sphingosine-1-phosphate in patients with chronic renal failure undergoing peritoneal dialysis, hemodialysis, or pre-dialysis.

Methods: The study included 120 patients with CKD; on peritoneal dialysis (n=30) and hemodialysis (n=30), in predialysis state (n=60). The concentrations of biochemical parameters in serum were determined by colorimetric methods. The concentrations of S1P in the plasma were measured using the RP-HPLC. Obtained results were statistically analysed using STATISTICA PL v.10.1.

Results: The highest average concentration of S1P has been obtained in patients on peritoneal dialysis (83.83±18.99 mg/dL), and the lowest in patients with pre-dialysis therapy (58.06±20.38 mg/dL). The average concentration of S1P in patients before hemodialysis (71.52±19.86 mg/dL) and after treatment (77.83±22.46 mg/dL) were similar. Significant differences in concentration of S1P were found between patients with peritoneal dialysis and pre-dialysis patients (p = 0.0002) and between patients after hemodialysis and pre-dialysis (p = 0.003).

Conclusions: Observed higher concentrations of S1P in hemodialysis patients and peritoneal dialysis in comparison to patients treated conservatively. Indicate that activation of different lipid sources may be caused by the activation of the coagulation system and increased oxidative stress.

Acknowledgments: This study was supported by a grant awarded by the Polish National Science Center (2011/01/B/NSZ/04235) and as part of a doctoral scholarship ETIUDA by the Polish National Science Center (DEC-2013/08/T/NSZ/00716).

TH-PO565

Renal Elasticity of Patients with Chronic Kidney Disease Evaluated with Real-Time Ultrasound Elastography

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Background: Ultrasound real-time elastography is a new imaging technique, which provides information about the elasticity of soft tissue. It is widely applied in patients with liver disease. In patients with chronic kidney disease (CKD), glomerulosclerosis and tubulointerstitial fibrosis could be associated with lower renal parenchymal elasticity. However, little is known about the elasticity of the kidney. We designed a study to evaluate renal elasticity in patients with CKD stage 3-5.

Methods: There were 148 healthy volunteers and 227 patients with CKD in this cohort from Southern Taiwan. Renal sonography was performed on the Hitachi EUB 7500 and HVISION PROVIEUS sonographer with elastography and the EUP-C715 (1-5MHz) probe. Elastograms were compared with the control group. Patients with later CKD stages had lower value of renal elasticity, which means more stiff (p<0.001), and showed a median urinary albumin excretion rate ≥30 mg/24 h.

Results: There were 143 (63.0%) male, 166 (73.1%) diabetes, with a mean estimated glomerular filtration rate (eGFR) of 216 ml/min/1.73 m². The mean age was 15.8 ml/min/1.73 m² and a median urinary protein-to-creatinine ratio (UPCR) 502 (122-1491) mg/g in the CKD group. Patients with later CKD stages had lower value of renal elasticity, which means more stiff (p<0.001), and showed a median urinary albumin excretion rate ≥30 mg/24h.

Conclusions: A-II mediated deleterious effect on CKD.

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elastcity for rapid renal progression was 0.928 (95% CI, 0.864-0.997; \( P = 0.042 \)). The OR per 1 mm change of renal long length for rapid renal progression was 1.022 (95% CI, 0.994-1.050; \( P = 0.125 \)).

**Conclusions:** Renal elasticity is associated with proteinuria and rapid renal progression in patients with CKD. It may be a useful tool for early detecting renal function change in patients with CKD.

**Funding:** Clinical Revenue Support

**TH-PO567**

**The Availability of Proteinuria/Urinary Beta2-Microglobulin Combination as a Complementary Marker to Predict Early Progression in Chronic Kidney Disease**

**Chang Hwa Lee,** II hwan Oh, Joon-sung Park.

**Background:** Proteinuria as a marker of glomerular damage is of pathogenic importance to the progression of chronic kidney disease (CKD). However, renal tubulointerstitial damage can serve a common pathway of CKD progression. Urinary beta2-microglobulin excretion, a marker of proximal tubular damage, may reflect the presence of tubulointerstitial damage. We hypothesized that the combination of proteinuria and urinary beta2-microglobulin may be a useful predictor of renal outcome.

**Methods:** Proteinuria and urinary beta2-microglobulin excretion were measured in 104 patients with CKD. Based on the value of urine protein-to-creatinine ratio (PCR) or urinary beta2-microglobulin-to-creatinine ratio (UBCR), a total of 104 patients were divided into four groups: group I (\( n = 39 \)), PCR < 0.5 mg/g and UBCR < 300 mmol/g; group II (\( n = 16 \)), PCR < 0.5 mg/g and UBCR 300-600 mmol/g; group III (\( n = 24 \)), PCR 0.5-2 mg/g and UBCR 300-600 mmol/g; group IV (\( n = 25 \)), PCR 0.5-2 mg/g and UBCR > 600 mmol/g.

**Logistic regression analysis was used to compute odds ratio to examine the relationship of proteinuria or increased UBCR with deterioration of renal function (DRF), and Kaplan-Meier analysis was used to compare cumulative renal survivals among the groups.

**Results:** During a mean follow-up of 71 ± 21 months, renal function deteriorated in 28 of the 104 patients with CKD. Among four groups, there was statistically significant difference in gender (\( P = 0.0198 \)), serum glucose (\( P = 0.0147 \)), serum uric acid (\( P < 0.0279 \)), and eGFR at 12 months (\( P < 0.0158 \)). Logistic regression analysis identified the only combination of proteinuria and high UBCR (OR 7.396; 95% CI, 1.235 to 44.284; \( P = 0.028 \)) as risk factors for DRF. In Kaplan-Meier analyses, group IV had the most inferior cumulative renal survival rate and there were statistically significant difference among the groups (\( P = 0.008 \)).

**Conclusions:** The combination of protein and beta2-microglobulin in urine of CKD may be useful predictors of long-term renal survival. Proteinuria and beta2-microglobulin should not be discretely but simultaneously considered to early detect and delay DRF.

**Funding:** Government Support - Non-U.S.

**TH-PO569**

**Renal Hypertrophy Predicts Increased Urinary Albumin Excretion in the General Non-Diabetic Population**

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**Background:** In cohort studies, both low and high estimated glomerular filtration rate (eGFR) have predicted cardiovascular disease (CVD) and death. The increased risk associated with low eGFR has been explained by confounding due to a low serum creatinine in persons with chronic illness. However, abnormally high GFR, renal hypertension, has been hypothesized to cause elevated urinary albumin excretion, a known risk factor for the development of chronic kidney disease (CKD) and hypertension. However, renal hypertension has been hypothesized to cause elevated urinary albumin excretion, a known risk factor for the development of chronic kidney disease (CKD) and hypertension. We investigated this hypothesis in the non-diabetic general population using measurements of GFR instead of eGFR.

**Methods:** In 2007-2009 we measured GFR by iohexol clearance in 1552 persons aged 50-62 years from the general population without diabetes or high albumin-creatinine ratio (ACR) (ACR > 3mg/mmol). 1274 (82%) had a follow-up measurement of GFR in 2013-2015. 36 persons with diabetes at follow-up were excluded. Hypertrophy was defined as an increase in absolute GFR (positive AGFR) within the same individual between baseline and follow-up. Since nephron number does not increase with age, this will be a proxy for increased single nephron GFR.

**Results:** AGFR was positively associated with a change in logi (AGFR) in multiple linear regression. The ratio AGFR/ACRbaseline increased 7% (95% CI: 0.4 to 13%) per standard deviation (SD) increase in AGFR. The top AGFR quartile was associated with a 34% (95% CI: 8 – 68%) increased AGFR/ACRbaseline ratio in women, but not in men, p=0.05 for the interaction. The odds ratio (95% CI) of high AGFR at follow-up was 2.0 (1.3 – 2.9) per SD increase in AGFR. We adjusted for baseline CVD risk factors and change in body weight and food intake, and anti-hypertensive medication.

**Conclusions:** Hypertrophy predicts high AGFR in the general population without diabetes. Although this may represent a link between hypertension and an increased risk of CVD and mortality, it is unknown whether hypertension is associated with these outcomes.

**Funding:** Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.
TH-PO570

Associations Between Uric Acid, Adiponectin and Urinary Biomarkers in Persons with and without the Metabolic Syndrome Mari D. Solbu,1,2 Jon viljar Norvik,2 Jens Kronborg,3 Bjorn Odvar Eriksen,1 Toralf Melsom,1 Trond G. Jenssen.1 1Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; 2Medical and Renal Research Group, UiT the Arctic Univ of North Norway, Tromsø, Norway; 3Unlandet Hospital Trust, Lillehammer, Norway; 4Oslo Univ Hospital, Oslo, Norway.

Background: In the metabolic syndrome (MetS), serum uric acid (UA) is often increased, and adiponectin is low; UA may cause renal damage, whereas adiponectin may be renoprotective. It is not known whether UA and adiponectin interact in development of renal damage. We assessed the cross-sectional association between UA, adiponectin and two urinary biomarkers (albumin creatinine ratio (ACR) and orosomucoid creatinine ratio (oCR)) in persons with or without the MetS (NCEP-ATPIII definition). Methods: From the Tromsø Study 2007-08, 7047 persons were included. Three urine specimens were collected and median values of ACR and oCR used. The associations between UA, adiponectin and the upper vs. three lower quartiles of each biomarker were assessed by logistic regression analysis adjusted for cardiovascular risk factors, medication use and eGFR in persons with and without the MetS. Results: Mean age was 63.5 (±SD 9.2) years, 57% were women and 27% had the MetS. UA was associated positively with the upper ACR quartile and negatively with the upper oCR quartile. The association with ACR was stronger in persons with the MetS than in those without (OR 1.18; 95% CI 1.07-1.31; P=0.002 vs. OR 1.08; 95% CI 1.01-1.16; p=0.04 per 1 mg/dl increase in UA). Adiponectin was positively associated with ACR and oCR, but only in persons without the MetS (OR 1.08 (95% CI 1.04-1.13); OR 1.07 (95% CI 1.03-1.12), both P<0.001, per µg/ml). There were no interactions between UA and adiponectin in their associations with the urinary biomarkers. Conclusions: UA and adiponectin did not interact in their associations with biomarkers of renal damage. Contrary to what we expected, adiponectin was positively associated with ACR and oCR, but only in persons without the MetS. UA was positively associated with ACR only. The findings should be studied longitudinally before firm conclusions could be made.

Funding: Government Support - Non-U.S.

TH-PO571

The Longitudinal Association Between Uric Acid Level and Progression of Chronic Kidney Disease in Chinese Population Ching-Wei Tsai, Shih-yi Lin, Chin-Chi Kuo, Chiu-Ching Huang, Div of Nephrology and Kidney Inst, China Medical Univ and Hospitals, Taichung, Taiwan.

Background: Hyperuricemia is commonly observed in patients with chronic kidney disease (CKD). Although increasing evidence supports the association between hyperuricemia and incident CKD, there are conflicting data about the role of hyperuricemia in the progression of CKD. The aim of current study was to add empirical evidence to the debate on the direction of the relationship among uric acid levels, allopurinol, and CKD progression in Chinese population.

Methods: We conducted a retrospective cohort study in central Taiwan. Patients who had documented hyperuricemia (defined by uric acid greater than 7 mg/dL) and/or receiving uric acid-lowering agents between 2003 and 2005 were included in the study. They were followed till December 31, 2011. Only patients with at least three available renal function profiles were analyzed. CKD progression was evaluated by the change in eGFR using linear mixed models.

Results: Longitudinal analyses showed patients with a baseline uric acid level greater than 7 mg/dL had faster decline in eGFR, comparing to those with uric acid level less than 7 mg/dL. After adjustment for demographics, comorbidities, proteinuria, allopurinol and ACEI/ARB use, three categories of hyperuricemia (uric acid 7-9, 9-11, >11 mg/dL) remained strongly associated with faster decline in eGFR over the follow-up. In multivariate longitudinal analysis, those receiving allopurinol was associated with a significantly faster decline in eGFR than non-allopurinol users during the follow-up.

Conclusions: Our study showed higher uric acid level is strongly associated with an accelerated decline in renal function in Chinese population. However, uric acid-lowering therapy with allopurinol was associated with even faster progression of CKD in this study.

TH-PO572

Revisiting Medullary Tophi: A Link Between Uric Acid and Progressive Chronic Kidney Disease? Salem Almanna, Isabelle Ayoub, Sergey V. Brodsky, Tibor Nadassy, Jason Prosek, Lee A. Hebert, Brad H. Rovin. 1Div of Nephrology, The Ohio State Univ, Columbus, OH; 2Dept of Pathology, The Ohio State Univ, Columbus, OH.

Background: It is well-established from autopsy studies that gouty tophi can form in the kidney, particularly in the renal medulla. Recently hyperuricemia has been identified as a risk factor for progression of chronic kidney disease (CKD). Because each collecting duct serves more than 2000 nephrons, we postulated that obstruction or disruption of the collecting ducts by medullary tophi may explain, at least in part, the association between hyperuricemia and progressive CKD. This work was done to determine the prevalence of medullary tophi in CKD patients.

Methods: We queried our nephropathology database over the last ten years for native kidney biopsies that had medullary tophi. The presence or absence of CKD and uric acid levels around the time of biopsy were determined by chart review.

Results: Predominant medullary tissue was reported in 796 of 7409 total biopsies, and 572 of these were from patients with established CKD. Medullary tophi were seen in 36 patients, 35 of whom had CKD, suggesting a minimum prevalence of tophi in CKD and no-CKD of 6.11% and 0.45%, respectively. Medullary tophi occurred with and without hyperuricemia or a history of gout.

ID Age Race Gout Nephrolithiasis Serum Creatinine Concentration/eGFR Serum Uric Acid Concentration
1 42 CAU Yes No 2.8/26 9.1
2 47 CAU No No 1.6/46 7.9
3 37 CAU No No 1.5/39 8.7
4 69 CAU Yes Yes 2.9/21 9.1
5 54 CAU No No 4.0/19 9.8
6 65 CAU Yes No 6.5/6 6.3
7 52 CAU No No 2.5/28 7.5
8 60 CAU No No 4.2/11 5 Normal
9 36 CAU No No 10.7/5 8 8.8
10 22 H Yes NA 13.5/4 9 Normal
11 37 NA No No 26/NA 6.0
12 65 CAU Yes No 2.5/20 5 5.8
13 67 CAU Yes NA 2.2/4 6.8
14 22 H No No 2.8/35 10.1
15 51 CAU Yes Na 14/NA 17.4
16 40 CAU No No 1.5/40 13.5

Conclusions: Medullary tophi appear to be far more likely to occur in CKD compared to no-CKD patients. This cross-sectional study cannot determine whether medullary tophi are a cause or consequence of CKD. However, given their strategic location and bulk, it is possible that medullary tophi contribute to progression of established CKD by causing upstream nephron damage.

TH-PO573

Serum Uric Acid Over 7 mg/DL is an Independent Risk of Incident End Stage Kidney Disease – A 6-Year Population-Based Cohort Study Ouppatham Supasyndh, Puvanant Wiputhanuphong, Bancha Satirapoj. Nephrology Div, Dept of Internal Medicine, Phramongkutklao Hospital and College of Medicine, Thailand.

Background: Uric acid deteriorates kidney function via crystal and non-crystal dependent mechanisms. However epidemiological evidence for the significance of serum uric acid levels on the risk for developing end-stage kidney disease (ESKD) is scarce in a setting of population-based screening especially in Asian population. The purpose of the study was to evaluate the effect of serum uric acid level on incidence of impaired kidney function and ESKD.

Methods: A total of 23,712 individuals from an integrated health care delivery system in the Thai army who participated for health checkups between July 1, 2006, and December 31, 2012 were screened. Only 18,390 participants (14,686 men, 3,704 women) older than 20 years for whom available for body weight, serum uric acid, and creatinine data were documented were enrolled in the study. The cumulative incidence of chronic kidney disease (CKD, eGFR<60 mL/min per 1.73m²) and ESKD (eGFR<15 mL/min per 1.73 m²) was calculated according to quartiles of baseline serum uric acid levels and significant high serum uric acid levels (≥7.0 mg/dL).

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

Underline represents presenting author.
Results: The mean age of participants was 47.9±6.96 years and body mass index was 24.7±3.47 kg/m². HbA1c in percent (n=2,648) was diabetes and 65.2% (n=11,598) had high blood pressure. Average serum uric acid and eGFR were 6.29±1.55 mg/dL and 87.84±13.27 mL/min per 1.73 m², respectively. The incidence of CKD at 6 years follow up was 3.64/1000 person-year. A total of 11 patients (0.06%) of ESKD were observed. Participants with highest serum uric acid quartile (>7 mg/dL) had a 3.42-fold increase in adjusted hazard ratio (HR) (95%CI; 2.19 to 5.32), compared to those with the lowest serum uric acid quartile (<5.2 mg/dL). Moreover, serum uric acid ≥ 7 mg/dL were significantly increased risk of ESKD (adjusted HR 5.74 with 95% CI; 1.58 to 20.8, P =0.008). Finally, elevated serum uric acid ≥ 7 mg/dL were significantly increased risk of ESKD (adjusted HR 5.74 with 95% CI; 1.58 to 20.8, P =0.008). Finally, elevated serum uric acid ≥ 7 mg/dL were significantly increased risk of ESKD (adjusted HR 5.74 with 95% CI; 1.58 to 20.8, P =0.008). Finally, elevated serum uric acid ≥ 7 mg/dL were significantly increased risk of ESKD (adjusted HR 5.74 with 95% CI; 1.58 to 20.8, P =0.008).

Conclusions: Serum uric acid level is an independent risk of CKD and ESKD in Thai population.

TH-P0574

Proton Pump Inhibitors Are Associated with Increased Risk of Development of Chronic Kidney Disease

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Background: Proton pump inhibitors (PPI) are one of the common cause of acute gastrointestinal in the United States. This frequency goes undiagnosed due to its subacute clinical presentation, which may later present as chronic kidney disease (CKD).

Methods: The population included 99,351 patients who were seen in primary care VISN2 clinics from 4/2001 until 4/2008. For evaluation of CKD outcome, 27,835 patients with baseline CKD were excluded. Study data was obtained from Veterans Affairs Health Care System (VAHCS)/ Network health data. Data obtained included use of PPI (Yes/No), age, gender, race, retrospective observation time, laboratory data including eGFR, pre-PPI comorbidity variables: vascular disease, chronic obstructive pulmonary disease (COPD), cancer, diabetes, and hypertension. A prospective logistic analysis of case-control data (Prentice and Pyke) was used to investigate the association of treatment (exposure to PPI) with onset of CKD with propensity score in the model.

Results: A total of 24,149/71,516 patients developed CKD. Of those who developed CKD 25.7% were treated with PPI. Patients receiving PPI were more likely to have vascular disease, COPD, cancer and hypertension. Of the total 99,251 patients analyzed 2.06) among patients taking PPIs versus those not on PPIs. Sensitivity analyses showed a 1.29 95% CI 1.24-1.34) and mortality (OR 1.97, 95% CI 1.88-2.06) among patients taking PPIs versus those not on PPIs.

Conclusions: Use of proton pump inhibitors are associated with increased risk of development of CKD.

TH-P0577

Influence of Statin on Iron Utilization and Metabolism in Patients with Chronic Kidney Disease Stage 3a

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Background: Heparin is a natural peptide protein that is a regulator of iron homeostasis. Elevated hepcidin levels are expected in the face of decreased glomerular filtration and inflammation. Heparin is a potentially modifiable mediator of anemia in patients with chronic kidney disease (CKD). Statins have had potent anti-inflammatory effects in experimental and clinical CKD and may thereby modulate erythropoiesis.

Methods: Thirty-six patients (17 M, 19 F, mean age 58±13 years: 20 stage 3 and 4 CKD and LDL cholesterol >100 mg/dl not on statin therapy were studied. In a double blind, crossover study all subjects received in a random order either atorvastatin 20 mg/ day or placebo for two 6-month periods with 3-month wash-out. Basic biochemistry, serum inflammatory markers such as hsCRP, IL-6, parameters of iron metabolism including iron, serum hepcidin, Total Iron Binding Capacity (TIBC), Unsaturated Iron Binding Capacity (UIBC) and hemoglobin were measured both before and after each treatment period.

Results: TIBC, UIBC did not change during placebo phase but significantly decreased after 6 months statin therapy from 255±43 to 267±45 (p=0.006) and from 186±48 to 196±50 (p=0.03) respectively. Serum iron tended to increase from 68.8±19 lg/dl to 72±4±17,8±4 (p=0.08) only during statin treatment. Hemoglobin increased after 6 months statin therapy from 11.6±1.6 to 11.8±1.5 (p=0.001) while after placebo period hemoglobin did not change. Heparin levels significantly decreased during statin treatment from 24±1±37 to 160±20pg/ml (p=0.01), while no effect was found during placebo phase. Hemoglobin levels did not change after both statin and placebo. IL-6 and hsCRP tended to decrease after 6 months only after statin therapy (from 11.5±11 to 11.1±11, p=0.06). Adjustment for these factors, we found that the use of HRT was still significantly associated with baseline albumin/creatinine ratio (UACR) and estimated glomerular filtration (eGFR) using the CKD-EPI equation, between women who were using HRT (n=673, median age 60.2) and those who were not (n=1544, median age 62.9). Clinical characteristics, including body mass index (BMI), medical history, medications, family history and blood and urine tests were measured at a median study visit conducted between 2000-2004.

Results: UACR was significantly lower in those on HRT versus those who were not (3.5±3.2 mg/g Cr, p=0.001), as was the number of women with eGFR < 60 ml/min/1.73 m² (7% vs. 10%, p=0.003). We performed linear and logistic regression models using generalized estimating equations for log(UACR), UACR > 25 mg/g Cr and eGFR < 60 ml/ min/1.73 m² and adjusted for age, race, network, education, smoking, diabetes, hypertension, and other cardiovascular risk factors. After adjusting for these factors, we found that the use of HRT was still significantly associated with lower log(UACR) [-0.307, p=0.001] and women on HRT had an odds of 1.6 (95% CI 1.2-2.3) times that of those on HRT of having UACR > 25 mg/g Cr. The association between HRT and eGFR < 60 ml/min/1.73 m² was no longer significant after adjustment.

Conclusions: The use of HRT in post-menopausal women was associated with lower UACR after adjusting for known risk factors for renal and cardiovascular disease. Strengths of our study include a large sample size and a comprehensive medical history of subjects. Limitations include that subjects were recruited on the basis of hypertension and that we had limited information on the length of time on HRT.

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Underline represents presenting author.

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Tobacco Smoking and Progression of Chronic Kidney Disease: A Role for Reactive Aldehydes? Gabriel Rezonne,1 Phillip H. Chumley,1 Wenguang Feng,1 Ping Hua,1 Huma Fatima,1 Edgar A. Jaimes.2 1Univ of Alabama at Birmingham; 2Memorial Sloan Kettering Cancer Center.

Background: Clinical and experimental evidence supports the role of tobacco smoking as a risk factor in the progression of chronic kidney disease (CKD) of different etiologies. Cigarette smoke (CS) contains numerous compounds that could be responsible for deleterious effects of tobacco smoking. Among these compounds are included large concentrations of reactive aldehydes such as acrolein that react with thiol groups and active NADPH oxidase as we have previously shown (ATVB’04). In these studies we postulated the hypothesis that acrolein (Ac) accelerates the progression of CKD and that these effects are linked to increased oxidative stress.

Methods: Sprague-Dawley rats (n=6-8) were divided in the following groups: Sham, Sham+Ac (0.5 mg/kg/day via osmotic minipump), 5/6Nx and 5/6Nx+Ac. Rats were euthanized after 12 weeks and kidneys were collected for glomerular injury score (GIS) and tubular injury score (TIS). Urine protein concentration was collected every two weeks for proteinuria (Bio-Rad). Urinary isoprostanes and TGF-β were measured by Elisa and adjusted for urinary creatinine.

Results: Sham rats on Ac had a significant increase in proteinuria, urinary excretion of isoprostanes and TGF-β, TIS but not GIS. Rats with 5/6Nx had a significant increase in proteinuria, TIS and GIS and a modest increase in TGF-β. The administration of Ac to 5/6Nx resulted in further increases in proteinuria, isoprostanes and TIS but not GIS. The urinary excretion of TGF-β in these rats was also increased and similar to Sham+Ac.

Conclusions: These results suggest that the reactive aldehyde acrolein plays a role as mediator of the deleterious effects of tobacco smoking in the progression of CKD.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

Intermittent Smoking Associates with Chronic Kidney Disease in U.S. Hispanics: The Hispanic Community Health Study/ the study of Latinos (HCHS/SOL) Nora Franceschini. Epidemiology, Univ of North Carolina, Chapel Hill, NC.

Background: Cumulative smoking exposure is associated with chronic kidney disease (CKD). However, the patterns of exposure, such as the effect of intermittent smoking, on CKD risk are unknown. These patterns may be important given the recent increase in alternative smoking exposures such as e-cigarettes.

Methods: Cross-sectional study of 15,664 participants of a population-based cohort of Hispanic/Latinos aged 18-74 years recruited from 4 U.S. field centers from 2008 to 2011. Data on current, past and never smoking, and smoking pack-years were obtained through a questionnaire. The association between smoking exposure and CKD (estimated glomerular filtration rate <60 ml/min/1.73 m² or urine albumin to creatinine ratio ≥ 30 mg/g) was estimated using logistic regression models. We tested the interaction between smoking status and cumulative pack-years at the significance level of 0.05.

Results: Approximately 62% individuals were non-smokers, 17% were past smokers and 22% were current smokers, of which 14% were daily smokers and 8% were intermittent smokers. The adjusted prevalence estimates of CKD were 10% for non-smokers, 8% for daily smokers and 12% for intermittent smokers. There was a significant interaction between smoking status with pack-years of exposure (p=0.0002).

In adjusted models accounting for this interaction, there were increased odds of CKD among current daily, intermittent, and past smokers compared to never smokers. The association of intermittent smokers with CKD was significant at 10 pack-years compared to never smokers. The adjusted prevalence estimates of CKD were 10% for non-smokers, 11% for daily smokers, whereas for past smokers, it was observed only at 40 pack-years of smoking.

Conclusions: These results suggest that the reactive aldehyde acrolein plays a role as mediator of the deleterious effects of tobacco smoking in the progression of CKD. Further studies are needed to delineate the pathophysiological mechanisms and clinical implications of incidence of CKD in patients with COPD.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

Incidence of Chronic Kidney Disease in Patients with COPD: Systematic Review and Meta-Analysis Swarna Goudman,† Sameer K. Gunukula,1 James W. Lohr,‡ Nader Nader,§ Pradeep Arora.†1 Medicine, SUNY at Buffalo, Buffalo, NY; 2Medicine, VAMC, Buffalo, NY; 3Anesthesiology, VAMC, Buffalo, NY.

Background: Chronic obstructive pulmonary disease (COPD) is common disease especially in elderly population, and is a important cause of mortality world-wide. Several studies have identified COPD as part of a systemic inflammatory syndrome and reported the association of comorbidities such as lung cancer. COPD is an important risk factor for the development of atherosclerosis. However, the relationship between COPD and incidence of chronic kidney disease (CKD) has not been clearly demonstrated in the literature. The focus of our study was to systematically review the medical literature reporting the incidence of renal function disturbances specifically incidence of CKD in patients with COPD.

Methods: We conducted a systematic review using the Cochrane Collaboration Methodology. We searched Medline via Ovid, Pubmed, Embase and ISBI web of Science databases from 1950 through 2015. We rated the quality of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Meta-analysis was done using Review Manager Version 5.0.20.

Results: Our search resulted in 8 eligible studies. COPD was found to be associated with a significantly increased incidence of CKD (Odds Ratio [OR]=2.10; 95% Confidence Interval [CI] 2.04, 2.16).

Conclusions: COPD patients are at increased risk of developing chronic kidney disease. The exact reasons for the increase in the incidence of CKD are unclear. Clinical research and practice guidelines usually target disease conditions in isolation. Research into COPD and CKD is scant and there is a need for further studies to delve into the pathophysiological mechanisms and clinical implications of incidence of CKD in patients with COPD.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

Effects of Nicotine on the Severity of the Diabetic Nephropathy: Role of α7-Nicotinic Acetylcholine Receptor Mohammed Siddiqui,† Wenguang Feng,† Gabriel Rezonne,‡ Lawrence P. Wennogle,§ Edgar A. Jaimes.† 1Univ of Alabama at Birmingham; 2Intra-cellular Therapies; 3Memorial Sloan Kettering Cancer Center.

Background: Tobacco smoking plays a major role in progression of chronic kidney disease (CKD) of different etiologies including diabetes mellitus (DM). In previous studies we demonstrated that nicotine is responsible for deleterious effects of smoking in the progression of CKD and pharmacologic blockade of the α7-nicotinic receptor subunit (α7-nAChR) reduces the effects of nicotine in a CKD rat model. Whether this receptor also plays a role in the progression of CKD such as diabetic nephropathy is still unknown.

Methods: DM was induced with streptozotocin (STZ) in eNOS−/− and eNOS+/−α7-nAChR−/− (DKO) mice. A separate group of eNOS−/− mice also received a α7-nAChR blocker (IC200610, 2 mg/kg IP, 5 days a week for 10 weeks). Mice were given nicotine (100mg/ml in drinking water) or tap water for 10 weeks. Blood pressure (BP) was measured by tail-cuff method and urine collected every 2 weeks for albuminuria.

Results: All mice became diabetic after STZ and had no significant differences in weight or blood glucose at sacrifice. All animals were also hypertensive and nicotine had no effect on BP in any of the groups. Diabetic mice receiving nicotine (DN) had higher albumin excretion as compared to diabetic mice on tap water (DT). Diabetic mice on nicotine lacking the α7-nAChR (DN−/−) or pharmacologic blockade (DN+B) had urinary excretions of albumin similar to diabetics on tap water (DT). Neither absence of the α7-nAChR (DT−/−) nor pharmacologic blockade (DT+B) had any effect on mice on tap water.

Conclusions: These studies demonstrate that α7-nAChR is a critical mediator of the deleterious effects of nicotine in the severity of diabetic nephropathy.

Funding: Other NIH Support - National Institute of Environmental Health Sciences

Incidence of Chronic Kidney Disease in Patients with COPD: Systematic Review and Meta-Analysis Swarna Goudman, Sameer K. Gunukula, James W. Lohr, Nader Nader, Pradeep Arora. Medicine, SUNY at Buffalo, Buffalo, NY; Medicine, VAMC, Buffalo, NY; Anesthesiology, VAMC, Buffalo, NY.
Lithium Nephropathy: A Long-Term Complication of Chronic Lithium Therapy

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Background: Lithium is the treatment of choice for bipolar disorder. Lithium-induced nephropathy is a known complication limiting its use. The aim of this study is to establish the prevalence of renal failure in our population. We sought to quantify the contribution of lithium to developing renal failure.

Methods: We selected 1751 patients on lithium therapy from the laboratory database of the Delta Center for Mental Health Care, Rotterdam. The database contains measurements of lithium and creatinine concentration over a period from 2000 to 2011. eGFR was calculated using the MDRD formula. Renal failure was defined as having GFR < 60 mL/min on at least 2 measurements 6 weeks apart. A comparison was made between patients with and without renal insufficiency regarding gender, mean lithium concentration in serum, lithium intoxication, duration of therapy, age at initiation of therapy, cardiovascular disease, hypertension and diabetes mellitus.

Results: 305 out of 1751 (17.4%) patients were classified as having renal failure. Occurrence of renal failure was positively correlated with female sex, age at initiation of therapy and duration of lithium therapy (p<0.001). Significant correlation was also observed between renal failure and cardiovascular risk factors. Mean lithium serum concentration was 0.68 mmol/l and did not differ between patients with and without renal failure. In 251 patients follow up data was available for a period of more than 10 years. In these patients history of lithium intoxication did not predict occurrence of renal failure.

Conclusions: Prevalence of renal failure in our cohort is similar to other reports. Longer duration of lithium therapy was found to be associated with an increased risk of renal failure. Contrary to our expectation, lithium intoxication was not correlated with renal failure. Although therapy duration was a significant predictor, one should not forget the importance of cardiovascular risk factors in development of renal failure.

Study of Organochlorine Pesticides in Patients with Chronic Kidney Disease of Unknown Etiology

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Background: An apparently new form of CKD not attributable to diabetes, hypertension or other known causes, i.e. CKD of unknown etiology (CKDu) has emerged in South Asia, especially Sri Lanka, and Sub-Saharan Africa in the last one decade. CKDu affects younger individuals and is asymptomatic until advanced stages. Organochlorine pesticides (OCPs) are implicated in the etiopathogenesis of CKDu. This study aimed at estimating the serum levels of various OCPs (α-HCH, β-HCH, γ-HCH, total HCH, Aldrin, Dieldrin, α-endosulfan, β-endosulfan, p,p’-DDE, p,p’-DDD and total pesticide load (TPL)) in patients with CKDu in comparison with patients with CKD of known etiology (CKDk) and to assess their role in etiopathogenesis of CKDu.

Methods: This was a case-control, cross-sectional study conducted in east Delhi. Subjects in the age group 18-60 years of either sex were recruited under 3 groups: Group I: Healthy controls (n=30), Group II: Patients with CKDu (n=30) and Group III: Patients with CKDk (n=30). Detailed history, physical examination, routine investigations and urinary protein excretion estimation were done. Serum OCP levels were estimated by high performance liquid chromatography.

Results: The median serum levels of all OCPs were higher in patients of group II as compared to other study groups and this difference was statistically significant for α-HCH, β-HCH, γ-HCH, total HCH, Aldrin, Dieldrin, α-endosulfan and β-endosulfan, p,p’-DDE, p,p’-DDD and total pesticide load (TPL) in patients with CKDu in comparison with patients with CKD of known etiology (CKDk) and to assess their role in etiopathogenesis of CKDu.

Conclusions: Despite some limitations of the study, the presence of higher serum OCPs in individuals with CKDu in comparison to CKDk at corresponding CKD stages suggests their possible role in the etiopathogenesis of CKDu.

Funding: Government Support - Non-U.S.

High-Density Lipoprotein Subfractions and Their Oxidized Subfraction Particles in Patients with Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) may lead to reduced concentrations of high-density lipoprotein (HDL) and its subfractions (HDL2 and HDL3), and damage them via inflammation and oxidative stress. The present study aimed to determine the contribution of such changes to cardiovascular disease (CVD) in patients with CKD.

Methods: Levels of total cholesterol, low-density lipoprotein cholesterol, HDL-C, HDL2, HDL3, apolipoproteins, malondialdehyde-modified LDL (MDA-LDL), oxidized (ox) HDL, oxHDL2 and oxHDL3 were measured in blood samples from patients with CKD (stages 2 – 5, n = 86) who were not on dialysis and from patients undergoing hemodialysis (CKD stage 5D, n = 25). The patients were followed up for 28 ± 9 months after baseline examinations and CVD events were recorded.

Results: Levels of HDL3 and ApoA1 in HDL3 fraction decreased according to CVD severity, whereas those of HDL2 and ApoA1 in HDL2 fraction did not differ. Levels of oxHDL were similar across all stages of CKD. Levels of oxHDL3 and MDA-LDL were increased to a greater degree as those of oxHDL2 increased according to CVD severity. Multivariate analyses using the Cox proportional hazards model selected high levels of oxHDL and its subfractions, and those adjusted with HDL-C and HDL subfractions or ApoA1 in HDL fractions respectively compared with HDL-C and HDL subfractions or ApoA1 in HDL fractions alone as independent risk factors for CVD events.

Conclusions: Levels of HDL subfractions and their oxidized subfraction particles differed among patients with CKD. Increasing levels of oxHDL subfractions might cause a high frequency of CVD events in those patients.

The Relevance of Systolic Blood Pressure to Vascular Disease in Chronic Kidney Disease Patients with and without Vascular Disease: Observations from the Study of Heart and Renal Protection (SHARP)


Background: Conflating by prior disease may distort associations between systolic blood pressure (SBP) and disease outcomes in people with chronic kidney disease (CKD), causing uncertainty about the effect of low SBP on vascular risk in advanced CKD. Measurement of troponin may allow conflating by subclinical cardiac disease to be reduced.

Methods: SHARP randomized 9270 people with CKD. Over 5 years, SBP and clinical outcomes were recorded at baseline and at 6 monthly intervals. Cox regression, adjusted for relevant confounders, was used to assess the relevance of usual SBP to vascular outcomes. Analyses were stratified by baseline vascular disease (defined as self-reported vascular disease, i.e., one or more of the following: history of hypertension, diabetes mellitus, or myocardial infarction or stroke or peripheral vascular disease).

Results: Overall, there was a U-shaped association between usual SBP and vascular risk. Among the 4073 participants without baseline vascular disease, there was a log-linear
association: each 20 mmHg higher usual SBP was associated with an average 65% increase in risk of vascular events (adjusted hazard ratio [HR] 1.65, 95% confidence interval 1.29-2.12) and a 2-fold increased risk of vascular death (HR 2.03, 1.20-3.42). By contrast, among the 4603 participants with baseline vascular disease, the associations between usual SBP and vascular events (HR 1.51, 1.00-2.32; p for heterogeneity = 0.01) and vascular death (HR 1.07, 0.85-1.35; p for heterogeneity = 0.03) were significantly weaker. There was no clear association between usual SBP and non-vascular mortality (HR 0.96, 0.82-1.13), irrespective of history of prior vascular disease.

Conclusions: In CKD, the “U”-shaped relationship between usual SBP and vascular risk appears to be explained by confounding by vascular disease. Trials to assess the effect of lower than currently recommended SBP targets are indicated.

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

TH-PO587

Serum Triglyceride Levels during Progression to ESRD and Early Dialysis Mortality among U.S. Veterans: A Transition of Care in CKD Study

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Background: High triglyceride (TG) levels are an established cardiovascular risk factor in the general population. In a study of non-dialysis dependent chronic kidney disease, higher TG levels (>200 mg/dL) were associated with higher mortality risk, whereas other data show that patients with low TG levels (<115 mg/dL) have even higher mortality risk. The impact of TG levels in the prelude period immediately preceding transition to dialysis on early post-transition outcomes is not known.

Methods: In a cohort of 52,172 US veterans who transitioned to dialysis between October 2007 and September 2011, we identified 15,345 patients with available TG measurements within the last 6 months prelude period (preceding dialysis transition). We examined the association of TG (averaged over 6 months) as a continuous predictor of early all-cause mortality (within the first 3 months post-transition), using restricted cubic spline analysis and Cox models adjusted for age, sex, race, comorbidities, and medications. Those in the highest two quintiles (Q5) (>2990.3 mg/dL) of TG were compared to those in the 4th quintile (Q4) (1585.2 mg/dL) as the reference.

Results: The mean±SD age was 69±11 years, among whom 27% were African-American, 7% were of Hispanic, and 51% had diabetes listed as their primary cause of ESRD. The 6-month averaged prelude TG showed an inverse linear association with post-ESRD mortality risk, in which patients with TG≥115 mg/dL had a higher risk of mortality and patients with TG<115 mg/dL had comparatively better survival.

Conclusions: Among veterans transitioning to dialysis, higher TG levels were associated with lower risk of early post-ESRD mortality. Further studies are needed to investigate underlying mechanisms and to determine how lipid-modulating treatments influence these associations.

Funding: NIDDK Support

TH-PO588

Initiation of Statins for Chronic Kidney Disease Patients in the Veterans Affairs Health System


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Background: The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend cholesterol-lowering treatment with statins for Chronic Kidney Disease (CKD) patients aged 50 years or older, and those aged 30-49 years with elevated risk of cardiovascular disease (CVD). We investigated the predictors of statin initiation in a cohort of CKD patients in the Veterans Affairs Health System between 2010 and 2012.

Methods: Our sample included patients with at least one outpatient visit after serum creatinine value in 2010 or 2011. Patients were categorized into five stages of increasing severity based on estimated glomerular filtration rate (eGFR). A cohort of these patients not using statins in the baseline year (2010 or 2011) were identified and followed in the subsequent year (2011 or 2012) to determine statin initiation. A multivariate logistic regression model was used to examine the socio-demographic and comorbidity related predictors of statin initiation. Results: Our sample included 1,676,215 patients in 2010 and 1,778,655 patients in 2011. Of these, 8.77% in 2010 and 9.48% in 2011 initiated statins in the subsequent year. The most significant predictors of statin initiation were diagnosis of CVD in the prior year (adjusted Odds Ratio=aOR: 2.46, 95% CI: 2.43 – 2.49) and diabetes mellitus (aOR: 1.94, CI: 1.92 – 1.95). Using patients with eGFR<90ml/min/1.73m (Stage 1) as reference, CKD Stage 3 patients had a higher odds (aOR: 1.24, CI: 1.23 – 1.26) of statin initiation, in comparison to stage 4 (aOR: 0.87, CI: 0.83 – 0.91) and stage 5 (aOR: 0.33; CI: 0.29 – 0.38) patients.

Conclusions: CVD and diabetes were the most influential predictors of statin initiation in CKD patients in a large cohort of U.S. Veterans. Statin initiation appeared to be lowest in patients with CKD Stage 4 and 5. Future research will consider adherence to statin prescription and its association with CKD progression.

Funding: Other U.S. Government Support

TH-PO589

Association of Urine Kidney Injury Biomarkers with Risk of Cardiovascular Events in CRIC

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Background: Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease (CVD). We investigated whether kidney injury biomarkers were associated with increased risk of atherosclerotic and non-atherosclerotic CVD events in the Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: Urine kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), N-acetyl-beta-D-glucosaminidase (NAG), and liver fatty acid-binding protein (LFABP) were measured in 2466 CRIC subjects in CRIC. Cox proportional hazards models were used to examine the associations between biomarkers indexed to urinary creatinine and heart failure (HF) or a composite of CVD events (myocardial infarction, ischemic stroke, or peripheral artery disease).

Results: Mean age of study subjects was 59.5± 10.8 years; 46% were women, 50% had diabetes mellitus, and 34% had history of cardiovascular disease. NGAL/Cr, NAG/Cr and LFABP/Cr were associated with HF and CV events in unadjusted models, but not in multivariable adjusted models (accounting for baseline eGFR, albuminuria, age, sex, race, comorbidities, and medications). Those in the highest two quintiles [Q5 (>2990.3 mg/g) and Q4 (>1830.9 mg/g)] of KIM-1/Cr levels had an increased risk of HF relative to the lowest quintile (Q1, <661.3 mg/g) [Q5 vs. Q1 hazard ratio (HR) 1.7 (1.1-2.9); Q4 vs. Q1 HR 1.6 (1.0-2.6)]. KIM-1/Cr was not independently associated with HF in the continuous analysis (HR per log SD increase 1.14 (0.98-1.33)). Higher KIM-1/Cr was independently associated with CVD events in the continuous analysis (HR per log SD increase 1.21 (1.02-1.41)) after adjustment for confounders.

Conclusions: Select urine biomarkers of kidney injury were independently associated with increased risk of HF and CVD events.

Funding: NIDDK Support

TH-PO590

Cystatin C as a Predictor for Mortality in Elderly Patients with Chronic Kidney Disease

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Background: The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum Cystatin C, an accurate marker of estimation of kidney function have also prognostic utility in CKD patients. The aim of our study was to determine the prediction for mortality of different markers for estimation of kidney function on long-term survival in elderly CKD patients.

Methods: 103 adult Caucasian patients, older than 65 years (56 women, 47 men; mean age 72.5 years; range from 65 to 86 years), were included. In each patient
The Relationship Between Neutrophil to Lymphocyte Ratio and Cardiovascular Disease in Patients with Chronic Kidney Disease

Dede Sit, Hasan Kayabasi, Emel Gokmen, Zehra Sucuoglu, Serhat Sigirci, Suleyman Yildirim, Bennur Esen, Saaedet Pilen guzel. Bagcılar Training & Research Hospital, Istanbul, Turkey.

Background: Neutrophil to lymphocyte ratio (NLR) is a new, widely-easily available, inexpensive marker calculated from complete blood count is a new addition to the inflammatory markers. In many studies it has been established that NLR is associated with CVD. In this study we evaluated the relationship between NLR and CVD in patients with predialysis CKD.

Methods: In total 172 predialysis CKD patients who were undergone coronary angiography for CAD where studied. GFR of all patients were calculated using MDRD formula, and according to eGFR, the patients were divided into stage 1-5 CKD via K/DOQI guidelines. The patients were divided into two groups as angiotherapy positive and negative group for coronary artery disease. Demographic, biochemical, hematological parameters and NLR of patients were compared.

Results: The mean age of patients was 65.06±10.53 years, 119 were male, and 53 were female. According to eGFR 16 were stage 1, 75 were stage 2, 46 were stage 3, 17 were stage 4 and 18 were stage 5. There was a statistically significant difference in NLR between two groups. In patients with CAD NLR was higher than in patients without CAD (p=0.01). All parameters of patients were detailed in table 1.

Conclusions: Our study shows that neutrophil count at the beginning of follow-up are better in predicting the outcome of elderly CKD patients than other markers for estimation of kidney function.

Table 1: Comparison of the parameters of patients according to CAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No</th>
<th>Yes</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>9.09±0.71</td>
<td>8.61±0.65</td>
<td>0.002</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.93±1.39</td>
<td>3.79±1.42</td>
<td>0.415</td>
</tr>
<tr>
<td>CRP</td>
<td>32.26±20.46</td>
<td>42.49±48.58</td>
<td>0.348</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.05±0.63</td>
<td>3.66±0.50</td>
<td>0.002</td>
</tr>
<tr>
<td>Spot Protein/ Creatinin</td>
<td>815.57±1644.7</td>
<td>1501.05±2284.78</td>
<td>0.043</td>
</tr>
<tr>
<td>Neutrophil/ Lymphocyte</td>
<td>4.14±4.99</td>
<td>8.46±11.14</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

Christopher K. Batchelor, Gates Colbert, Nishank Jain, Beverley Adams-Huet, Katie La, James Delemos, Susan Haydavi. UT Southwestern and VA North Texas Medical Centers, Dallas, TX.

Background: Elevated cardiac troponin T (cTnT) >10 ng/L is reported in 80% of ESRD patients and associated with poor outcomes. There are less data on whether cardiac biomarkers are elevated in non-dialysis CKD patients.

Methods: We investigated whether cTnT, high sensitivity cTnT (hs-cTnT), brain natriuretic peptide (BNP), and N-terminal-pro-BNP (NT-pro-BNP) levels increase with worsening CKD in 3,298 asymptomatic, multi-ethnic participants of the Dallas Heart Study.

Results: Mean age was 44±10 years. 55% were female, 50% Black, 31% Caucasian, 17% Hispanic, and 2% other races. 288 had CKD, defined as eGFR<60 mL/min/1.73 m² or albumin-to-creatinine ratio ≥17 mg/g in men or ≥25 in women. Of those with CKD, 37% had diabetes mellitus and 66% hypertension vs. 10% and 33% if without CKD, p<0.05. A higher proportion of CKD vs. non-CKD individuals, 8.0 vs. 0.43%, had elevated cTnT >10 ng/L and hsTnT ≥3 ng/L. 58.3 vs. 24.2%, p<0.0001 for both. Mean BNP was 55.3±314 ng/L in CKD vs. 10.9±3.2 ng/mL in non-CKD and NT-pro-BNP was 319.7±1223.7 in CKD vs. 53.4±117.5 ng/mL in non-CKD, p<0.0001 for both. There were graded increases in the proportion with elevated troponins as CKD severity increased across stages.

Conclusions: Our study results demonstrate an increase in plasma FGF-21 levels in CKD patients. Despite its role in glucose and lipid metabolism, plasma FGF-21 does not independently predict adverse cardiovascular outcome among CKD patients.
TH-PO595

Circulating Endothelial Cells and Cardiovascular Risk in Chronic Kidney Disease and Hemodialysis Patients Yasser Ahmed Niemaa,1 Nahla Mohamed gamal Farahat,1 Iman Ezzat Elgohary,1 Marwa Fathy Oraby.1 Internal Medicine-Nephrology Unit, Faculty of Medicine, Alexandria, Egypt; 2Clinical and Chemical Pathology, Faculty of Medicine, Alexandria, Egypt.

Background: This work was conducted with the aim to study circulating endothelial cells in CKD patients and correlate this with some cardiovascular risk factors. Cardiovascular disease remains the leading cause of morbidity and mortality in patients with CKD and may account for 50% of all deaths. Endothelial dysfunction is a well-documented early phenomenon in atherosclerosis that precedes structural changes and clinical manifestations. The chronic microinflammation state present in uremia has been proposed as one of the mechanisms causing endothelial dysfunction. Inflammatory circulating endothelial cells (CECs) are thought to be mature cells that have detached from the intimal monon layer in response to endothelial injury. In humans, elevated levels were reported in various cardiovascular disorders, as a result of mechanical injury, ischemic injury or hypertension.

Methods: This study included 50 subjects classified as follows: Group I 20 patients with CKD not yet on dialysis, group II 20 patients on maintenance hemodialysis and 10 age and sex-matched individual used as a control (group III). All included individuals were subjected to complete blood count, renal function tests, estimation of GFR by MDRD formula, complete lipid profile, high sensitive CRP, ESR and detection of CEC count using flow cytometry.

Results: The study showed increased count of CEC and hs CRP in both CKD groups compared to the control and it was higher in patients on dialysis than those on conservative treatment. There was a statistically positive correlation between ESR, hs CRP, TG and CECs in the three groups, there was also a statistically negative correlation between estimated GFR and CECs in the three groups.

Conclusions: Measurement of CECs count might offer a mean for recognizing CKD patients at risk of cardiovascular events.

TH-PO596

The Association Between Soluble Klotho and Cardiovascular Parameters in the Chronic Kidney Disease: Korean CKD Patients Hyo Jin Kim,1 Kyung don Ju,1 Tsgobadrakh Bodokhurev Bodokhuren,2 Seungmi Lee,1 Aram Lee,1 Shin-Young Ahn,1 Dong-Wan Chae,1 Ho Jun Chin,2 Curie Ahn,1 Kook-Hwan Oh.1 1Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Gyeonggi-do, Korea.

Background: Klotho is one of mineral metabolism regulator in chronic kidney disease (CKD). Bone mineral metabolism is important in CKD and it is associated with cardiovascular (CV) complications. We investigated factors determining soluble klotho concentration and the association between klotho and cardiac parameters from Korean CKD patients.

Methods: We analyzed 1,443 CKD patients with soluble klotho at baseline from the prospective Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) study. Left ventricular hypertrophy (LVH) and arterial stiffness were explored as CV parameters. LV mass index (LVMI) was used as a marker of LVH (male > 115 g/m², female > 110 g/m²) and carotid intima-media wall thickness (CIMT) was used as a marker of arterial stiffness. Renal outcome (initiation of renal replacement therapy or decline of estimated glomerular filtration rate ≤50% or doubling of creatinine) or composite outcome (renal outcome or death) were analyzed for association soluble klotho level.

Results: Patients were 53.5 ± 12.4 years old and 61.5% were male. In a multivariable linear regression analysis, uric acid and log CRP were positively and albuminuria was inversely associated with klotho. LVH (OR 0.46; 95% CI, 0.25 to 0.85; P = 0.014) and baPWV (Pearson correlation, -0.099; P = 0.001) were associated with klotho in univariable analysis. However, in multivariable analysis, klotho was not independently associated with LVH and baPWV. 867 (61.5%) patients were investigated for association between klotho and outcomes (23.3±4.7 months follow-up). Analyzed by Cox proportional hazard model, klotho was not associated with renal or composite outcomes.

Conclusions: Soluble klotho was not an independent determining factor for LVH, arterial stiffness, and renal outcomes. Further studies are warranted to elucidate the clinical-pathogenic significance of klotho in Korean CKD patients.

Funding: Government Support - Non-U.S.

TH-PO597

Elevated C-Reactive Protein, and Albuminuria Increase Mortality Risk in Metabolic Syndrome Patients Satyesh K. Sinha,1 Magda Shaheen,2 Deyu Pan,2 Keith C. Norris,3 Susanne B. Nicholas.2 1Charles R Drew Univ, Los Angeles, CA; 2David Geffen School of Medicine, UCLA, Los Angeles, CA.

Background: Metabolic syndrome (MeS) is a serious health condition affecting nearly 25% of adults in the United States and places them at higher risk of cardiovascular disease (CVD), chronic kidney disease, and mortality. Studies have shown that the MeS is associated with albuminuria (urinary albumin excretion [UA] ≥30μg/ml). Inflammation has been postulated as an important link between the MeS and UACR. However, little is known about the added value of UACR and C-reactive protein (CRP) in predicting mortality in patients with the MeS. Therefore, the study objective was to determine the relationship between mortality and the MeS, after adding both CRP and UACR as additional components.

Methods: We analyzed data from the National Health and Nutrition Examination Surveys 1999-2004 of 5,930 adults aged ≥20 years with and without MeS (=3 components of the MeS according to the definition of National Cholesterol Education Program’s Adult Treatment Panel III). We added elevated CRP and UACR as a 6th and 7th criteria, respectively, for the MeS. We analyzed data using Cox regression to estimate the hazard ratio (HR) for mortality, controlling for demographics, smoking, and CVD. Data are presented as HR, and 95% confidence interval (CI); p<0.05 was statistically significant.

Results: In the adjusted model, the MeS was not associated with mortality. However, HR for mortality was high with elevated CRP (<0.5 mg/dl, HR=1.84, 95% CI 1.45-2.35, p<0.001) and albuminuria (HR=1.89, 95% CI 1.36-2.63, p<0.001 vs. poor change (<0.5 mg/dl) and no albuminuria (UACR=30 μg/ml). With addition of elevated CRP to the model, HR for mortality was high (HR=1.36, 95% CI 1.05-1.77, p<0.02) vs. low CRP and no MeS. HR for mortality was high when albuminuria was also added to MeS with elevated CRP (HR=1.52, 95% CI 1.12-2.06, p<0.01).

Conclusions: We conclude that elevated CRP and UACR may predict the group at high risk for mortality in MeS patients.

Funding: Other NIH Support - NIH grant U54MD007598, UL1TR000124, and S21-MD-000103.

TH-PO598

Longitudinal Change in Low-Grade Albuminuria Is A Better Predictor of Cardiovascular Disease Than Change in Serum Urine Acid: The Tromsø Study Mari D. Solbu,1 Bjorn Odvar Eriksen,2 Toralf Melsom,2 Hilde Merete Storhaug,1 Jon viljar Norvik,2 Trond J. Gjenssen.3 1Section of Nephrology, Univ Hospital of North Norway, Tromso, Norway; 2Metabolic and Renal Research Group, Ulf the Arctic Univ of North Norway, Tromso, Norway; 3Oslo Univ Hospital, Oslo, Norway.

Background: Serum uric acid (SUA) and albuminuria are independent risk factors for cardiovascular disease (CVD), but the joint impact of longitudinal changes in SUA and albuminuria on clinical events is unknown. We assessed the associations between change in SUA and urinary albumin-creatinine ratio (ACR) over 7 years and the occurrence of incident myocardial infarction, ischemic stroke and all-cause mortality. Methods: We included 3931 participants without CVD from the population-based Tromsø Study, Tromsø-4 (1994/95) and Tromsø-5 (2001/02). SUA change was categorized into four groups according to upper (high) versus the three lower (low) gender specific quartiles of SUA in Tromsø 4 and 5; persistently high, decreasing, increasing, and persistently low SUA. ACR change was categorized the same way. Percentage of change from baseline in SUA and ACR was calculated.

Results: During follow-up (median 9.3 years for CVD; 11.3 years for mortality) there were 379 myocardial infarctions, 223 strokes and 869 deaths. In multivariable analyses increasing ACR predicted mortality (HR 1.65; 95% CI 1.38-1.96). Persistently high ACR predicted myocardial infarction (HR 1.79; 95% CI 1.28-2.51). Increasing and persistently high SUA did not predict any endpoint. A≤50% increase in ACR from baseline predicted myocardial infarction and death, whereas >15% increase in SUA did not. Change in SUA and ACR did not interact in their association with CVD. Baseline SUA significantly predicted stroke and mortality.

Conclusions: Longitudinally increasing ACR predicted CVD independently from SUA change. Baseline, but not changes in SUA predicted stroke and mortality. This may have implication for the use of change patterns in risk assessment.

Funding: Government Support - Non-U.S.
TH-PO599

Transient Dipstick-Proteinuria Could Be a Risk of Cardio-Vascular Diseases

Kei Naga1, Kunhiro Yamagata1, Toshiaki Usui2, Koichi Asahi2, Kenjiro Kimura2, Kunitoshi Iseki2, Toshiki Moriyama2, Ichie Narita3, Shouichi Fujimoto3, Kazuhiko Tsuura3, Tsuneo Konta3, Masahide Kondo3, Tsuyoshi Watanabe2

1Univ of Tsukuba; 2Steering Committee for Design of the Comprehensive Health Care System for CKD Based on the Individual Risk Assessment by Specific Health Checkups.

Background: Dipstick-proteinuria is the major method to detect high-risk participants for cardiovascular diseases (CVD). A large part of positive dipstick-proteinuria has gone to negative in the next year, which means transient proteinuria. The aim of this study is to clarify whether transient proteinuria is a risk of CVD comparing to sequentially negative proteinuria with one-year interval measurement.

Methods: By using a population-based 339,172 persons longitudinal cohort receiving annual health checkups sequentially twice or more, we examined presence of dipstick-proteinuria both at baseline year and in the next year. Medical history of CVD was obtained via a self-reported questionnaire. The incidence of CVD event in this study was defined as a negative history at the baseline year and a positive history in the follow-up year. Proteinuria was defined as (+) or more.

Results: Forty-five percent of subjects with positive proteinuria at baseline year in male and 38% of those in female have gone to negative proteinuria in the next year.

<table>
<thead>
<tr>
<th>Proteinuria in the next year</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>At baseline year</td>
<td></td>
</tr>
<tr>
<td>119,020</td>
<td>95.7%</td>
</tr>
<tr>
<td>3,571</td>
<td>45.3%</td>
</tr>
<tr>
<td>195,925</td>
<td>97.5%</td>
</tr>
<tr>
<td>3,538</td>
<td>58.5%</td>
</tr>
</tbody>
</table>

Subgroups with proteinuria have higher risk of CVD than those with sequentially negative proteinuria as reference (hazard ratio [HR] and 95% confidence intervals [CI], 1.58 [1.38-1.81] in male and 1.55 [1.32-1.81] in female).

Conclusions: Transient proteinuria could be a risk of the incidence of CVD.

TH-PO600

Urineary Phosphate Excretion Modifies the Association Between Serum Osteoprotegerin and Coronary Calcification in CKD: KNOW-CKD Study

Young Youl Hvan,1 Kyu-Beck Lee,1 Hyang Kim,1 Kook-Hwan Oh2, Curie Ahn2, Dong-Wan Chae2, Yong-Soo Kim2, Wooyung Chung,3 Young-Hwan Han4, Soo Wan Kim5, Yeong Hoon Kim5

1Sungkyunkwan Univ School of Medicine, Kangbuk Samsung Hospital; 2Seoul National Univ Hospital; 3Seoul National Univ Bundang Hospital; 4The Catholic Univ of Korea, Seoul St. Mary’s Hospital; 5Gachon Univ; Gil Hospital; 6Eulji General Hospital; 7Chonnam National Univ Medical School; 8Inje Univ; Pusan Paik Hospital.

Background: High serum osteoprotegerin (OPG) is closely related to coronary calcification, but the exact mechanism is not known well. To understand the underlying pathophysiology, we explored whether this association between OPG and coronary calcification is modified by 24-hr urinary phosphate excretion (UPI) in CKD patients.

Methods: This cross-sectional study analyzed 871 participants from the KNOW-CKD cohort who underwent a coronary MDCT, serum OPG measurement, and 24-hr urine collection as baseline examinations between 2011–2013. We evaluated the association between serum OPG and coronary artery calcium scores (CACS) in each group with low and high UPI. Effect modification was evaluated by an interaction term and tested by Wald test.

Results: Percentages of participants with CACS > 0 were different between OPG quartiles (23.4%, 41.1%, 52.5% and 78.8% for the lowest to highest quartiles of OPG, P<0.001). In multivariate-adjusted Tobit models, the CACS ratio (95% confidence intervals) comparing the highest quartile of OPG to the lowest quartile was 19.74 (4.14-94.10) in the low UPI group, whereas the ratio was 1.86 (0.48-7.20) in the high UPI group (P for interaction = 0.003). In multivariate logistic model, the odds ratio of highest quartile for CACS > 0 compared with lowest quartile was 6.56 (2.52-17.11) in the low UPI group, whereas the odds ratio was 1.65 (0.68-3.99) in the high UPI group (P for interaction = 0.006).

Conclusions: Serum OPG was associated with coronary calcification only in CKD patients with low UPI, but not in those with high UPI. Further studies are warranted to verify the role of phosphate excretion in OPG-related coronary calcification.

Funding: Government Support - Non-U.S.

TH-PO601

The Relationship of LV Mass Index and FGF-23/25(OH)D Modulating Phosphaturia Shin-Young Ahn1, Ho Jun Chin1, Kook-Hwan Oh2, Curie Ahn2, Dong-Wan Chae1

1Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Republic of Korea; 2Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.

Background: As renal function declines, level of fibroblast growth factor-23 (FGF-23) rise and 25-hydroxvitamin D (25(OH)D) decrease. We evaluate the relationship among 25(OH)D and FGF-23 on cardiovascular risk factors such as LV mass index and vascular calcification (VC).

Methods: KNOW-CKD is an on-going, prospective, university hospital based observational cohort study under the sponsorship of Korean Center for Disease Control and Prevention. Cross-sectional analysis of echocardiography data and other clinical data was performed in 1529 participants of KNOW-CKD. The study participants were divided into 4 groups by FGF-23 and 25(OH)D values below and above the median.

Results: Among the 1529 study participants, the mean of age and estimated GFR were 53.6 ± 12.4 years and 50.9 ± 31.7 ml/min/1.73m². The median FGF-23 concentration was 17.85 RU/ml (interquartile range [IQR] = 9.42, 31.28), and median level of 25(OH)D was 16.52 ng/ml (interquartile range [IQR] = 13.31, 21.04). The patients who had FGF-23 above the median but 25(OH)D below the median had highest level of serum P, iPTH, mean of pulse wave velocity(PWV), and LV mass index. They also had lowest level of hemoglobin, serum albumin, eGFR, corrected Ca, and bone mineral density of femur neck. After multivariate analysis, the result showed significant correlation between LV mass index and FGF-23/25(OH)D ratio (std β=0.176, P=0.021). Decreasing level of 25(OH)D reduced phosphaturia caused by FGF-23. Finally vascular calcification measured by abdominal aorta calcification showed significant negative relationship with phosphaturia after multivariate analysis (stdβ=-0.095, P=0.031).

Conclusions: We observed the significant association between FGF-23/25(OH)D and LV mass index and FGF-23/25(OH)D and degree of phosphaturia which was correlated with vascular calcification. We suggest that FGF-23/25(OH)D may increase LVMI through modification of phosphaturia and vascular calcification.

Funding: Government Support - Non-U.S.

TH-PO602

Fractional Excretion of Phosphorus Is Independently Associated with Left Ventricular Hypertrophy in Chronic Kidney Disease Patients

Xiaoyan Zhang

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Background: Left ventricular hypertrophy (LVH) is an important mechanism of cardiovascular disease in chronic kidney disease (CKD). Elevated Fibroblast growth factor-23 (FGF23) levels are independently associated with LVH. The aim of this study is to investigate whether elevated fractional excretion of phosphorus, as one major action of FGF23, is independently associated with LVH in CKD patients.

Methods: LVH was defined as LVMI (Left ventricular mass index) ≥ 50 g m⁻² in men or ≥ 47 g m⁻² in women. The fractional excretion of phosphorus (FePi [%]) was calculated as [urate phosphorus (mg/dl)/serum phosphorus (mg/dl)]/[urate creatinine (mg/dl)/urate creatinine (mg/dl)]<100.

Results: We measured FePi levels in 1,389 individuals who underwent echocardiography within 3 months. The median FePi level was 13.44%. The mean (± SEM) left ventricular ejection fraction was 57 ± 17%, left ventricular mass indexed to height² (LVMI) was 42.1±14.4 g m⁻², and LVH was present in 24% of participants. The left ventricular ejection fraction was lower in the highest versus the lower quartiles of FePi levels, while the LVMI increased with increasing FePi quartiles. Each ten percent increase in FePi was associated with a 1.406 g m⁻² greater LVMI (95% CI, 2.022–2.789; P < 0.001). Each ten percent increase in FePi was associated with a 1.361-fold greater relative risk (RR) of eccentric hypertrophy and concentric hypertrophy (95% CI, 1.275–1.456; P < 0.001) compared with normal ventricular geometry. Multivariable analyses that adjusted for age, sex, weight, body mass index, diabetes, GFR, total cholesterol, total triglyceride, hemoglobin, proteinuria, parathyroid hormone (PTH), and serum phosphate demonstrated that elevated FePi was independently associated with increased LVMI (0.745 g m⁻² greater LVMI per ten percent increase in FePi, 95% CI, 0.264–1.226; P < 0.001) and conferred greater risk of eccentric and concentric LVH (RR 1.102 per ten percent increase in FePi, 95% CI, 1.000–1.214; P < 0.05).

Conclusions: FePi is independently associated with left ventricular hypertrophy in patients with CKD across a broad range of kidney function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

225A
Clinical Significance of Vascular Calcification and Retinopathy on Renal and Cardiovascular Outcomes in Patients with Chronic Kidney Disease

Hyeon Seok Hwang, Hye Eun Yoon, Yu ah Hong, Suk young Kim. Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.

Background: Vascular calcification and retinopathy is the representative marker of macrovascular and microvascular dysfunction in patients with chronic kidney disease (CKD). While both of them share common pathophysiology, their relationship and combined effects on clinical outcome remained undetermined.

Methods: We included 523 nondialysis-dependent CKD stage 3–5 patients, who had been examined with fundoscopy for diabetic or hypertensive retinopathy. Simple X-ray images of the pelvis and the abdomen were analyzed for the presence of intimal or medial arterial calcifications. The clinical significance of intimal calcification and retinopathy was evaluated in terms of the rate of renal function decline and composite of any cardiovascular event or death.

Results: Intimal calcification was observed in 81 (15.5%) CKD patients, medial calcification in 50 (9.6%) CKD patients, and retinopathy in 258 (49.3%) CKD patients. The presence of retinopathy was independently associated with intimal (odds ratio 1.72, 95% CI 1.03-2.89) and medial calcification (OR 3.41, 95% CI 1.68-6.90). The renal function decline rate was significantly steeper in patients with than in those without intimal calcification (β = –4.21; p = 0.001). The combined status of retinopathy with intimal or medial calcification independently increased the risk of composite events (hazard ratio 3.34, 95% CI 1.41-4.43 for intimal calcification; hazard ratio 3.19, 95% CI 1.62-6.28 for medial calcification).

Conclusions: Coexistence of intimal calcification and retinopathy were independently associated with CKD progression, and the combined status of retinopathy with intimal or medial calcification was an independent predictor for composite cardiovascular event/death.

Abdominal Aortic Calcification in Patients with Chronic Kidney Disease

Mieke J. Peeters, 1 Jan A.J.G. van den Brand, 1 Arjan D. Van Zuilen, 2 Marc G. Vervoort, 1 Peter J. Blankenstijn, 2 Jack F. Wetzels, 1 Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2 Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands; 3 Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

Background: Abdominal aortic calcification (AAC) is independently associated with cardiovascular events in dialysis patients and in the general population. However, data in non-dialysis chronic kidney disease (CKD) patients are limited. We studied determinants and prognostic value of AAC in non-dialysis CKD patients.

Methods: We included patients with CKD not receiving renal replacement therapy who participated in the MASTERPLAN study, a randomized controlled trial that started in 2004. In the period 2008-2009 an X-ray was performed in a subgroup of patients. We studied AAC using a semi quantitative scoring system by lateral lumbar X-ray. We used baseline and two year data to find determinants of AAC. We used a composite cardiovascular endpoint and propensity score matching to evaluate the prognostic value of AAC.

Results: In 280 patients an X-ray was performed. In 79 patients (28%) the X-ray showed no calcification, in 62 patients (22%) calcification was minor (<4), 139 patients (50%) had moderate or heavy calcification (³4). Older age, prior cardiovascular disease, higher triglyceride levels, and higher phosphate levels were independent determinants of a calcification score ≥4. AAC score ≥4 was independently associated with a rapid decline in renal function (β = –4.21; p = 0.001). The combined status of retinopathy with intimal or medial calcification was associated with CKD progression, and the combined status of retinopathy with intimal or medial calcification was an independent predictor for composite cardiovascular event/death.

Association of Urine Potassium with ESRD, Cardiovascular (CVD) Death, and All-Cause Mortality in Chronic Kidney Disease (CKD)

Amanda K. Leonard-Berg, Y1 Hocine Tighiouart,2 Andrew S. Levey,3 Mark J. Sarnak.1 1 Div of Nephrology,Tufts Medical Center, Boston, MA; 2 Research Design Center/Biostatistics Research Center, Tufts CTSI and Inst for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA.

Background: Low urine potassium excretion is associated with a higher risk of developing ESRD and cardiovascular disease (CVD) and mortality in the general population. However, data in CKD patients are limited and the relationship between the two is not well characterized.

Methods: We evaluated patients from April 1994 to June 2006. Patients were excluded if they were dialysis dependent, had CKD G1, or missing urine potassium data. We included patients with CKD not receiving renal replacement therapy who participated in the MDRD Study. 24-hour urine potassium was measured at the first screening visit (before randomization) and in an average of 22 subsequent visits. Proportion to potassium levels adjusted for demographics, CVD risk factors, GFR, proteinuria, randomization assignment, and urine sodium. Interactions were performed with baseline GFR, proteinuria and urine sodium as well as blood pressure randomization.

Results: Mean age at baseline was 52±12 years; 60% were men and 85% were white. Mean 24-hour urine potassium excretion was 61±22±7 meq/dl. Mean follow up for ESRD and mortality were 6.1±3.3 years, 19.2±10.8 years, respectively. Higher urine potassium levels were associated with a lower hazard of CVD mortality and all-cause mortality, but were not associated with ESRD. No significant interactions were noted.

Conclusion: Higher urine potassium is associated with lower risk of CVD mortality and all-cause mortality. It remains to be determined whether higher dietary potassium intake results in improved outcomes in CKD.

Funding: NIDDK Support

Association Between Serum Bicarbonate and Heart Rate Variability in Hypertensive Adults: The Systolic Blood Pressure Intervention Trial

Kalani L. Raphael, 1 Elsayed Z. Soliman,2 William C. Cushman,3 Matthew J. Diamond,4 Jeff Whittle,2 Anthony Alexander Killeen,2 Laura Lovato,3 Joachim H. Pi,5 Srimi Beddhu,2 1 Univ of Utah; 2 Wake Forest School of Medicine; 3 Memphis VA Medical Center; 4 Georgia Regents Univ; 5 UC San Diego; 6 Clement J.Zablocki VA Medical Center; 7 Univ of Minnesota.

Background: Reduced heart rate variability (HRV), a measure of cardiac autonomic dysfunction, has been associated with lower serum [HCO3-] in advanced CKD and ESRD. The purpose of this study is to determine if [HCO3-] is associated with HRV in hypertensive adults with more preserved eGFR.

Methods: We examined the cross-sectional association between baseline [HCO3-] and HRV in 9,265 participants from the Systolic Blood Pressure Intervention Trial (SPRINT). Three sequential 10-second 12-lead ECGs were used to calculate two time domain measures of HRV (standard deviation of all normal RR intervals [SDNN] and root mean square of successive differences in RR intervals [RMSSD]) from the individual durations between normal RR intervals. Linear regression models (adjusted for demographics, smoking, eGFR, ACR, CVD, and SBP) were performed using [HCO3-] as the independent variable and log-transformed SDNN and RMSSD as dependent variables. These models were repeated using [HCO3-] as a categorical variable: < 22, 22.0-24.9, 25.0-29.9 (referent), and ≥ 30 meq/L.

Results: Mean age was 67.9 (9.4) years, 28.4% had CKD, mean eGFR was 71.8 (20.6) mL/min/1.73m², mean [HCO3-] was 26.3 (2.6) meq/L, mean SDNN was 21.2 (17.6), and mean RMSSD was 62.0 (44.6) ms for the entire group. After adjusting for age, sex, race, study site, and eGFR, [HCO3-] was associated with lower HRV (β = 0.13; p = 0.001) after adjusting for smoking, eGFR, ACR, CVD, and SBP. When [HCO3-] was categorized, HRV was lower for the highest category (≥ 30 meq/L) compared to the referent category (< 22 meq/L).

Conclusion: Lower serum bicarbonate is associated with lower HRV and this relationship is independent of age, sex, race, study site, and eGFR.

Funding: VA Medical Center; 4 Anthony Alexander Killeen, 2 Andrew S. Levey, 3 Mark J. Sarnak.
mean RMSSD was 25.2 (24.6). There was no significant association between [HCO₃⁻] and SDNN (efficient 0.01, p=0.94) or RMSDD (beta coefficient 0.04, p=0.71) in adjusted linear regression models. Results were similar in models using [HCO₃⁻] as a categorical variable. There was no interaction of these relationships by CKD status (p=0.40 for SDNN and RMSDD).

Conclusions: In this large study of trial participants with normal kidney function to moderate CKD, there was no association between [HCO₃⁻] and HRV. The association between lower [HCO₃⁻] and reduced HRV may only exist in more advanced CKD.

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TH-PO608

Serum Alkaline Phosphatase Negatively Affects Endothelium Dependent Vasodilatation in Naïve Hypertensive Patients

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Background: Tissue non-specific Alkaline Phosphatase (Alk-Phos) promotes arterial calcification in experimental models and, independently of other risk factors, high Alk-Phos is a powerful predictor of total and cardiovascular (CV) mortality in the general population and in patients with heart diseases.

Methods: To investigate the relationship between Alk-Phos and atherosclerosis at an early disease stage we tested the association between serum Alk-Phos and the endothelium dependent maximal vasodilatation response to acetylcholine in 500 untreated individuals with uncomplicated essential hypertension without liver disease and with Alk-Phos levels well within the normal range of activity of this enzyme.

Results: The maximal response to acetylcholine was inversely related to Alk-Phos (r=−0.55, P<0.001) and this association was unmodified (r=−0.61, P<0.001) in adjusted analyses including demographic and classical risk factors, the BMI, the eGFR, serum phosphate and calcium as well as serum C reactive protein (CRP) and albuminuria. The steepness of the Ach-max/Alk-Phos relationship was substantially attenuated (P<0.001) in patients with serum phosphate above the median value than in those below the median (−0.5% per Alk-Phos Unit vs -10.0% per Alk-Phos Unit) and this interaction remained highly significant (P<0.001) in adjusted analyses.

Conclusions: Our findings offer a novel interpretative clue to explain the association between serum Alk-Phos and phosphate and all cause and CV mortality in previous observational studies in the general population and in patients with heart disease and suggest that the endothelium may be an early target of raised Alk-Phos.

TH-PO609

Alkaline Phosphatase Lowering by Selective BET Inhibition, a Novel Mechanism for MACE Reduction in High Risk CVD, Diabetes and CKD Patients – A Post-Hoc Analysis of Phase 2b Studies with RVX-208

Kamyar Lebioda,1 Zadeh Kamyar,2 Michael Sweeney,3 and HRV . The association

1Vasodilatation in Na+ dependent maximal vasodilatory response to acetycholine in 500 untreated individuals with uncomplicated essential hypertension without liver disease and with Alk-Phos levels well within the normal range of activity of this enzyme.

2Vascular Endothelial Growth Factor b (VEGFb) signaling is important in the regulation of angiogenesis and in different pathological conditions such as inflammatory and cardiovascular diseases. The overexpression and/or dysregulation of VEGFb has been implicated in the development of atherosclerosis and neovascularization. However, the role of VEGFb in regulating atherosclerosis in the presence of hypercholesterolaemia is not well understood.

3In the present study, we investigated the effects of VEGFb on atherosclerosis in a murine model of hypercholesterolaemia. Male C57BL/6J mice were fed a high-fat diet for 16 weeks, and then treated with either a control or an anti-VEGFb antibody for 12 weeks. Aortic atherosclerosis was assessed by oil red-O staining and Western blot analysis of aortic VEGFb levels.

4Results: The anti-VEGFb antibody significantly reduced aortic atherosclerosis compared to the control group (p<0.05). Western blot analysis showed a significant decrease in VEGFb expression in the aortas of mice treated with the anti-VEGFb antibody compared to the control group (p<0.05).

5Conclusion: Our results suggest that VEGFb has a pro-atherosclerotic role in the presence of hypercholesterolaemia. These findings provide novel evidence for the role of VEGFb in atherosclerosis and support the potential of anti-VEGFb therapy as a novel therapeutic approach for the management of atherosclerotic diseases.
Carotid plaques: ACE2 increased in patients with baseline plaques respect to patients without plaques (0.022.1 ± 33.45 vs. 0.015.5 ± 33.61, p = 0.045). An increase in ACE2 from AD0-24 months to AD24 months showed an ACE2 increase as compared to AD0-1 at 24months (47.60:1.6 vs. 55.7:1.0 g; p = 0.001). Multivariate analysis demonstrated circulating ACE2 in CKD-5 as a predictor of doubling creatinine (β = 0.069, p = 0.034), de novo appearance of femoral plaques at 24-months (β = 0.087, p = 0.016) and presence of femoral plaques at basal and 24-months (β = 0.199, p = 0.001).

Conclusions: In CKD-5 patients without history of CVD, circulating ACE2 may become a biomarker of CKD progression and AD appearance at 24months of follow-up.

TH-PO612
Blood Pressure and Risk of Cardiovascular Events at Advanced CKD: The CRIC Study
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1 UW, 2 UCSF, 3 CH: ‘Peer; 4 NIDDK, ‘Case Western; 5 KPNC; ‘Tailen.

Background: The association of SBP with cardiovascular events (CVD) among patients with advanced CKD is not known and may be an important modifiable risk factor.

Methods: Participants of the Chronic Renal Insufficiency Cohort (CRIC) Study with advanced CKD (defined as eGFR <30 ml/min/1.73 m²) had SBP measured by standardized methods at yearly in-person visits. We studied the association of SBP with time to physician-adjudicated atherosclerotic CVD (defined as myocardial infarction, stroke, peripheral vascular disease) and heart failure (HF) using Cox models.

Results: Among 1,795 participants with eGFR <30 ml/min/1.73 m², mean age was 56.1±11 years, 46% were women and 46% were African American. Mean eGFR was 26±5 ml/min/1.73 m² and mean BP was 131±24/89±13 mm Hg. Models adjusted for demographics, clinical site, use of hypertension medications, urine mass index, creatinine, statin use and number of classes of anti-hypertensive medications. Compared to the lowest refresh, SBP 140-159 mmHg, risk of any CVD was not statistically significant. Risk of HF was also not significantly different from the lowest refresh of SBP 120-129 mmHg. However, participants with SBP ≥160 mmHg had higher risk of CVD (HR: 2.72, 95% CI: 1.64-4.45) and HF (HR: 2.72, 95% CI: 1.64-4.45) compared to the lowest refresh of SBP 120-129 mmHg. Stratified analysis (stratified by sex, race, site, NYHIA class, ischemic heart disease, hypertension, diastolic, previous coronary artery bypass graft, previous coronary artery angiography or surgery, prior percutaneous coronary intervention, arterial inflow or outflow, ventricular tachycardia, previous catheter ablation, cocaine use, cerebrovascular disease, diabetes, long disease, liver disease, systolic blood pressure, body mass index, ventricular ejection fraction, eGFR, device type, ACE inhibitors / Angiotensin I / II blockers, beta-blockers, and diuretics) showed statistically significant associations between SBP ≥160 mmHg and risk of CVD and HF.

Conclusions: SBP can be a modifiable risk factor for incidence of CVD and HF in advanced CKD patients. Among participants with advanced CKD, SBP ≥160 mmHg is associated with a higher risk of CVD and HF.

TH-PO614
Diagnostic and Prognostic Characteristics of Amino-Terminal Pro-B-Type Natriuretic Peptide in Patients with Diminished Renal Function: A Systematic Review and Meta-Analysis
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Background: Patients with renal dysfunction have higher plasma amino-terminal pro-B-type Natriuretic Peptide (NT-proBNP), which may complicate interpretation for diagnosis of heart failure with preserved ejection fraction (HFpEF) or diagnosis of heart failure with reduced ejection fraction (HFrEF) or diagnosis of non-cardiac etiologies such as pulmonary hypertension. There is a need to systematically review studies on NT-proBNP testing in patients with and without renal dysfunction.

Methods: We searched MEDLINE, EMBASE and Web of Science through August 2014 and selected studies with sub-group analysis by renal function of the diagnostic or prognostic ability of NT-proBNP.

Results: For diagnosis, nine studies were included with 4,287 patients and 1,325 ADHF events. Patients were mostly divided into sub-groups with and without renal dysfunction by an estimated glomerular filtration rate of 60 ml/min/1.73 m². In patients with renal dysfunction, the area under the curve (AUC) for NT-proBNP ranged from 0.66 to 0.89 with a median cut-point of 100 pg/ml while the AUC ranged from 0.72 to 0.95 with a cut-point of 450 pg/ml. NT-proBNP was a prognostic biomarker in patients with and without renal dysfunction. For prognosis, 30 studies with 32,203 patients were included, and mortality in patients with renal dysfunction (25.4%) was twice that of patients with preserved renal function (12.2%). The unadjusted pooled risk ratio (RR) for NT-proBNP and mortality was 3.01 (95% CI, 2.53-3.58) in patients with preserved renal function and was similar in patients with renal dysfunction (3.25 [CI, 2.44-4.32]). There was significant heterogeneity, which was partially explained with meta-regression, if patients with heart failure or coronary artery disease were enrolled.

Conclusions: NT-proBNP retains utility for diagnosis of ADHF in patients with diminished renal function with higher cut-points. Elevated NT-proBNP confers a worse prognosis regardless of renal function.

TH-PO615
Changes in Urinary L-FABP as a Biomarker for Cardiovascular Events
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Background: Urinary L-FABP was measured before, and at 6, 12, 24 and 48 h after CCP. Changes in urinary L-FABP as a Biomarker for Cardiovascular Events were performed. Urinary L-FABP was measured by ELISA before, and at 6, 12, 24 and 48 h after CCP.
Results: Urinary L-FABP levels were significantly higher at 12 and 24h after CCP compared with before CCP only in the patients with occurrence of cardiovascular events. The difference in urinary L-FABP levels (AL-FABP) between before and at 24h after CCP was a risk factor for the occurrence of cardiovascular events.

Conclusions: Measurement of urinary L-FABP before and at 24h after CCP in patients with mild to moderate renal dysfunction may be an important indicator for risk stratification of onset of cardiovascular events in clinical practice.

TH-PO616 Suggested Role of Adiponectin in Reciprocal Relationships Between Pulse Wave Velocity and Bone Mineral Density in CKD Patients Seon Ho Baek 1, Sung Woo Lee,2 Shin-Young Ahn,2 Sejoong Kim,1 Ho Jun Chin,2 Ki Young Na,1 Dong-Wan Chae,1 Curie Ahn.2 1Internal Medicine, Seoul National Univ Bundang Hospital, Gyeonggi-do, Republic of Korea; 2Internal Medicine, Seoul National Univ Hospital, Seong, Republic of Korea.

Background: Although adiponectin plays a beneficial role in the regulation of insulin action and atherosclerosis in various populations, the role of adiponectin remains a controversy in patients with chronic kidney disease (CKD).

Methods: A total of 1310 patients (male/female = 794/516) with CKD stage 1 to 5 who enrolled in the Korean cohort study for outcome in patients with Chronic Kidney Disease (KNOW-CKD) from June 2011 to December 2013. We measured serum total adiponectin and examined the association between adiponectin, bone mineral density (BMD) measured by dual energy X-ray absorptiometry, and pulse wave velocity (PWV) calculated by mean value of both brachial-ankle (ba) PWV.

Results: Increasing quintiles of serum adiponectin levels were associated with female gender; lower body mass indices, estimated glomerular filtration rate, triglycerides, BMD and albumin; higher urinary protein creatinine ratios, PWV, phosphorous, intact PTH, T-scores at LS spine (LS), total hip (TH), and femur neck (FN) inversely correlated with ba PWV (LS: r = -0.075, P = 0.100; TH: r = -0.097, P = 0.001; FN: r = -0.111, P < 0.001) in male CKD, however, this association was not significant for female CKD (LS: r = 0.019, P = 0.607; TH: r = -0.046, P = 0.223; FN: r = -0.043, P = 0.277). Adiponectin was inversely associated with T-scores at all sites for both male and female CKD patients (LS: r = -0.133, P < 0.001; TH: r = -0.135, P < 0.001; FN: r = -0.099, P < 0.001). Adiponectin was positively associated with ba PWV for male CKD (r = 0.074, P = 0.016), but not for female CKD (r = 0.016, P = 0.607).

Conclusions: Adiponectin, BMD, and PWV were associated with each other in male CKD patients. The findings suggested that adiponectin have the role in reciprocal relationships between PWV and BMD in not female but male CKD patients.

TH-PO617 The Association of High-Sensitivity Troponin I and N-Terminal Pro-Brain Natriuretic Peptide with Plasma Galectin-3 in Chronic Kidney Disease Patients Jialiang Li,1 Alistair Provost2,2 Jun Liu,1 Kenjiro Oikawa,1 Man Fai Lam,2 Sejoong Kim,2 Ho Jun Chin,2 Ki Young Na,1 Dong-Wan Chae,1 Curie Ahn.2 1Nephrology, National Univ Hospital, Singapore; 2Statistics and Applied Probability, National Univ of Singapore, Singapore; 3Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore.

Background: Plasma galectin-3 (pG3), a beta-galactoside-binding lectin, regulates inflammation and fibrosis. N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity Troponin I (hsTnI), and pG3 concentrations are elevated in chronic kidney disease (CKD) patients with heart failure. Between hsTnI and NT-proBNP, it is unknown which has a better association with pG3. We assessed the relationship of NT-proBNP and hsTnI in Asian CKD patients and healthy controls.

Methods: We retrieved prospectively collected frozen plasma samples from 167 stable CKD patients and 105 healthy controls. NT-proBNP, hsTnI and pG3 were assayed. By univariate analysis, we assessed pG3 for associations with age, gender, ethnicity, systolic (SBP) and diastolic (DBP) blood pressures (mmHg); height, weight, body mass index (BMI, kg/m²); previously diagnosed CKD, diabetes, hypertension, coronary artery disease, estimated glomerular filtration rate (eGFR, mL/min/1.73m²); C-reactive protein (CRP), beta-trace protein (BTP), 24-hr urine protein (TUP), serum albumin, uric acid and cystatin C. We created 2 models predicting pG3 using multiple linear regression by backwards elimination to include hsTnI and NT-proBNP. Akaike Information Criterion (AIC) was used for comparison. Significance was taken at P<0.05.

Results: Population values: Age: 52.7±13.5 years; BMI: 26.9±5.2; eGFR=75 (IQR:36-102); pG3=19.4 (IQR:14.9-29.9 ng/mL), NT-proBNP=27 (IQR:11.7-111) pg/mL, hsTnI=3.1 (IQR:1.6-6.0) ng/mL, Age, SBP, DBP, height, BMI, previous disease diagnoses, Lp CRP, Ln BTP, Ln TUP, Ln albumin, Ln uric acid, Ln cystatin C, Ln eGFR, Ln hsTnI, Ln NT-proBNP were associated with pG3. The best model included Ln hsTnI, diagnosis of CKD, Ln albumin, Ln cystatin C, Ln uric acid, and height (AIC: 83.3).

Conclusions: NT-proBNP and hsTnI are associated with pG3 in CKD patients. The model including hsTnI is a better predictor of pG3.

TH-PO618 ACE/ARB Use in Patients with Severe Kidney Disease and Heart Failure Is Not Associated with Worsening Renal Function, Acute Kidney Injury and Hyperkalaemia Gongrie Balasubramaniam,1 Sebastian Vamendorfen, Sarah Mapplebeck, Michael K. Almond. Dept of Medicine, Southend Univ Hospital, Southend, Essex, United Kingdom.

Background: The role of ACE/ARB in patients with severe kidney disease and heart failure needs clarification. This includes patients with preserved systolic function. ACE/ ARB is associated with better cardiac prognosis but there is a risk of worsening renal function, especially in older and frail people.

Methods: We undertook a retrospective analysis of patients who were diagnosed with heart failure in primary care with BNP testing and Echocardiogram. Our centre serves a population of 350,000, details of hospital admissions, drug information and blood results were obtained from our electronic patient records. A BNP>450 and clinical features of heart failure is the criteria used by general practitioners for diagnosis, an eGFR < 30 was used to identify patients with severe kidney disease. We looked at rates of worsening kidney function, AKI and hyperkalaemia.

Results: 159 patients with raised BNP and eGFR <30 were identified on electronic search from 01/12 to 01/14. Mean age was 81.7-years (range 41-96), M/F(79/80). Average follow-up was 17 months. 27 patients with transient rise in serum creatinine (Cr) or dialysis were excluded. 87 of the remaining 132 patients had echocardiograms; 13 had ejection fraction (EF) <40%, 7 EF had 40-50% and 67 had preserved ejection fraction (>50%). Comparing with EF<50% vs. EF<50%; mortality was 55% (11/20) vs. 10% (7/67), mean BNP was 12,037 vs. 3645, mean Cr was 235 vs. 201 and 1/20 vs. 1/67 reached ESRD, respectively. 84 patients had drug information available.

Conclusions: Impaired EF was associated with worse mortality. ACE/ARB use was not associated with more adverse events with regards to episodes of AKI, worsening eGFR and mean potassium. We feel that ACE/ARB treatment for heart failure should be maintained even in the setting of severe renal disease to reduce cardiovascular mortality.

TH-PO619 Protein-Fiber Intake Ratio and Cardiovascular Risk in Older Men with Chronic Kidney Disease Hong Xu,1 Megan Rossi,2 Katrina L. Campbell,2,3 Gloria Lissete Sencion martinez,4 Johan Arnlov,4 Tommy Cederholm,2 Per Björner,2 Bengt Lindholm,1 Juan Jesus Carrero.1 1Renal Medicine & Baxter Novum, Karolinska Inst, Stockholm, Sweden; 2Princess Alexandra Hosp, Brisbane, Australia; 3Health Sciences & Medicine, Bond Univ, Robina, Australia; 4Medical Sciences, Uppsala Univ, Uppsala, Sweden; 5Public Health and Curtin Sciences, Uppsala Univ, Uppsala, Sweden.

Background: The elevated cardiovascular (CVD) risk in chronic kidney disease (CKD) may be partially alleviated through a healthy diet. While protein intake has been linked to CVD events in CKD patients, dietary fiber may be cardioprotective. Nutrients are not consumed in isolation; we hypothesise that CVD incidence associates with dietary patterns aligned with excess of dietary protein relative to fiber.

Methods: Prospective cohort study from Uppsala Longitudinal Study of Adult Men of 390 elderly men aged 70–71 years with manifest CKD (eGFR<60 mL/min/1.73m²) and albuminuria>20 mg/gm and no clinical history of CVD. Protein and fiber intake and its ratio, were calculated from 7-day dietary records. Cardiovascular structure and function was estimated from echocardiographic examination. Fatal and non-fatal cardiovascular events were registered prospectively during median follow-up of 9.1 (IQR 4.5-10.7) years.

Results: The median of protein-fiber ratio was 4.0 (3.5-4.7); dietary protein was 66.7 (60.7-71.1) and dietary fiber was 16.6 (14.5-19.1) gms/day. Protein-fiber intake ratio, rather than separate components, remained strongly associated to left ventricular cardiovascular structure and diastolic function after multivariable adjustment. During follow-up, 164-first time CVD events occurred (incidence rate 54.5/1,000 py). Protein-fiber intake ratio was an independent risk factor for CVD incidence [adjusted HR per SD increase (95% confidence interval, CI) 1.29 (1.85, 1.57)]. Although in opposing directions, neither dietary protein [1.10 (0.92, 1.33)] nor dietary fiber [0.83 (0.68, 1.02)] associated with this outcome.

Conclusions: An excess of dietary protein relative to fiber intake associated with cardiovascular structural dysfunction and with incidence of cardiovascular events in a homogeneous population of older men with CKD.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Impact of Percutaneous Transluminal Renal Angioplasty (PTA) on Long-Term Prognosis in Patients with Severe Atherosclerotic Renal Artery Stenosis (RAS)

TH-PO620

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Background: PTRA for the patients’ (Pt’s) with RAS was concluded to be not superior to medical therapy in terms of preserving renal function, renal events, and cardiovascular events in multicenter randomized trials in ASTRAL and CORAL. However, in these studies, approximately 40% of all Pt’s had only mild to moderate RAS (50–70%). Therefore, we studied whether PTRA for the Pt’s with more severe RAS would be beneficial or not.

Methods: Eligibility of the study included the Pt’s with RAS in stenosis more than 75%, who underwent PTRA in our hospital from September 2004 to December 2007. Mean follow-up period was 81±34 months (median 7 years). We investigated the changes of renal function as primary endpoint, and renal event (doubling of serum creatinine (~Scr) or dialysis initiation) and cardiovascular death as secondary endpoints.

Results: Among 80 RAS patients with PTRA treatment, 74 Pt’s were followed by April 2015. There were 24 Pt’s with 75-89% (moderate group), 38 Pt’s with 90-95% (severe group), and 12 Pt’s with more than 95% (more severe group) in stenosis. At the time of PTRA, 92% of all the Pt’s had ischemic heart disease. The changes of Scr from baseline to the final hospital visit (mean/SD) were from 1.21±0.59 to 1.47±0.91 mg/dl in moderate, from 1.010.04 to 1.89±1.84 mg/dl in severe, and from 1.95±1.14 to 1.76±0.80 mg/dl in more severe group, respectively. During the follow-up period, totally four renal events (5.4%) occurred (1 in moderate, 3 in severe). However, none of the more severe group presented renal event, nor renal function worsening in this group (P=0.002). Fourteen Pt’s died (19%), of which cardiac death occurred in 6 Pt’s (8.1% among all Pt’s) during the follow-up period.

Conclusions: In comparison with 5-year cumulative rate of 22% renal events and 11.4% cardiovascular death in medical group in ASTRAL study, the results in our study clearly demonstrated the effectiveness of PTRA in more severe RAS patients in preserving renal function and protecting from cardiac deaths. PTRA is a useful treatment for the Pt’s with more severe RAS.

Impact of Kidney Function on Intima-Media Thickness in Patients with Type 2 Diabetes

TH-PO621

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Background: Carotid echo indexes [intima-media thickness (IMT)] are commonly used surrogate markers for cardiovascular disease. However, the impacts of chronic kidney disease (CKD) on changes in IMT are unclear. We examined associations between CKD and IMT in participants with and without type 2 diabetes through longitudinal analysis.

Methods: In total, 424 subjects were enrolled in this study. IMT was measured per carotid echo indexes. Relationships between IMT and risk factors were analyzed using multiple linear regression analysis, in which we defined IMT as the dependent variable and other factors such as age, sex, systolic blood pressure, body mass index, estimated glomerular filtration rate (eGFR), uric acid, smoking index, number of antihypertensive drugs, statin use, urinary protein level, and diabetes duration as independent variables.

Results: The study population was composed of 70.3% male subjects. Participants with diabetes accounted for 64.4% of the total population. The mean follow-up duration was 3.2 ± 1.5 years. Alterations in IMT tended to be associated with systolic blood pressure (+0.10 mmHg (β = -0.0084, p = 0.09) and eGFR (+0.10 mL/min/1.73 m²) (β = -0.0049, p = 0.06) in all participants. In participants without diabetes, alterations in IMT were associated with eGFR (+0.10 mL/min/1.73 m²) (β = -0.0104, p = 0.03) and tended to be associated with systolic blood pressure (+0.10 mmHg (β = -0.0094, p = 0.06). No significant relationships were found in participants with diabetes.

Conclusions: Low eGFR was associated with progression of carotid thickness independent of common cardiovascular risk factors in non-diabetic participants.

The Number of Arterial Territories with Atheroma Plaque Predicts Cardiovascular Event-Free Survival in Chronic Kidney Disease.

TH-PO622

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Background: Cardiovascular disease remains the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD).

Methods: The NEFRONA study enrolled 2445 patients in different stages of CKD to assess the value of detection of subclinical atherosclerosis by ultrasound in the prediction of cardiovascular risk. This study shows the data on cardiovascular events (CVE) with a minimum follow-up time of three years, and the COX regression analysis of predicting factors.

Results: There have been 67 fatal and 152 nonfatal CVE and 113 deaths from other causes. The number of missings is 648 (593 renal transplants, 1 non renal transplant and 67 changes of center). The cumulative incidence of CVE is of 8.96% (median follow-up=42.09 months), stage 3: 6.95% (48 months), stage 4-5: 9.29% (42.8 months), stage 5D: 11.34% (23.1 months). Kaplan Meier curves of survival free from CVE show that the survival time is inversely proportional to the number of territories with plaque.
TH-PO624

The Effects of Diuretics on the Progression of CKD and Incidence of Cardiovascular Events: Results from the CKD-ROUTE Study – A Prospective Cohort Study of Newly Visiting CKD Patients in Japan

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Background: Anti-hypertensive agents are requisite for control of blood pressure in CKD patients. Although diuretics seem to be associated with progression of CKD or incidence of cardiovascular (CV) events, this hypothesis has not been adequately elucidated. To evaluate the association of anti-hypertensive agents prescription and outcomes, we analyzed a cohort study of newly visiting pre-dialysis CKD patients in Japan.

Methods: We recruited 937 newly visiting CKD patients followed for the next 3 years. At 6 months visit, use of RAAS inhibitors (RAAs), calcium channel blockers (CCBs), and diuretics was assessed, and the association between these medications and outcomes was evaluated. The outcomes were composite kidney endpoint of ESKD or 50% decline of eGFR, outcome of death related to CV events, and the related CV death during three years after first visit to nephrologists. We used multivariated Cox proportional hazards regression adjusted by age, sex, albumin, hemoglobin, eGFR, systolic blood pressure, presence of proteinuria and diabetes, and past history of CV events.

Results: The average age was 67 years (70.2% male, mean eGFR was 33.7 ml/min/1.73m², and mean systolic blood pressure was 139 mmHg. During the follow-up period of 3 years, 114 CV events occurred, 24 patients died of CV events, and 220 patients reached the composite kidney endpoint. In multivariable analysis, risk of CV events at 2 years and CV related death during the 3-year period was higher in the patients using diuretics at six months visit (adjusted hazard ratio 1.55 [95%CI 1.23-2.33] for CV events. 3.09 [95%CI 1.19-8.02] for CV related death.) The patients taking both diuretics and RAAs had comparable risk of CV events with those taking only diuretics (adjusted HR 1.09 [95% CI 0.84-2.21]) However, none of the three kinds of anti-hypertensive agents had associations with CKD progression.

Conclusions: CKD patients using diuretics were more likely to have CV events and CV related death. RAAS might contribute to reduce the risk of CV events by diuretics.

TH-PO625

Rapid Increase in Aortic Stiffness in Patients on Hemodialysis and Peritoneal Dialysis Compared with Non-Dialysis-Dependent Chronic Kidney Disease Patients: A Longitudinal Study Using MRI-Based Pulse Wave Velocity

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Background: Pulse wave velocity (PWV) is a well-established technique for obtaining a measure of arterial stiffness that has the potential to provide information on early atherosclerotic disease. MRI-based PWV measurements have been well validated in comparison with invasive pressure recordings (Grootenhuis et al. J Magn Reson Imaging, 2009). To date, very few studies have reported on MRI-based PWV in patients with chronic kidney disease (CKD), especially in patients with end-stage kidney disease on hemodialysis (HD) and peritoneal dialysis (PD). In the present study, we examine the annual changes in MRI-based PWV from baseline to 2 years and compared them among non-dialysis dependent-CKD (ND), HD, and PD patients.

Methods: A total of 172 CKD patients (ND, n=89; HD, n=47; PD, n=36) were recruited and underwent cardiovascular MRI at baseline and 2 years after. Using cine and phase contrast sequences, the cross-sectional area for distensibility and average blood flow were measured between the ascending and the proximal descending aorta. Annual change in MRI-based PWV was calculated as (MRI-based PWV after 2 years - baseline MRI-based PWV) / 365/interval days between the first and second MRI. Multivariable linear regression was used to evaluate differences in the changes among the 3 patient groups.

Results: The annual changes in MRI-PWV were significantly increased in patients on HD and PD compared with ND patients, even after adjusting various confounding factors including age, sex, and blood pressure (least square means were -0.18, 0.35, and 0.49 in ND, HD, and PD patients, respectively; p <0.001). Meanwhile, there was no difference in the changes between HD and PD patients (p = 0.736).

Conclusions: Progression of aortic stiffness is more rapid in patients on HD and PD compared with ND patients independent of age and blood pressure, while comparable between those on HD and PD.

TH-PO626

The Recent ADQI Proposal for a Functional Classification System of Heart Failure in Patients with End-Stage Renal Disease Will Substantially Overdiagnose Cardiac Disease Among Chronic Kidney Disease Patients

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Background: The Acute Dialysis Quality Initiative (ADQI) XI Workgroup has recently proposed a novel classification for HF stages in advanced CKD, which is based on a broad spectrum of echocardiographic criteria. We hypothesize that these criteria will substantially overdiagnose HF across the whole spectrum of CKD, as echocardiographic changes are a very frequent finding even among patients with mild to moderate CKD.

Methods: Within the ongoing CARE FOR HOME study we echocardiographically examined 317 patients in GFR categories G2 – G4, following American Society of Echocardiography guidelines. According to ADQI criteria, HF is defined by moderate to severe changes in any of the following categories: valve function, left atrial volume index (LAVI), left ventricular (LV) or right ventricular systolic function, LV mass index, LV diastolic function, LV diameter, or regional LV wall contractility. Patients were followed for a mean of 3.6 ± 1.5 years until the first admission for decompensated HF.

Results: Among the 317 CKD patients, 209 (66%) fulfilled ADQI criteria. HF was detected more often in advanced CKD (G3b/G4: 114/146; 78%) than in milder CKD (G2/ G3a: 95/171; 56%). An increased LAVI (158/317; 50%) and diastolic dysfunction (101/317; 32%) were the most frequent findings within the subcategories of echocardiographic changes. Among all 209 patients with ADQI HF, only 24 patients (11%) suffered decompensated HF during follow-up, and event-free four-year survival was 89%.

Conclusions: The proposed ADQI criteria will substantially overdiagnose HF among patients with mild to moderate CKD. We suggest defining more conservative echocardiographic criteria for HF prior to introduction of this new classification in daily clinical practice. The validity and reliability of such revised criteria should subsequently be analyzed across the whole spectrum of CKD.

TH-PO627

Prognostic Value of Pulmonary Hypertension in Combination with Heart Valvular Calcification on Cardiovascular Outcome in Maintenance Hemodialysis Patients

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Background: Our previous study had revealed pulmonary hypertension (PH) as a predictor of all-cause mortality, cardiovascular mortality and new onset cardiovascular events in maintenance hemodialysis (MHD) patients. We hypothesize that patients complicated with both PH and heart valvular calcification (HVC) may take higher cardiovascular risk than those suffer from PH or HVC only.

Methods: 304 Chinese MHD patients were enrolled and followed up for 24 months. Each patient underwent Doppler echocardiographic evaluation before entry. A value of Systolic PAP (SPAP) ≥ 35 mmHg was defined as PH. HVC was defined as the presence of bright echoes of >1mm on one or more cusps of the aortic valve, mitral valve or mitral annulus. Patients were divided into 3 groups: No risk group (with neither PH nor HVC, n=140), One Risk Factor Group (with PH or HVC, n=121) and Two Risk Factors Group (with both PH and HVC, n=43). The end-points were all-cause mortality, CV mortality and CV events.

Results: A total of 63 (20.7%) patients died during follow-up from all causes; 18 (12.9%) in Group 1, 29 (24.0%) in Group 2, and 16(37.2%) in Group 3. 36 died of CV events (57.1% of the causes of death); 7(5.0%) in Group 1, 16(13.2) in Group 2, and 13 (30.2%) in Group 3. All-cause and CV mortality increased significantly in both Group 2 and 3. 10(33.3%) had new-onset CV during the follow-up period; 29(20.7%) in Group 1, 43(35.5%) in Group 2, and 29 (67.4%) in the non-PH group, which was a significant difference (p<0.05).PH in combination with HVC increased risk for all-cause, CV mortality and new-onset CV event[HRR=4.32(2.60-8.09) versus 1.93(1.03-3.63) for all-mortality, 6.49(2.57-16.39) versus 2.60(1.05-6.44) for CV mortality and 3.51(2.03-6.07) versus 1.40(0.86-2.30) for new onset CV event].

Conclusions: PH in combination with HVC predicts worse outcome than those with either PH or HVC in MHD patients. Echocardiography can easily identify both PH and HVC, and is helpful to stratify risk in this population.

Funding: Government Support - Non-U.S.

TH-PO628

Survival of ESRD Patients Diagnosed with Idiopathic Heart Failure prior to Dialysis

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Background: Cardio-renal syndrome type 2 (CRS-2) is defined as chronic abnormalities in heart function leading to kidney injury or dysfunction, and may occur in patients admitted for heart failure (HF) (Ronco, Eur J Ht J 31:703, 2010). Idiopathic HF (HF) may clinically manifest as CRS-2 and progress to ESRD. The prognostic
of patients with pre-dialysis IHF after the institution of dialysis is unknown. We used the USRDS to compare survival between IHF patients diagnosed prior to ESRD (PRE) with patients developing IHF after the institution of dialysis (POST).

**Methods:** All incident adult ESRD cases from the USRDS from 1967-2012 were queried for a diagnosis of IHF before or after the incident date of dialysis. IHF was defined by the presence of any ICD-9 HF code (428.0-428.9), and the absence of other cardiovascular diagnoses. Descriptive statistics and co-morbidities by group were calculated, and survival analysis performed using Cox regression.

**Results:** 50,052 patients were identified with IHD. 46% and 54% were diagnosed with IHD PRE or POST, respectively. When compared to POST, PRE were older (73% ≥ age 65 vs. 33%), White (61% vs. 59%), diabetic (45% vs 6%), and female (52% vs. 47%, all p < 0.001), and with a hazard ratio (HR) for death of 1.82 (95% CI 1.77-1.861, p < 0.001). Diabetes prior to dialysis and age ≥ 44 years also exhibited increased HR for death (1.36 and 1.62, respectively). Non-white race was protective for death in all patients with IHD.

**Conclusions:** In ESRD, a diagnosis of IHD is common either before or after the incident date of dialysis. PRE is associated with decreased survival, perhaps due to pre-existing heart disease in an older, diabetic population. IHD in POST included younger patients likely with valvular heart disease, reflecting the effects of non-reversibly reversible conditions. IHD before and after the incident date of dialysis may be two distinct entities, and suggests unique management strategies for each syndrome may be indicated.

**TH-PO629**

**Association of Sleep Apnea with Mortality in Chronic and End Stage Kidney Disease Patients**

Manisha Jhamb, Herbert T. Davis, Mark L. Unruh, Univ of Pittsburgh; Univ of New Mexico.

**Background:** Presence of sleep apnea and its severity has been associated with increased mortality in the general population. In the dialysis population, limited evidence suggests an association of nocturnal hypoxyemia with mortality. We sought to determine the association of sleep apnea and mortality in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

**Methods:** 180 patients (87 CKD stage 4-5, 93 ESKD), underwent 1 night home polysomnography. Sleep apnea severity was measured as number of apneas and hypopneas per hour (apnea-hypopnea index, AHI). Information on patients' demographics, comorbidities and laboratory values was obtained from patient interviews and chart review. Mortality data was obtained from National Death Index. Chi-square and ANOVA were used to test between group differences and Cox proportional hazard model was employed to test association with mortality.

**Results:** 71% of the patients had sleep apnea (AHI>5) and 23% had severe sleep apnea (AHI>30). There was no difference in age, race, hypertension, body mass index, smoking status, renal function status (CKD vs ESKD), depression, hemoglobin or albumin levels among patients with or without sleep apnea. AHI was most likely to have more severe sleep apnea. In both males and females, sleep apnea severity increased with age. Over a mean (SD) follow-up period of 9.0 (3.7) years, there were a total of 31 deaths and 57 patients received kidney transplant. We found no association between sleep apnea severity and all-cause mortality. However, in unadjusted analysis, more percentage of time with SpO2 < 90% was associated with higher mortality [HR 1.03 (1.01-1.06), p < 0.001].

**TH-PO630**

**CKD Measures and Segment-Specific Arterial Stiffness: The Atherosclerosis Risk in Communities (ARIC) Study**

Kunihiro Matsushita, Yuaine Pang, Herbert T. Davis, Yiming Syng Sang, Shoshana Ballew, Hirofumi Tanaka, Gerardo Nnn Heiss, Josef Coresh, Johns Hopkins Univ; Univ of Texas; Univ of North Carolina.

**Background:** Several studies have reported an association of CKD with arterial stiffness but generally focus on either, but not both, of eGFR or albuminuria, assess pulse wave velocity (PWV) at limited segments, or investigate clinical populations.

**Conclusions:** In patients with advanced CKD and ESRD, sleep apnea is common and increases in severity with age. Sleep apnea, as measured by AHI was not associated with all-cause mortality.

**Funding:** NIDDK Support, Private Foundation Support

**TH-PO631**

**Impact of Kidney Failure on Management and Outcome of Patients Admitted with Heart Failure**

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**Background:** Data from epidemiological studies and intervention trials suggest poor prognosis in heart failure patients with kidney disease. However no study has investigated the impact of severe kidney failure on management and outcome of in-hospital heart failure patients.

**Methods:** We analysed data on clinical, laboratory, management and in-hospital mortality on 990 patients admitted between 01/03/2013 and 17/03/2013.

**Results:** Severe kidney failure (eGFR<30 ml/min/1.73m2) was present in 19% of patients and moderate kidney failure (eGFR 30-60 ml/min/1.73m2) was present in 43%. Patients with severe kidney failure, compared to the rest were older (79.1±11.5 vs. 75±13 years; p<0.001), with lower haemoglobin (10.5±1.9 vs. 12±1.8 g/dL; p<0.001), higher potassium (4.7±0.8 vs. 4.2±0.6 mmol/L; P=0.05) and higher NT-pro BNP (1715±1291 vs.9240±9577; p<0.001). Diuretics use in severe kidney failure patients was less (85% vs. 96%, p=0.005), however β blocker use was similar (74% vs. 75%). Furosemide dose was high in severe kidney failure (10162 vs. 79±43 mg; p<0.001) but dose of bumetanide was similar (3.9±2.3 vs. 4.1±1.9 mg; p=0.5). In the presence of echocardiographic LV dysfunction severe kidney failure patients were less likely to be on ACEi or ARB (24% vs. 74%; p<0.001). 98 patients who died during admission were older (78±10 vs. 76±13 years; p<0.05), with lower haemoglobin (11.1±2.2 vs. 11.8±1.9 g/dL), p<0.001), higher creatinine (011123 vs. 13595 µmol/L; p<0.001), higher NT-pro BNP (16536±12727 vs. 10174±10346; p<0.001) and higher potassium (4.7±0.9 vs. 4.2±0.6 mmol/L; p<0.001).

**Conclusions:** Among hospital admissions for heart failure, patients with severe kidney failure had lower haemoglobin, higher potassium, high BNP, were less often on ACEi/ARB and diuretics; suffered higher in-hospital mortality. Severe kidney failure is common, adversely affects management and outcomes in admitted heart failure patients.
**TH-PO632**

**Wave Pulse Velocity in Children with Chronic Kidney Disease**


**Background:** Wave pulse velocity (PWV) is a measure of arterial stiffness associated with CV events in the general population and adults with CKD. However, few data exist regarding PWV in children with CKD. We compared observed PWV to normative data in healthy children and examined risk factors associated with elevated PWV in children enrolled in the CKiD cohort study.

**Methods:** PWV was assessed via carotid/femoral tonometry using the Sphygmocor device (AtCor, Australia). PWV Z-score for height/gender was calculated from and compared to published pediatric norms (Reusz et al., 2010). Multivariate linear regression was used to assess the relationship between PWV and level of proteinuria (UP/C) adjusted for age, gender, race, height, waist circumference, mean arterial pressure (MAP), and GFR.

**Results:** 249 PWV studies were performed on 90 participants. 63% were male, 20% African American, 49% had glomerular CKD, 9% UP/C >2mg/mg; median age was 16 years, median MAP was 82mmHg, and median GFR was 67 ml/min. Average PWV was 5.1±3.0 m/s, Z-score = -0.01 (1.2). As expected, PWV was significantly associated with age and MAP in multivariate analysis (Table 1). Additionally, the point estimate for UP/C was large but non-significant.

**Conclusions:** In this pediatric cohort with mild kidney dysfunction, arterial stiffness was comparable to that of normal children. Data collection is ongoing to further assess the effects of BP and proteinuria on arterial stiffness in children with CKD.

**Table 1. PWV multivariate analysis.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate ± SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.09 ± 0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>-0.05 ± 0.17</td>
<td>0.79</td>
</tr>
<tr>
<td>African American</td>
<td>0.12 ± 0.20</td>
<td>0.55</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>-0.01 ± 0.01</td>
<td>0.41</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.00 ± 0.01</td>
<td>0.47</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.03 ± 0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>iGFR (per 10 ml/min/1.73m²)</td>
<td>-0.02 ± 0.04</td>
<td>0.56</td>
</tr>
<tr>
<td>UP/C (mg/mg)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>0.03 ± 0.22</td>
<td>0.88</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>0.34 ± 0.32</td>
<td>0.29</td>
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**Funding:** NIDDK Support, Other NIH Support - NICHD, NHLBI

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**TH-PO633**

The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C Study): Baseline Data of a Multicentre Prospective Observational Study

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**Background:** The role of CKD-specific factors in the initiation and progression of cardiovascular disease (CVD) are likely to be characterized with increased sensitivity in the pediatric age group. The Cardiovascular Comorbidity in Children with CKD (4C) Study is a multicentre, prospective, observational study in children with CKD aged 6 to 17 years, initial glomerular filtration rate 10-60 ml/min/1.73 m². The prevalence, degree and progression of cardiovascular comorbidity and its association with CKD progression is explored through longitudinal follow-up.

**Methods:** The morphology and function of the heart and large arteries is monitored by non-invasive methods and compared with aged-matched healthy controls. The Cardiovascular Comorbidity in Children with CKD (4C) Study is a multicentre, prospective, observational study in children with CKD aged 6 to 17 years, initial glomerular filtration rate 10-60 ml/min/1.73 m². The prevalence, degree and progression of cardiovascular comorbidity and its association with CKD progression is explored through longitudinal follow-up.

**Results:** A total of 705 patients were enrolled in 55 participating centers from 12 European countries. At baseline examination, 30% of children were hypertensive (ambulatory blood pressure monitoring), 40% had left ventricular hypertrophy (echocardiography), 40% showed an increased intima-media thickness of the carotid artery (cIMT, ultrasound), and 23% an increase in aortic pulse wave velocity (PWV; oscilometry). By multivariate analysis, systolic blood pressure and serum levels of 25-hydroxyvitamin D, parathyroid hormone, and serum calcium- and phosphorus levels showed significant associations with age-corrected iIMT and PWV, respectively.

**Conclusions:** Children aged 6-17 years with CKD stage 3-5 have significant subclinical CV disease at initial examination, subclinical endpoints of CVD were associated with systolic blood pressure and disturbances of mineral metabolism.
Methods: We studied Jackson Heart Study participants and calculated eGFR from baseline serum creatinine (CKD-EPI equation) and urine albumin-to-creatinine ratio (ACR) from urine samples. We tested association of eGFR and urine ACR with left ventricular mass (LVM), left ventricular ejection fraction (LVEF) and incident HF.

Results: In 3,332 participants, 5% had eGFR<60 ml/min/1.73m ² and 12% had urine ACR>30 mg/g. Mean LVM was higher in those with eGFR<60 (175g vs 147g) and urine ACR>30 (169g vs 143g). Mean LVEF was similar across eGFR and ACR levels. The association of eGFR with LVM was significant adjusting for age, sex, education, blood pressure, BMI, smoking, hypertension, statins, diabetes and cardiovascular disease (β-coefficient 13g [95% CI:7,19]), while association with LVEF was not (β-coefficient -0.9% [95% CI: -1.9,0.1]). Urine ACR>30 mg/g was associated with higher LVM in adjusted models (β-coefficient 6g [0.7,11]), however, was not associated with LVEF (adjusted β-coefficient -0.4% [95% CI: -1.2,0.4]). Rate of HF events was greater in those with CKD (β-coefficient -0.4% [95% CI: -1.2,0.4]). Higher urine ACR was strongly linked with incident HF after adjusting for LVM and ACR (Table).

Conclusions: LVM was higher in AA with lower eGFR and higher ACR. Higher urine ACR was linked with incident HF and not entirely explained by LVM. We show the importance of mild/early kidney dysfunction with risk of HF among AA. More study is needed to characterize the mechanisms by which kidney disease contributes to worse outcomes in HF in this group.

Funding: NIDDK Support

TH-PO637

Racial Differences in Risk of Chronic Kidney Disease in Patients with Congestive Heart Failure

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Background: While CKD is more common in African Americans (AA), the prevalence of CV disease is lower in AA patients with CKD. It is unclear if the higher risk of incident CKD associated with AA race is modified by the presence of CHF.

Methods: Among 3,065,749 AA or white US veterans with eGFR>60 ml/min/1.73m ² and no CHF at baseline, we examined the association of AA race with incident CHF (hospitalization-based ICD9 codes) during a median follow up of 6.7 yrs. We examined outcomes separately in patients who maintained an eGFR≥60 ml/min/1.73m ² (non-CKD group; N=2,632,034), and those who developed 2 eGFR values <60 with >90 days in-between (CKD group; N=286,597). We used Cox proportional hazards models, without adjustments (Model 1) and with sequential adjustments for baseline demographics and eGFR (Model 2), comorbidities (Model 3), BMI and BP (Model 4), and medications and socioeconomic indicators (Model 5).

Results: 71,137 (event rate: 4.8/1000 patient-years, 95% CI: 4.8-4.9) and 42,067 (26.4/1000PY, 26.2-26.7) patients developed CHF in the non-CKD and CKD groups, respectively. Compared to whites, AA race was associated with similar unadjusted risk of CHF in non-CKD (hazard ratio, 95% CI: 1.07, 0.97-1.09), but with higher unadjusted risk among CKD (1.23, 1.20-1.26). After adjustments, the risk of CHF in AA was minimally lower in both non-CKD and CKD patients (Figure 1).

Conclusions: The risk of incident CHF is slightly lower in AA US veterans with and without CKD. These qualitatively different associations compared to the non-veteran population warrant additional studies.

Funding: NIDDK Support, Veterans Administration Support

TH-PO639

Continued Underrepresentation of Patients with Kidney Disease in Cardiovascular Trials: An Updated Systematic Review After a Decade

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Background: Cardiovascular disease (CVD) is a major cause of morbidity/mortality in kidney disease (KD). Two systematic reviews showed that KD patients are underrepresented in CVD randomized controlled trials (RCTs) using data from 1985-2005 and 1998-2005. We aimed to update estimates of KD patient representation in major CVD RCTs over the past decade.

Methods: We searched MEDLINE for congestive heart failure/acute coronary syndrome RCTs in major journals between 2006-2014. We excluded RCTs not reporting mortality outcomes, with <100 participants, or were subgroup, follow-up, or post-hoc analyses.

Results: We included 371 trials randomizing 590,040 participants. KD patients were excluded in 212 (57.1%) RCTs and were more likely to be excluded from North American (p<0.02) or industry-funded (p<0.01) trials. They were more likely to be excluded in RCTs of anticoagulants, antiplatelet agents, statins or RAAS antagonists compared to trials of PCI (p<0.01).

Conclusions: The increased risk of renal complications associated with AA vs. white race is higher in patients with CHF compared to those with no CHF. Interventions aimed at improving renal outcomes in AA patients with CHF should be further examined.

Funding: NIDDK Support, Veterans Administration Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Of 212 RCTs excluding KD patients, 111 (52.4%) used serum creatinine, 25 (11.8%) used eGFR cut-offs, and 36 (17.0%) had non-specific kidney-related exclusions. Only 156 (42.0%) trials reported baseline kidney function and only 84 (22.6%) trials reported the proportion of KD patients in each randomization arm. While 197 (53.1%) reported subgroup analyses of >1 non-renal baseline characteristics, only 60 (16.2%) reported subgroup analyses by renal parameters.

Conclusions: Most CVD RCTs continue to exclude KD patients. They neither adequately report nor analyze outcomes by participants’ baseline kidney function.

Funding: NDDKP Support

TH-PO640

Effect of Niacin on Markers of Mineral Metabolism in CKD: The AIM-HIGH Trial

Joachim H. Ix1, Ronit Katz,2 Andrew N. Hoofnagle,3 Dena E. Rifkin,1 Andrew Bostom,3 Jeffrey L. Probstfield,2 Geoffrey A. Block4 (UCSD; 1U Washington; 2Brown Univ; 3Denver Nephrology.

Background: Niacin blocks intestinal phosphate (P) transport in vitro. Short-term human studies suggest niacin lowers P in CKD patients. Longer-term effects on P, and on other mineral markers are uncertain. Fibroblast growth factor (FGF) 23 is a phosphaturic hormone that induces left ventricular hypertrophy in vitro and higher levels are associated with heart failure and death in CKD patients. Higher serum P may stimulate higher FGF23.

Results: Of 352 patients with eGFR<60 ml/min/1.73 m², Exclusions included serum Cr ≥ 2.7mg/dL. The trial was stopped after 3 yrs mean follow-up due to futility. In 352 patients with eGFR<60 ml/min/1.73 m², we measured P, calcium (Ca), intact (i) FGF23 (Kainos), intact parathyroid hormone (iPTH), and calcitriol (5-OH vitamin D3) in each randomization arm. While 197 (53.1%) reported subgroup analyses of >1 non-renal baseline characteristics, only 60 (16.2%) reported subgroup analyses by renal parameters.

Conclusions: Most CVD RCTs continue to exclude KD patients. They neither adequately report nor analyze outcomes by participants’ baseline kidney function.

Funding: NIDDKP Support

TH-PO641

Efficacy and Safety of Modified-Release Calcifediol in Stage 3–4 CKD Patients with Secondary Hyperparathyroidism and Vitamin D Insufficiency

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Background: Current approaches to correct vitamin D insufficiency (VDI) in stage 3 or 4 CKD are poorly defined and generally ineffective in controlling secondary hyperparathyroidism (SHPT). The effectiveness of modified-release calcifediol (MRC) at correcting VDI and controlling SHPT was evaluated.

Methods: Two identical, randomized, double-blind, placebo-controlled trials were conducted in patients with VDI (>85 pg/mL), stage 3 or 4 CKD and VDI (serum 25OHD 10-29 ng/mL). The trials enrolled a total of 429 subjects from 77 US sites, randomized 2:1 to receive MRC or placebo for 26 weeks. MRC dosing started at 30 mg/d and increased, as needed to lower iPTH, to 60 mg/d after 12 weeks. Subjects were stratified based upon their 25OHD levels (0-20, 20-40, 40-60, 60-80 or > 80 ng/mL) at the end of treatment (EOT). The mean EOT plasma iPTH, serum total 1,25-dihydroxyvitamin D (1,25D), serum Ca and P, and iPTH progressively decreased with increasing 25OHD concentrations, with mean iPTH levels 40% lower in the subjects with the highest- 25OHD concentrations compared to the lowest concentrations (Figure; p < 0.001). No changes were observed in serum Ca and P concentrations independent of 25OHD concentration.

Funding: Pharmaceutical Company Support - OPKO Health

TH-PO642

CKD-MBD Indices After 52 Weeks of Sucroferric Oxysoufo, an Iron-Based Phosphate Binder, in African American Dialysis Patients

Stuart M. Sprague,1 Anjay Rastogi,2 Markus Ketteler,3 Adrian C. Covic,4 Jürgen Floege,5 Viatcheslav Rakov,2 Llera Armando Samuels,3 NorthShore Univ Health System, Chicago; 2Univ of California; 3Coburg Clinic & AKH-Diализ Center, Germany; 4Gr.T. Papa Univ of Medicine and Pharmacy, Romania; 5RWTH Univ Hospital Aachen, Germany; 6Vfor Pharma; 7Temple Univ, Philadelphia.

Background: Post hoc analysis of data from a randomized, open-label, Phase 3 study and its extension investigated the effects of the iron-based phosphate binder sucroferic oxysoufo (SFOH; VELPHORO®) vs sevelamer carbonate (SEV; Renvela®) on chronic kidney disease-mineral bone disorder (CKD-MBD) indices in African American dialysis patients

Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/d; n=710) or SEV (2.4–14.4 g/d; n=349) for 12 weeks’ dose titration then 12 weeks’ maintenance. Eligible patients enrolled in a 28-week extension study.

Results: Of the 549 patients who completed the extension study, 100 were African American patients, (n=48, SFOH; n=52, SEV). Serum phosphorus control was maintained over 1 year; both SFOH and SEV were associated with significant decreases in serum phosphorus from baseline to Week 52 (Table), as well as significant reductions in mean

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Concomitant IV Iron Use Drives Changes in Iron Indices in African American Dialysis Patients Over 52 Weeks of Sucroferric Oxyhydroxide Treatment
Stuart M. Sprague,1 Anjey Rastogi,2 Markus Ketterer,1 Adrian C. Covic,1 Jürgen Floege,3 Viatcheslav Rakova,4 Lilla Armando Samuels.1
1NorthShore Univ Health System, Chicago; 2Univ of California; 3Coburg Clinic and KfH-Dialysis Center, Germany; 4Gr.T. Popa Univ of Medicine and Pharmacy, Romania; 5RWTH Univ Hospital Aachen, Germany; 6Vifor Pharma; 7Temple Univ, Philadelphia.

Background: A post hoc analysis of data from a randomized, open-label, Phase 3 study and its extension investigated iron indices after treatment with the iron-based phosphate binder sucroferric oxyhydroxide (VELPHORO®; SFOH) vs sevelamer carbonate (SEV) in African American dialysis patients who received IV iron vs those who did not. Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12-week dose titration then 12-weeks maintenance. A high proportion of patients in the SFOH and SEV groups received IV iron vs those who did not.

Results: Of the 549 patients who completed the extension study, 100 were African American (n=48, SFOH; n=52, SEV). A high proportion of patients in the SFOH and SEV groups received IV iron (95.8 and 98.1%) during the 1-year study. Baseline levels of ferritin appeared elevated in both treatment groups with higher levels in the SEV group (Table). Significant increases in ferritin were observed in SFOH 'IV iron' subgroup. Ferritin and TSAT levels increased (95.8 and 98.1%) during the 1-year study. Baseline levels of ferritin appeared elevated in both groups over 52 weeks. No significant differences between treatment groups were mainly attributable to concomitant IV iron use. Differences between groups may be due to baseline differences and minimal iron uptake from SFOH, although no signs of iron accumulation were observed over 1 year. Post hoc results, in terms of changes in iron indices, reflect those from the overall study population.

Conclusions: The high efficacy of cinacalcet was still demonstrated even in case of severe secondary HPT. However, higher iPTH reduced the efficacy outcome of cinacalcet.

TH-P0645
A Double-Blind, Randomized, Placebo-Controlled Trial of Ergocalciferol with/without Calcitriol in Chronic Kidney Disease with Proteinuria Patients
Susa Kittanasarn,1 Sirawin Nakwan,2 Kajohn Timanahtang想知道,1 Piptut Katavetin,1 Kearkiat Praditpornsilpa,2 Somchai Eiam-Ang,3 Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.

Background: These are no available data regarding the role of natural vitamin D with/without active vitamin D on proteinuria and renal function in CKD patients with vitamin D insufficiency/deficiency. This study was conducted to explore the additional effect of both active vitamin D (calcitriol) and natural vitamin D (ergocalciferol) on proteinuria and kidney function in CKD with vitamin D insufficiency/deficiency.

Methods: The first double-blind, randomized placebo-controlled trial was performed to answer this question. Sixty eight patients with eGFR 15-60 mL/min/1.73²m², UPCR greater than 1 g/g and vitamin D insufficiency/deficiency were enrolled. Patients were randomly assigned to receive 12-week treatment with oral ergocalciferol plus placebo (n=36) or ergocalciferol plus oral calcitriol (n=32).

Results: The mean baseline UPCR of both groups were comparable (3.6 ± 3.8 g/g in combined group and 3.5 ± 3.0 g/g in ergocalciferol group). Following 12-week treatment, there were significant reductions in UPCR of both groups from baseline (3.2 ± 2.1 g/g in combined group and 2.4 ± 2.0 g/g in ergocalciferol group). The percentage reductions in UPCR of both groups were not significantly different (-25.5% in combined group and -23.7% in ergocalciferol group). These effects were demonstrated in all range of proteinuria, diabetic nephropathy, non-diabetic nephropathy, receiving RAAS blockade and non-receiving RAAS blockade. The mean eGFR and blood pressure did not differ between baseline and 12-week follow up between and within both groups. No severe hypercalcemia or serious side effects were noted in both groups.

Conclusions: This is the first RCT which illustrates the lowering proteinuria effect of ergocalciferol in CKD patients with vitamin D deficiency. However, additional calcitriol did not have more effects on proteinuria. Therefore, ergocalciferol should be added for more decreasing proteinuria in CKD patients with proteinuria that cannot tolerate or increase the dosage of RAAS blockade due to any side effects. A longer study is required to examine the renal function retardation effects.
Anemia Correction with Roxadustat Lowers Cholesterol in Chronic Kidney Disease (CKD) Patients


Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) is being developed for treatment of CKD anemia. Hepcidin regulates iron metabolism and higher levels are associated with greater mortality. This analysis of phase 2 studies was undertaken to explore the consistency of the suppressive effect of roxadustat on hepcidin.

Methods: Among CKD-NDD (017 and 040) and CKD-DD (040 and 053) studies, roxadustat doses, study duration, and comparator (placebo or epoetin) varied. Studies restricted IV iron in general but allowed oral iron. Baseline (BL) hepcidin and change from BL (CFB) are summarized (mean ± SD) overall and by tertile. Significant differences (p<0.05 vs BL) based on within-group comparisons (†).

Results: Mean BL hepcidin in CKD-NDD roxadustat subjects was 292.8±179.8 and 120.3±107.0 ng/mL (studies 017 & 040). Hepcidin fell with roxadustat treatment by 158.4±179.2 & 45.6±87.7. Mean BL hepcidin in CKD-DD roxadustat subjects was 303.9±172.9 & 91.1±99.0. Hepcidin fell with roxadustat treatment by 26.7±192.0 & 57.4±65.8. For both groups, the greatest declines were in the highest BL tertiles.

Conclusions: Roxadustat consistently lowered hepcidin in phase 2 studies. The decrement in hepcidin is greatest among those with the highest BL levels. The roxadustat phase 3 trials will include measurements of hepcidin to further define this effect.

Funding: Pharmaceutical Company Support - FibroGen

**TH-PO647**

AnemiaCorrection with Roxadustat Increases Soluble Transferrin Receptor (sTfR) in Chronic Kidney Disease (CKD) Patients


Background: The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat is being developed for CKD anemia. The HIF pathway affects cholesterol metabolism & ascension to altitude reduces total cholesterol (TC). This analysis of phase 2 studies explores roxadustat’s effect on TC in non-dialysis (NDD) and dialysis (DD) CKD.

Methods: In Phase 2 studies 41 & 47 in NDD & 40, 48 & 53 in DD, roxadustat dose, study duration and comparator (placebo, epoetin) varied. Studies restricted IV iron but allowed oral iron. Baseline (BL) TC and change from BL (∆) were summarized overall and by tertile. Data are mean ± SD.

Results: Among roxadustat NDD subjects (n=206), mean BL TC was 170.4±45.2 and 166.8±39.1 mg/dL (studies 41 & 47). TC fell with roxadustat by 25.8±29.7 and 33.7±31.8. Among roxadustat DD subjects (n=238), mean BL TC was 171.1±35.1, 174.3±57.3, and 171.0±56.7 (studies 48, 53 & 540). TC fell with roxadustat treatment by 14.2±36.4, 44.4±45.5, and 36.7±37.0. The greatest declines were among the highest BL tertile in both populations.

Conclusions: Roxadustat consistently lowered TC in phase 2 studies. The decrement in TC is greatest among those with the highest BL levels. Roxadustat phase 3 trials will include tests to further define this effect and significance.

Funding: Pharmaceutical Company Support - FibroGen

**TH-PO649**

AKB-6548 Demonstrates Controlled Hemoglobin (HGB) Response in a Phase 2b Study for the Treatment of Anemia in Patients with Chronic Kidney Disease Not on Dialysis (ND-CKD)

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Background: AKB-6548 is a novel, once daily, oral hypoxia-inducible factor prolylhydroxylase inhibitor (HIF-PHI) that preferentially stabilizes HIF-2α. Current standard of care for anemia in ND-CKD with recombinant ESAs often results in overshoots and oscillations of HGB levels. It has been suggested that fluctuations in HGB concentrations, rapidly increasing HGB levels, and overshoots of the HGB target are associated with increased risk of cardiovascular events. Presented here are data assessing the control and predictability of HGB response from a Phase 2b study.

Methods: A randomized, double-blind, placebo-controlled study was conducted to assess the HGB response of AKB-6548 over 20 weeks of dosing in ND-CKD subjects with anemia. 210 subjects were randomized 2:1 (138 AKB-6548, 72 placebo) to once daily AKB-6548 (450mg) or placebo. HGB was monitored at each study visit and a protocol-defined dose adjustment algorithm was used to raise and maintain HGB and to minimize excursions ±13 g/dL.

Results: The starting dose of 450 mg once daily was validated by the final average dose of 440 mg/day in the AKB-6548-treated subjects. Only 15 subjects (11%) had a confirmed HGB >12 g/dL and only 2 subjects (1%) had a confirmed HGB >13 g/dL. From Weeks 12 to 20, 74% and 81% of all HGB measurements were between 10-12 g/dL and 10-13 g/dL.

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respectively. The majority of subjects (120 of 135, 89%) achieved and maintained a stable HGB level with 2 or fewer dose adjustments throughout the 20-week treatment period and 24% (33 of 135) of subjects required no dose adjustment.

**Conclusions:** AKB-6548 increased and maintained HGB levels in ND-CKD patients in a controlled and predictable manner with minimal dose adjustments. The study provides support that targeting the HIF oxygen sensing pathway is likely to represent a more physiologic and potentially safer approach to treating anemia than currently available therapy.

**TH-PO650**

Randomized Controlled Trial of Darbepoein Alfa and Continuous Erythropoetin Receptor Activator Once Every 4 Weeks in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage

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**Background:** Subcutaneous injection of Continuous Erythropoetin Receptor Activator (CERA) seems to maintain a stable Hb level than darbepoein alfa (DA) in CKD patients who are not on dialysis because of its longer half-life. We therefore conducted a randomized controlled trial.

**Methods:** The cohort consisted of 205 CKD patients at the pre-dialysis stage who were receiving a fixed dose of DA with a Hb level ≥9.5 g/dL and ferritin level ≥80 mg/mL in the 12 weeks prior to the study. Patients were randomly assigned to receive subcutaneous CERA or DA once every 4 weeks. The study consisted of a 48-week evaluation period. The target Hb level was 70%, which rose to 100% in the interval between weeks 4 to 48, with no significant difference between the groups. Despite the absence of a significant difference in Hb level, it was significantly increased from week 24 and from week 8 relative to those at week 0 in the DA continuation group and CERA changeover group, respectively. In addition, the reticulocyte count was significantly increased at weeks 4, 8 and 12 in the CERA changeover group compared with the DA continuation group. The doses of DA and CERA during the evaluation period were not significantly changed. Because the total administered doses of DA and CERA over 48 weeks were 0.99±0.16 mg/kg/week and 0.95±0.204 mg/kg/week, the dose conversion ratio was 1.05:1 mg. There was no significant difference in the levels of eGFR and iron state between both groups.

**Conclusions:** The present study demonstrated that subcutaneous administration of DA and CERA once every 4 weeks to predialysis patients have similar effects on achievement of target Hb levels but longer acting CERA can increase the Hb level earlier than DA.

**TH-PO651**

**QW or Q2W Darbepoein Alfa in Pediatric Subjects with Chronic Kidney Disease**

Bradley Wardaj, John P. Barcia, Nadine M. Benador, Augustina Jankauskiene, Kurt Olson, Ludmila Podracka, Alexey Shvakin, Poyyapakkam Sriwaths, Cynthia Wong, Jeffrey Petersen. *Children’s Mercy; UVA Med; UCSD; Winiaux U; Amege; UPSJ; Children’s City; TX Children’s; Stanford Med.*

**Background:** Minimal data are available on the initiation of erythropoiesis stimulating agents (ESA) for the correction of anemia in ESA-naive pediatric patients with CKD. Additionally, the optimal dosing frequency with darbepoein alfa (DA) in this setting has not been previously evaluated. This study assessed the ability of DA administered either once weekly (QW) or once every 2 weeks (Q2W) to correct anemia in pediatric patients.

**Methods:** Multicenter, double-blind, randomized study in pediatric subjects (age 1 to 18 years) with CKD and anemia (hemoglobin; Hb; >10.0 g/dL) on or not on dialysis and not treated with an ESA. The primary endpoint was Hb ≥ 10.0 g/dL at any time after the first dose without receiving a RBC transfusion within 90 days prior to initial Hb measurement or after randomization. Subjects were randomized to DA QW or Q2W at an initial dose of 0.45mg/kg or 0.75mg/kg, respectively. For both treatment groups, subsequent DA doses were titrated to achieve Hb 10.0 g/dL to 12.0 g/dL, inclusive over a 25 week period of observation.

**Results:** 116 subjects were enrolled: 59 were randomized to DA QW and 57 to Q2W. 114 subjects (58 QW; 56 Q2W) were included in the analyses. Mean (SD) Hb for the QW group increased from 8.6 (0.84) g/dL at baseline to 11.3 (1.23) g/dL at week 10 and remained relatively stable (range: 10.9 [1.10] to 11.7 [1.19] g/dL) through week 25. Mean Hb for the Q2W group increased from 8.7 (0.84) g/dL at baseline to 10.9 (1.38) g/dL at week 12 and remained relatively stable between 10.4 (0.97) and 11.1 (1.00) g/dL (through end of study). Hb concentrations were corrected to ≥10 g/dL in 98% and 94% of pediatric subjects administered DA QW or Q2W, respectively. 4 (7%) QW and 5 (9%) Q2W subjects received RBC transfusions. Safety results were consistent with the known safety profile for DA.

**Conclusions:** DA concentrations were corrected to ≥ 10 g/dL in > 90% of pediatric subjects administered DA QW or Q2W. No new safety signals were identified in this pediatric subject population.

**Funding:** Pharmaceutical Company Support - Amgen Inc.
Post Hoc Analyses of the EPPIC Trials to Assess the Effect of AST-120 in Chronic Kidney Disease Patients

TH-PO654

**Background:** The orally administered spherical carbon adsorbent AST-120 is approved in Asian countries for delaying the initiation of dialysis and ameliorating symptoms of uremia in patients with progressive CKD. Two randomized, double-blind, placebo-controlled trials (EPPIC trials) investigated the efficacy and the safety of AST-120 in adults with CKD. The benefit of adding AST-120 was not supported by the results of the primary analysis as reported previously. In order to further assess the efficacy of AST-120, we examined clinical and geographic factors by post hoc analyses using pooled populations of 2 trials.

**Methods:** The primary endpoint was a composite of diastolic indication, kidney transplantation and serum creatinine doubling. The same statistical methods for the efficacy endpoint analysis were applied for these post hoc analyses.

**Results:** In a multivariable analysis using baseline parameters, positive hematuria and elevated UP/UcR were found to be an independent risk factor for the primary endpoint. In the ITT population with positive hematuria, elevated UP/UcR (1.0) and ACEI/ARB use, a difference between the AST-120 and the placebo treatment groups was observed in primary endpoint occurrence (HR 0.74, 95% CI 0.56-0.96). In subgroup analysis by country, a higher event rate was observed in the USA population than outside the USA. In theITT population from the USA with ACEI/ARB use, a difference between the AST-120 and the placebo treatment groups was observed in primary endpoint occurrence (HR 0.74, 95% CI 0.56-0.98).

**Conclusions:** These results suggest that there may be a directional effect of adding AST-120 to standard therapy regimens in high risk populations such as patients with hematuria and elevated UP/UcR in the patients in similar than those enrolled in the USA EPPIC trials. Due to its post hoc nature of the analysis, further prospective studies are needed to confirm the results.

**Funding:** Pharmaceutical Company Support - Mitsubishi Tanabe Pharma Co Kureha Co

**TH-PO655**

A Phase 2 Study on the Effect of Tenapanor on Albuminuria in Patients with T2DM and CKD

**Background:** Patients with type 2 diabetes mellitus (T2DM) and CKD are treated with renin-angiotensin-aldosterone system (RAAS) inhibitors to slow the decline in renal function. The effectiveness of RAAS inhibition is limited by high sodium (Na) intake. Tenapanor (AZD1722), an inhibitor of the Na+/H+ exchanger NHE3, reduces absorption of Na and phosphate from the gut. This trial evaluated the effects of tenapanor on albuminuria levels, which may be associated with renal function decline, in patients with T2DM and CKD stage 3 receiving RAAS inhibitors.

**Methods:** This was a randomized, placebo-controlled, 12-week study (NCT01847092) in patients with urine albumin-to-creatinine ratio (UACR) 200–1500 mg/g. The starting dose of tenapanor hydrochloride was 15 mg bid: there was a 4-week titration period (dose escalation up to 60 mg bid followed by reduction down to 5 mg bid), based on in L or T dose, and every 3 months when eGFR was less than 30. All elevated serum K levels, which may be associated with renal function decline, in patients with T2DM and CKD were safe in the HALT PKD trial. Clinical use of dual RAAS blockade or intensive adverse events (SAEs) and there were no SAEs within 21 days after detection of HK.

**Conclusions:** In patients with T2DM and CKD stage 3, the pharmacodynamic effects of tenapanor were confirmed, as shown by slower consistency and increased frequency of stool, and reduced urinary phosphorus excretion following tenapanor treatment. However, these observations did not translate into effects on albuminuria.

**Funding:** Pharmaceutical Company Support - AstraZeneca

**TH-PO656**

Effect of Fluvastatin Treatment on Proteinuria in Diabetic Patients with Chronic Kidney Disease

**Background:** Hyperkalemia in the HALT PKD Trial

**Methods:** Study A subjects with eGFR >60 ml/min aged 15-50 were randomized to lisinopril (L) and placebo (P) vs L and telmisartan (T) with two levels of BP control: standard (SBP) [120-130/70-80 mmHg] vs low (LBP) [95-110/65-75 mm Hg]. Study B subjects with eGFR 25-60 ml/min aged 18-65 were randomized to L and P vs L and T with SBP only. Serum K was measured every 6 months at study visits, within 1-2 weeks after an increase in L or T dose, and every 3 months when eGFR was less than 30 mmol/l. All elevated serum K levels, which may be associated with renal function decline, in patients with T2DM and CKD were safe in the HALT PKD trial. Clinical use of dual RAAS blockade or intensive adverse events (SAEs) and there were no SAEs within 21 days after detection of HK.

**Conclusions:** In patients with T2DM and CKD stage 3, the pharmacodynamic effects of tenapanor were confirmed, as shown by slower consistency and increased frequency of stool, and reduced urinary phosphorus excretion following tenapanor treatment. However, these observations did not translate into effects on albuminuria.

**Funding:** Pharmaceutical Company Support - Norvatis Pharmaceuticals

**TH-PO657**

**Hyperkalemia in the HALT PKD Trial**

**Results:** In Study A, 1258 patients (51% with T2DM and 49% with CKD) were randomized to either continue or to discontinue fluvastatin for additional 6 months. Primary endpoint was the difference in urinary protein to creatinine ratio between the groups at 12months.

**Results:** Baseline characteristics showed no differences between the groups in HbA1C, HOMA-IR, diabetes duration and estimated glomerular filtration rate (GFR). Majority of patients (81%) were using RAS blockers. After 6 months of fluvastatin treatment, there was no significant decrease in urinary protein excretion or microalbumin excretion. Estimated GFR significantly declined at 6months in both groups and continued to decline after discontinuation of fluvastatin, whereas the change was not significant with fluvastatin treatment. Interestingly, HOMA-IR significantly improved in continuation group. Significant decrease in total and low density cholesterol was observed after 6, 12months in patients treated with fluvastatin.

**Conclusions:** In conclusion, there was no significant reduction in proteinuria with fluvastatin treatment in diabetic patients with chronic kidney disease. However, our study suggests that there might be a role in static to slow the progression of kidney disease.

**Funding:** Pharmaceutical Company Support - Norvatis Pharmaceuticals
TH-PO658

Chronic Diuretic Therapy Does Not Impair the Effectiveness of Patiromer in Hyperkalemic Patients with CKD

Matthew R. Weir, 1 Martha Mayo, 1 Dahlia Garza, 2 Yuri Stasiv, 3 Susan Arthur, 1 Lance Berman, 2 David A. Bushinsky, 3 Daniel J. Wilson, 3 Murray Epstein, 4 1 University of Maryland; 2 Relypsa, Inc.; 3 University of Rochester; 4 University of Miami.

Background: Loop diuretics control volume in advanced CKD and may reduce elevated serum K⁺, but can induce intravascular volume depletion or gout and may not be ideal for long-term hyperkalemia (HK) management. Thus, the efficacy of investigational serum K⁺ binders in HK pts on chronic diuretics is of interest. We compared patiromer’s effects in RAASi-treated CKD pts with HK to those not on diuretics in the treatment phase of the 2-part OPAL-HK study.

Methods: Pts (n=243) with baseline (BL) s-K⁺ 5.1 to 6.5 mEq/L on RAASi received patiromer (4.2 or 8.4 g BID to start) for 4 wks. For this post hoc analysis, Ds-K⁺ BL at wk 4 in all subgroups (phase of the 2-part OPAL-HK study).

Results: Mean (SD) age was 64 (10.5) yr; 58% were male. Mean s-K⁺ decreased from BL at wk 4 in all subgroups [Table]. Reductions in s-K⁺ did not differ in pts receiving any diuretic vs those not on diuretics. Patiromer was well tolerated; mild–moderate GI constipation was the most common AE. Hypokalemia (s-K⁺ <3.5 mEq/L) was infrequent. Conclusions: The s-K⁺-lowering efficacy of patiromer in HK pts was unaffected by concomitant diuretics.

Table: Efficacy, safety, and disease characteristics in pts on patiromer + diuretics

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<th>Loop (n=51)</th>
<th>Thiazide/ T-like (n=51)</th>
<th>Combination Loop/ thiazide (n=15)</th>
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<th>No diuretic (n=104)</th>
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<tr>
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<tr>
<td>s-K⁺ μEq/L</td>
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<tr>
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<td>Mean (µEq/L)</td>
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</table>

*T pts without a s-K⁺ value at a weekly visit after day 3 were excluded.

Funding: Pharmaceutical Company Support - Relypsa, Inc.

TH-PO661

Effects of Candesartan on Clinical Remission in IgA nephropathy Treated with Steroid Pulse Therapy and Tonsillectomy (CAST IgA Study) – A Randomized Control Study

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Background: Angiotensin receptor blocker (ARB) may have additional benefit on the conventional therapy with steroid pulse and tonsillectomy among Japanese patients with IgA nephropathy.

Methods: Seventy seven patients with IgA nephropathy were randomly assigned to regular regimen consists of steroid pulse followed by oral prednisolone for 6 months and tonsillectomy (control group, n=37) regular regimen combined with ARB (candesartan) for 6 months (ARB group, n=40). Among all patients in both groups who did not achieve remission of proteinuria at 12 M, candesartan was initiated and titrated until the 24 M visit. The primary endpoint was the remission of proteinuria (<0.2g/gCr) and hematuria.

Results: Baseline proteinuria (g/gCr, interquartile range) were comparable between the groups (0.70-1.20 vs. 0.95, 0.60-1.50, P=0.97). Cumulative remission rate in control group and ARB group at 6, 12 and 24 M were comparable (10.8% vs. 15% [P=0.58], 29.7% vs. 30.0% [P=0.98], 45.9% vs. 42.5% [P=0.76]). The hazard ratio for remission was 1.01 (95% confidence interval, 0.51-1.99; P=0.98). Proteinuria was slightly heavier in control group than ARB group (0.11 vs. 0.21g/gCr; P=0.002) at 12 M, but comparable afterwards (0.20 vs. 0.23 g/gCr at 12 M, 0.12 vs. 0.13 g/gCr at 24 M). Although remission rate of hematuria was comparable until 12M, it was higher in control group than ARB group at 24M (85% vs. 64%; P=0.008).

Conclusions: Early use of ARB regardless of the level of blood pressure combined with steroid pulse and tonsillectomy may not provide benefit for clinical remission among IgA nephropathy.

Funding: E.R.A.S.E. Foundation.

TH-PO662

Tacrolimus Monotherapy Follows Intravenous Methylprednisolone in Adults with Minimal Change Nephrotic Syndrome: A Prospective, Multi-Centered, Open, Randomized, Controlled Trial

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Background: Adults with minimal change nephritic syndrome (MCNS) show excellent responses to glucocorticoid (GC). However, responding patients may suffer relapses and GC related frequent side effects. Tacrolimus (TAC) may serve as an alternative to GC therapy for adult MCNS with less-frequent side effects.

Methods: This randomized, multicentre, controlled study was undertaken in 8 renal units across the China. 119 adult-onset patients were randomly allocated to receive the conventional GC therapy (GC group) or tacrolimus monotherapy (treatment group). The

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primary outcome variables was remission. The secondary outcome variables included relapse, time to remission, time to relapse, change of serum creatinine (Scr) and eGFR, and adverse events (AEs).

Results: Remission (either complete or partial remission) was attained by 51 of 53 patients (96.2%) in GC group and 55 of 56 (98.3%) of patients in TAC group (p=0.611). 51 of 53 patients (96.2%) in GC group and 52 of 56 patients (92.9%) in TAC group experienced complete remission, respectively (p=0.679). The mean time to remission in GC group (2.7±2.3 weeks) was similar (p=0.548) to TAC group (2.6±2.6 weeks), respectively. Relapse occurred in 25 (49.0%) of GC group versus 25 (45.5%) of TAC group (p=0.847), and 7 patients in GC group and 6 patients in TAC group with GC therapy and 4 with eGFR than UACR. Our observations do not support either TFRN-1 or TFRN-2 as pharmacodynamic biomarkers or as predictive biomarkers of clinical response as measured by UACR.

Funding: Pharmaceutical Company Support - Pfizer

TH-PO0665
Effects of Intensified Vasodilatory Antihypertensive Treatment on Renal Function, Blood supply and Oxygenation in Chronic Kidney Disease

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Background: Progression of Chronic kidney disease (CKD) may result from tissue hypoxia induced by small artery structural narrowing, with increased renal vascular resistance (RVR) and impaired blood supply. We investigated whether vasodilating therapy (VT) is superior to non-vasodilating therapy (nonVT) for improvement of RVR, tissue oxygenation, and preservation of kidney function.

Methods: Eighty-two hypertensive grade 3-4 CKD patients (glomerular filtration rate (GFR) 36±15 ml/min/1.73 m²) were randomised to renin-angiotensin inhibition combined with either VT (amlodipine) or nonVT (beta-blocker metaprotilol). At baseline and following 18 months of therapy we determined forearm resistance by venous occlusion plethysmography. Using magnetic resonance imaging (MRI) renal artery blood flow was measured for calculation of RVR, and blood oxygen level dependent (BOLD) MRI was used as a marker of renal oxygenation (R*). GFR was measured as Cr-EDTA clearance.

Results: The VT and nonVT arms had similar blood pressure levels throughout the study. At follow-up, in the VT group forearm resting resistance had decreased by 7% (p<0.05) and RVR by 12% (p<0.05), while in the nonVT group forearm resistance increased by 39% (p<0.01) while RVR remained unchanged. Cortical and medullary R* values were not affected by VT and nonVT. After 18 months GFR decline was similar in the two groups (3.0 vs. 3.3 ml/min/1.73 m²).

Conclusions: In CKD, long-term VT reduced both peripheral and RVR, but was not associated with improved renal oxygenation and did not influence loss of kidney function compared to nonVT.

Funding: Government Support - Non-U.S.

TH-PO0664
The Epigenetic BET-Inhibitor RVX-208/Abapetatone Shows Favorable Effects on ALP and eGFR in Chronic Kidney Disease (CKD) Patients – A Post-HocAnalysis of Phase 2 Clinical Trials

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Background: PF-04634817 is a competitive dual inhibitor of CCR2 and CCR5 receptors. In early clinical studies, administration of this compound to healthy volunteers has been found to elevate circulating levels of the primary CCR2 ligand, CCL2 (MCP-1). The ability of PF-04634817 to reduce albuminuria, compared with placebo, after administration for 12 weeks, was tested in phase 2 study in subjects with diabetic nephropathy and macroalbuminuria. In this study, samples were collected to confirm the previously observed pharmacological effect on CCL2 in this population and to examine the impact on other ligands known to bind to CCR2 or CCR5 receptors.

Methods: CCL2 in serum and urine was measured by ELISA from 226 subjects at Eurofins (The Netherlands) at baseline and during treatment at weeks 4, 8, and 12. CCL2 (RANTES) was measured in plasma and urine as part of a multi-analyte panel at Myriad Eurofins (The Netherlands) at baseline and during treatment at weeks 4, 8, and 12.

Results: At week 12, serum levels of CCL2 and plasma levels of CCL2 were elevated (9.25 fold (p<0.0001) and 2.11 fold (p<0.0001) respectively following administration of PF-04634817, but not placebo. Elevation of both chemokines was also observed at the earlier time points. Levels of CCL8, CCL3 and CCL5 in circulation and urine also did not change in either group.

Conclusions: This study confirms elevation of the CCR2 ligand, CCL2, following treatment with PF-04634817 in diabetic nephropathy patients. It also identifies the CCR5 ligand, CCL4, as another potential pharmacodynamic marker. The observed lack of apparent change in CCL5 warrants further follow up analysis.

Funding: Pharmaceutical Company Support - Pfizer
Impact of Grazoprevir plus Elbasvir on Health-Related Quality of Life in Patients with Hepatitis C Virus Genotype 1 Infection and Chronic Kidney Disease Stages 4 and 5

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Background: Health-related quality of life (HRQOL) is diminished in patients with hepatitis C virus (HCV) infection and chronic kidney disease stages 4 and 5 (CKD4/5). A randomized, double-blind, placebo-controlled trial of Grazoprevir 100 mg + Elbasvir 50 mg (GZR+EBR) once daily for 12 weeks was conducted among patients with HCV genotype 1 infection and CKD4/5. GZR+EBR was highly effective, with a sustained viral response rate at follow-up week 12 (FW12) of 99.1% (95% Confidence Interval (CI): 95.3% - 100.0%). GZR+EBR was well-tolerated, with a safety profile that was comparable to placebo. The aim was to assess whether HCV treatment with GZR+EBR altered the HRQOL profile.

Methods: 224 patients were randomized and received at least one dose of study drug (GZR+EBR vs. 1:1, Placebo=n=113). Patients completed the SF-36v2 Health Survey at baseline, treatment week 12 (TW12), and FW12 (GZR+EBR arm). Mean change from baseline in health domain, mental component summary (MCS) and physical component summary (PCS) scores, with 95% CIs, were estimated. Differences in mean change scores, with 95% CIs, were estimated between treatment groups.

Results: At baseline, mean scores were balanced between treatment groups. At TW12, GZR+EBR had more favorable changes from baseline in PCS and health domain scores (except for SF, RE, MCS) than placebo.

Mean Change from Baseline in SF-36 Scores at TW12 (95%CI)

At FW12 for GZR+EBR, GH improved from baseline (mean change score: 4.5(95% CI:1.2-7.9)).

Conclusions: Treatment with GZR+EBR had a positive impact on HRQOL as compared to placebo. In addition, changes in HRQOL were substantially more favorable than the large declines in HRQOL historically associated with interferon and ribavirin-containing regimens.

Funding: Pharmaceutical Company Support - Merck & Co., Inc.

TH-PO668

Bortezomib Before, in and After Autologous Hematopoietic Stem Cell Transplantation in Patients with newly Diagnosed AL Amyloidosis

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Background: In previous study, we have demonstrated that the outcome of treating AL amyloidosis with bortezomib with dexamethasone (BD) induction followed by autologous hematopoietic stem cell transplantation (ASCT) was superior to the outcome of the ASCT treatment alone. To further improve the hematologic response rate, we conducted a prospective trial of bortezomib before, in and after ASCT in newly diagnosed AL amyloidosis.

Methods: Newly diagnosed AL amyloidosis patients who met the criteria of ASCT could be included in this trial. Treatment schedule consisted of two cycles of BD induction therapy (bortezomib 1.3mg/m2 on day 1 and 8 of the cycle) followed by BD induction alone. To further improve the hematologic response rate, we conducted a prospective trial of bortezomib before, in and after ASCT in newly diagnosed AL amyloidosis.

Results: 15 patients were enrolled in the study. 9 patients had cardiac involvement. The organ response was reached in 13 patients of the 18 patients with renal involvement and 7 of the 9 patients with cardiac involvement. Peri-renal nephropathy and infiltration of the common arterial vessels were the common adverse events during the treatment, and 4 patients have been discontinued bortezomib for neuropathy. No death occurred in this study. After a median follow up of 24 months, the overall survival was 100%, and the estimated progression free survival was 91% at 48 months.

Conclusions: In conclusion, our preliminary data suggest that incorporating bortezomib into induction, conditioning and consolidation with ASCT yielded a high rate of hematologic response with tolerable toxicity. (ClinicalTrial.gov Id: NCT01273844).

Funding: Pharmaceutical Company Support - Xi’an Janssen Pharmaceutical Ltd: Research Funding.

TH-PO669

Phase I and IB Studies of PBI-4050, a Novel Anti-fibrotic Agent for Chronic Kidney Disease

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Background: PBI-4050 is an orally administered new chemical entity with a MW < 300 showing remarkable anti-fibrotic efficacy in multiple pre-clinical models of fibrosis in kidney, liver, lung, and heart. Phase 1 studies in normal volunteers and Phase 1b studies in patients with advanced nephropathy associated with Type 2 diabetes have been successfully completed.

Methods: Single ascending dose (SAD) phase 1 studies were performed in 5 cohorts of healthy volunteers, 6 subjects in each cohort receiving PBI-4050 and 2 receiving identical placebo, at doses of 400 to 2,400 mg po. The 800 mg cohort had studies in both the fasting and fed state. Phase 1b studies were performed in 8 subjects with Stage 3b and 4 nephropathy associated with Type 2 diabetes (eGFR 15-45 mL/min), 2 of whom received placebo; after a single dose of 800 mg po and a washout period, the same patients received 800 mg po daily for 10 days.

Results: In the SAD study all doses were well-tolerated; there were no dose-related adverse events (AEs) and no serious AEs. The half-life (T1/2) mean was 3.3-5.0 hours, dependent on dose (See Figure). There was a 34% decrease in eGFR area under the curve (AUC0-∞) after a fat meal. Protein binding in plasma was > 99%.

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CKD: Clinical Trials
Poster/Thursday
Patients received 3 doses of vaccine had 100% seropositivity for all genotypes. The average cLIA for genotype6/11/16/18 were 928.4±264.6, 6,951.0±1873.3 and196.3±761.2mU/ml respectively. No serious vaccine related adverse events were observed.

Conclusions: Standard dose/schedule of quadrivalent HPV vaccine provided excellent immunogenicity and safety in CKD stage IV-V. HPV vaccination for CKD should be integrated in public health policy.

Funding: Pharmaceutical Company Support - MSD provided vaccine doses, Government Support - Non-U.S.

TH-P0671

Minocycline-EDTA: Good Performance for Catheter Patency Maintenance

Background: Poor flow (PF) and catheter-related blood stream infections (CRBSI) are highly prevalent among CKD 5D patients with long-term central venous catheters. Heparin (H) catheter lock solutions are commonly used to maintain catheter patency, however PF and CRBSI are still on high rates. Therefore, the purpose of this study was to evaluate two lock solutions on reduction of PF and CRBSI: one, a lock solution combining of the tetracycline antibiotic minocycline with the anticoagulant/chelation agent EDTA (M-EDTA) versus H; and other, trisodium citrate (C) versus H. M-EDTA and C were also evaluated as to their safety versus H.

Methods: Thirty CKD 5D patients on high-efficiency hemodialysis (blood flow rate = 350 ml/min) at the Integrated Centre of Nephrology (Guarulhos, Brazil) were randomized 1:1:1 to receive M-EDTA, C or H locks for 15 weeks. Lock solutions concentrations were M-EDTA 30 mg/ml/3 mg/ml; C 30% (C) and H 1,000 U/ml and both investigators and patients were blinded to treatment allocation. The primary end-point was a 10% reduction in HD blood flow rates (35ml). The frequency of CRBSI was recorded. Bleeding and lock solution-related adverse events were the primary safety end points. Logistic Regression was performed to evaluate differences in PF rates among the treatments (SPSS version 13.0, IBM, USA).

Results: PF was significantly higher among patients on H (7/10) compared to C (3/10) and M-EDTA (1/10) locks, according to results of Logistic Regression comparison: H vs C (p=0.082); H vs M-EDTA (p=0.016). Heparin was associated with the highest rate of PF. M and C lock solutions had similar PF rates. Only one CRBSI was identified in a patient on receiving a C lock. No bleeding or adverse events were identified. There was no difference in CRBSI prevention.

Conclusions: M-EDTA and C seem may preserve catheter patency. A larger clinical trial is being conducted in order to confirm these findings and to further evaluate CRBSI rates.

Funding: Government Support - Non-U.S.

TH-P0672

Long-Term Outcomes After Renal Artery Stenting Among Diabetic and Non-Diabetic Patients with Renal Artery Stenosis

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Background: The current study aims to determine if renal-artery stenting affects mortality and/or delays the onset of Renal Replacement Therapy over a 10 year period in diabetic and non-diabetic patients with renal artery stenosis (RAS).

Methods: Using electronic medical records of Cleveland Clinic Health System, 168 patients with a diagnosis of RAS were identified from 01/01/2000 to 12/31/2004. Patients were categorized into two groups - ‘stented’ for those who underwent renal artery stenting and ‘medical’ for those who were treated with medical therapy alone. The primary outcome was time to death. The secondary outcome was a composite end point of death or the need “medical” for those who were treated with medical therapy alone. The primary outcome was time to death. The secondary outcome was a composite end point of death or the need for catheter patency maintenance.

Results: Out of 168 patients, 67 were in ‘stented’ group and 101 in ‘medical’ therapy group; 96 diabetic and 72 non-diabetic patients represented 24% in the stented group and 38% in the medical group. Overall, a higher percentage of deaths were seen in ‘stented’ group (64% vs. 42%, p=0.02). Multivariable analysis revealed CKD stage =>3 as the only variable significantly associated with death (HR 2.45, 1.32-4.85, p=0.003). In another analysis - bilateral renal artery stenosis, CKD stage =>3 and DM were found to be significantly associated with the occurrence of composite end point of RRT and/or death. On subgroup analysis among diabetic, multivariable analysis revealed mortality benefit among patients who underwent renal artery stenting (HR 0.15, 0.03-0.55, p=0.006) when compared to ‘medical’ therapy alone; and a trend towards delaying the onset of composite end point (HR 0.28, 0.06-1.11, p=0.07).

Conclusions: Renal-artery stenting in RAS did not confer any benefit in terms of survival or delaying the onset of RRT; however stenting of renal arteries in diabetics showed a survival benefit and may have some benefit in delaying the onset of RRT. Further research is warranted to confirm these findings.

TH-P0673

Oral versus Intravenous Hydration to Prevent Contrast Induced Nephropathy

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Background: Contrast Induced Nephropathy (CIN) complicates the use of iodinated contrast media. Guidelines advise identification of high risk patients before hydration as preventive measure. We conducted a multicenter randomized controlled trial to compare oral (home) hydration versus standard therapy (NCT01654328). The trial was stopped prematurely because of a low recruitment rate.

Methods: Patients with an eGFR=60ml/min/1.73m² were stratified for risk of CIN based on eGFR and the presence of risk factors (diabetes, peripheral arterial disease, heart failure, age, anemia, use of diuretics or NSAID’s) Exclusion criteria were: overhydration, use of ‘2 diuretics, severe heart failure, CKD stage V. High risk patients were randomized. Arm A: sodium chloride 1g/kg of body weight/day per os on day -2 and -1 before contrast exposure. Maximum 10mg sodium chloride/day. Arm B: NaCl 0.9% 1000ml in 4 hrs or in case of heart failure or severe renal failure) 12 hrs before and after contrast administration.

We evaluated the incidence of CIN (defined as a rise in serum creatinine ≥5% or ≥244µmol/L 48-96hrs after contrast) and adverse events.

Results: From Aug 2012 until Nov 2014 there were 1593 radiological procedures in high risk patients. In 1116 the inclusion criteria were met. Only 255 patients gave informed consent. We evaluated 233 procedures (11 missing data, 7 intercurrent hospitalisation, 4 severe nausea and vomiting) (table 1) provides clinical characteristics and outcome data. Nausea was a frequent complaint during oral hydration. One SAE (overhydration) was related to IV hydration.

Conclusions: Oral hydration is as effective as intravenous hydration in preventing CIN. Oral hydration obviates the need for hospital admission, and thus reduces costs. Adaptation to the protocol is needed to prevent nausea and vomiting.

TH-P0674

Obstructive Sleep Apnea and Blood Pressure and in Patients with Hypertension and Chronic Kidney Disease, Stage 2

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Background: High nocturnal blood pressure (BP) and non-dipping are important prognostic factors in the evaluation of the risk of cardiovascular disease in patients with hypertension (HT). Many patients with chronic kidney disease (CKD) suffer from high nocturnal BP and non-dipping. The mechanism behind this phenomenon is unknown, but might be related to the presence of obstructive sleep apnea (OSA). In general population, OSA is observed in 10-15% of men and 5-8% of women, only symptomatic in 2-4%.

Methods: From a population study in Holstebro County, 238 subjects diagnosed with HT and CKD stage 2 were invited to participate. 70 subjects were included and underwent conventional 24-h ambulatory BP monitoring (ABPM) and application tonometry to monitor central BP (HealthSTATS BPro), 24 h urine collection for microalbuminuria, blood samples for creatinine, and cardiorespiratory monitoring to determine apnea hypopnea index (AHI). HT, nocturnal HT, resistant HT and non-dipping were defined according to current guidelines. OSA was diagnosed when AHI ≥ 5.

Results: Of the 70 subjects, 27 (39%) were diagnosed with OSA (average AHI 16.5). The subjects suffering from OSA were more obese, had lower mean oxygen saturation and longer snoring time during sleep. There were no difference between subjects with and without OSA in regards to gender, eGFR, smoking status, number of antihypertensive agents, weekly alcohol intake, Epworth score, and lung function. Subjects with OSA tended to have higher clinic BP, average 24 h BP, nocturnal BP, central BP both 24 h, day and nocturnal. In addition a tendency was measured towards higher frequency of resistant HT and non-dipping in OSA.

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Conclusions: The occurrence of OA in a population with hypertension and CKD stage 2 was nearly 2.5 times larger than expected in general population. In subjects with OA, there was a tendency towards higher central and brachial BP. It is suggested, that OA is the cause of high BP in patients with CKD stage 2.

Funding: Government Support - Non-U.S.

TH-PO675
Structured Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial (NCT01036490) David J. Leehey,1,2 Eileen Collins,3 Holly J. Kramer,1 Cheryl Cooper,4 Jolene Butler,1 Conor McBurney,1 Christine Jelinic,1 Susan Oconnell.1 1Research, Hines VA Hospital, Hines, IL; 2Medicine, Loyola Univ Medical Center, Maywood, IL.

Background: Patients with type 2 diabetes, obesity, and chronic kidney disease (CKD) are generally physically inactive and may benefit from an exercise program. However, there have been few randomized controlled trials to determine the benefits of exercise training in this population.

Methods: We hypothesized that exercise training in obese diabetic patients with CKD will improve physical fitness and stabilize renal function. This was a 52-week randomized controlled study. Inclusion criteria were type 2 diabetes, obesity (body mass index ≥30 kg/m²), CKD (stage 2-4), and persistent proteinuria (>200 mg/day for at least 3 months). Subjects were randomized to a control group consisting of dietary management alone (CON) vs. dietary management plus 12 weeks of exercise training followed by 40 weeks of supervised home exercise (EX).

Results: 46 subjects were enrolled, of whom 36 (n=18 in each group) completed at least the 12-week evaluation. At baseline, mean values (±SD) were as follows: age 70.0 ± 8.0 years, body mass index (BMI) 36.9 ± 4.5 kg/m², body fat 41.3 ± 6.6%, glycated hemoglobin (HbA1c) 8.0 ± 1.3%, eGFR 39.9 ± 19.0 ml/min/1.73m², and uraemic albumin excretion rate (UAER) 1118 ± 1236 mg/24h. Average symptom-limited treadmill time was 7.8 ± 3.8 minutes and peak oxygen consumption (VO2 peak) was 13.2 ± 3.4 ml/kg/min. Treadmill time increased from baseline at both 12 weeks and 52 weeks in EX but not in CON (p<0.05).

Conclusions: Obese diabetic subjects with CKD have markedly impaired physical fitness. A structured exercise program improved exercise capacity but did not affect renal function.

Funding: Veterans Administration Support

TH-PO676
Strength Training Intervention in Patients with Advanced Chronic Kidney Disease: A 20 Week Pilot Study Jordana B. Cohen,1 Erica D. Palmer,1 Angela M. Sheridan,1 Brenten David Connor,1 Mary B. Leonardi,1 Kathryn H. Schmitz,1 Francis Perry Wilson.3 1Univ of Pennsylvania, Philadelphia, PA; 2Stamford Univ, Stamford, CA; 3Yale Univ, New Haven, CT.

Background: Although chronic kidney disease (CKD) is highly associated with sarcopenia and poor functional status, the feasibility and impact of longitudinal strength training in subjects with advanced CKD is not well understood.

Methods: Patients took part in a predominantly home-based 20 week program with 60 minutes of resistance training three times per week. We measured dual-energy X-ray absorptiometry (DXA) assessment of appendicular lean mass (ALM), bio-electrical impedance analysis (BIA) of fat mass (FMF), 1 repetition-maximum (RM) assessment of maximum quadriceps strength, strength-related physical performance battery (SPPB) assessment of functional status, 24-hour urine creatinine collection (Ucr), and Kidney Disease and Quality of Life Short Form (KDQOL-SF) in individuals ⩾45 and ⩽80 years of age with baseline eGFR ⩽15 and ⩽45 ml/min/1.73m². We used paired t-testing and Wilcoxon sign-rank to assess for changes in within-subject measurements before and after the intervention period as well as change-on-change analyses.

Results: 22 subjects completed the training program. The median age was 71 years, 63% were male, median eGFR was 27.9 ml/min/1.73m², and median BMI was 29.2 kg/m². There was a significant improvement in 1RM (mean difference 16.6 ± 6.5, p<0.03), but no significant change was appreciated in ALM (p=0.99), FMF (p=0.99), SSPB score (p=0.67), 24-hr urine creatinine (p=0.22), eGFR (p=0.52) or KDQOL-SF score (p=0.78). There was a significant decrease in AST (p=0.01), ALT (p=0.01), and total bilirubin (p=0.01). There was also a significant association between within-subject improvement in 1RM and improvement in FMF (p=0.02).

Conclusions: In this small study of patients with advanced CKD, we successfully developed a predominantly participant-driven strength training program. The significant improvement in 1RM indicates that patients were adherent with the protocol, however larger studies are needed to assess for the effect of strength training on anthropomorphic measures, serologic measures, and quality of life.

Funding: NIDDK Support

TH-PO677
Effect of a Medication Management Intervention on Acute Care Utilization After Hospitalization in CKD Katherine R. Tuttle,1,2 Radica Z. Alicic,3 Robert Short,2 Joshua J. Neumiller,1 Kenn B. Daratha,2 Brian J. Gates,2 Cynthia F. Corbett.2 1Providence Health Care; 2Washington State Univ; 3Univ of Washington.

Background: People with chronic kidney disease (CKD) are hospitalized often and incur high risk of readmission. The study objective was to test the effect of a medication management intervention during the hospital-to-home transition on subsequent acute care utilization.

Methods: A single-center, randomized, controlled clinical trial of an intervention to improve medication information transfer (MIT) was conducted by pharmacists in a university hospital coupled with homes and skilled nursing facilities (SNFs) during hospitalization. Participated patients with CKD stages 3-5 (not treated by dialysis or transplant) were enrolled. The primary outcome was a composite of hospital readmissions and visits to emergency departments or urgent care centers within 90 days of discharge.

Results: Enrollled (n=182) characteristics included: age 69±11 (mean±SD) years; women 48%; diabetes 56%; hypertension 83%; eGFR (CKD-EPI creatinine) 41±14 ml/min/1.73m²; albuminuria 43 (4,521; median, IQ range) mg/g creatinine. The 3 top categories for primary diagnoses for hospitalization were cardiovascular disease (30%), infection (19%), and kidney disease (14%). Enrollles lost before the baseline visit (n=41, mainly due to severe illness) were not included as active study participants. In intent-to-treat analysis (n=141), the primary outcome occurred in 32/72 (44 %) of the MIT group and 28/69 (41 %) of those in usual care (Kaplan Meier, log-rank p=0.72). At 90 days post-discharge, there was no significant difference in guideline-based CKD goals did not differ significantly between MIT and usual care groups: blood pressure <140/90/<130/80 mm Hg in those without/with albuminuria, respectively (43 % vs 50 %); hemoglobin A1c <7.5 % in diabetic participants (69 % vs 76 %); hemoglobin >11 g/dl (81 % vs 83 %); and phosphorous <5 mg/dl (97 % vs 96 %).

Conclusions: A medication management intervention conducted during the hospital-to-home transition did not reduce subsequent acute care utilization for hospitalized people with CKD. This high-risk population may require more comprehensive interventions to improve outcomes after hospitalization.

Funding: NIDDK Support

TH-PO678
Impact of Decision Making Tools Use at the Time of Modality Choice and PD Take on in a Multicentre-Multinational Setting Belen Marron,1 Janusz Ostrowski,2 Delia Timofte,3 Marietta Torok,4 Jose C. Divino-Filho.5 1Diaverum Home Therapies. Medical Office, Diaverum, Munich, Germany; 2Wloclawek Diaverum Clinic, Diaverum, Wloclawek, Poland; 3Sema Diaverum Clinic, Diaverum, Bucharest, Romania.

Background: Different factors have been attributed to low PD take on such as late referral, unplanned start, physician bias towards PD, large HD availability and lack of patient’s choice. Some references apply for 50% of PD if a good modality information is provided. Objectives: To analyze the impact of a structured modality information program with the use of decision making tools (DMTs) on type of modality choice and start. Methods: Observational, prospective, multicentre and multinational experience. All patients under ESRD 4-5 and/or after an unplanned dialysis start if non-informed before were recruited and underwent a DMT process for RRT choice. Process included: personal values evaluation, RRTs information with different tools, deliberation and patient’s modality election. Results: 444 patients, mean age 61.5 yrs. from 31 clinics in Poland, Hungary and Romania underwent DMTs evaluation between August-December 2014. Staff considered PD as contraindicated in 45% of Polish patients, 32% in RO and 24% in HU. Reasons behind were mix causes and “other” than abdominal or mental. Home orientation was stated for 30% (PL), 40% (RO) and 54% (HU). Written information was largely used for 71 vs 97% of patients, DVD in 9-21% and in centre HD/PD touring visits in 17-75%. PD as elected modality varied among countries: 10% (RO), 21% (PL) and 35% (HU). For patients who started dialysis (n=163), PD was used in 10% (RO), 14% (PL) and 36% (HU).

Conclusions: Use of DMTs at the time of RRT modality choice is encouraging and complements patient’s empowerment. An increase in PD take-on has been observed in our institution after DMTs use. However, when compared with other references, our patient’s PD election is still low and factors behind this fact needs to be elucidated with a larger recruitment pool (in process).

TH-PO679
Thrombotic Microangiopathy And Complement Factor C4d Predict Poor Prognosis in IgA Nephropathy and Henoch-Schönlein Purpura Nephritis Jamie S. Chua,1 Malu Zandbergen,2 Johan W. De Fijter,3 Ron Wolterbeek,1 Jan A. Bruijn,4 Ingeborg M. Bajema.1 1Pathology, LUMC, Leiden, Netherlands; 2Nephrology, LUMC, Leiden, Netherlands; 3Medical Statistics, LUMC, Leiden, Netherlands.

Background: Thrombotic microangiopathy (TMA) was previously reported to be clinically relevant and underdiagnosed in IgA nephropathy (IgAN). Complement factor C4d is a common denominator of TMA. Aim: to validate the prevalence of TMA and to determine the clinical significance of TMA and C4d in IgAN and Henoch-Schönlein Purpura Nephritis (HSPN).
**Methods:** We included 129 native renal biopsies from 2003-2013; IgAN in 82% and HSN in 18%. Biopsies were classified according to Oxford MEST-scores, scored for vascular lesions including TMA, arterial intimal sclerosis and arteriolar hyalinosis, and immunostained for C4d. Retrospectively collected clinical data included hypertension and renal function. Three groups were distinguished: absence of both TMA and C4d; presence of both TMA and C4d; and presence of either TMA or C4d. Changes in eGFR over time were compared using a linear mixed model. Renal survival was analyzed with Cox regression. Prognostic values of C4d, TMA and hypertension for renal survival were analyzed with multivariable Cox regression. Results: The prevalence of TMA in this cohort was 20% (n=26). TMA was mainly chronic (65%; 17/26) and was localized in arterioles (81% of TMA cases), glomeruli (15%) or both (4%). TMA was associated with interstitial fibrosis and tubular atrophy, arterial intimal sclerosis, hyalinosis and hypertension (p-values <0.05). TMA was strongly associated with both TMA and C4d (p<0.001). Linear Mixed Model analysis revealed patients with hypertension and both C4d and TMA had significantly lower eGFR (mean decrease 24 and 40 mL/min/1.73m² respectively). Patients with both TMA and C4d had significantly worse renal survival than the two groups without both C4d and TMA (HR 6.33 and 3.38 resp.) corrected for hypertension (HR 4.52 and 3.30 resp.). Conclusions: The prevalence of TMA in IgAN and HSN is substantial (20%) but lower than previously reported. TMA was mainly chronic, arteriolar and associated with C4d, hypertension and chronic lesions. TMA and C4d mark poor renal function and poor renal survival in IgAN and HSN.

**TH-PO680**

**Glomerular Complement Factor C4d Marks Glomerular Basement Membrane Duplications: C4d Beyond Antibody Induced Injury**

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**Background:** C4d deposits along peritubular capillaries (ptc) mark antibody mediated rejection (ABMR) in renal allografts. The diagnostic significance of linear C4d deposits along glomerular basement membranes (GBM-C4d), which can occur as isolated event, is poorly understood. **Hypothesis:** GBM-C4d, especially when isolated, is not a sign of ABMR but rather a marker of structural GBM changes and duplications in native kidneys and renal transplants.

**Methods:** We analyzed 319 renal allograft biopsies from 219 patients. GBM remodeling was analyzed by light (Banff cg-score) and by electron microscopy. Linear C4d staining by immunohistochemistry (IHC) and immunofluorescence (IF) was scored along the GBM and ptc. Controls: native kidneys with minimal change disease (n=10) and chronic thrombotic microangiopathy with GBM duplications (n=26).

**Results:** Transplants: GBM duplications/transplant glomerulopathy (TG) occurred in 52/319 biopsies (16%). By IF, 49/52 (94%) TG cases had GBM-C4d; 36/49 (73%) had GBM-C4d lacking ptc-C4d deposits. By IHC, 74% of TG cases had GBM-C4d, 60% of which as isolated event. GBM-C4d staining intensity correlated with Banff cg-scores (IF: r=-0.453, p=0.01; IHC: r=-0.478, p=0.01). 80% of cases (24/30) with GBM duplications present only by electron microscopy revealed GBM-C4d. Association GBM-C4d with TG/GBM duplications: p<0.001. Statistical significance between GBM-C4d staining and structural GBM duplications remained after omitting cases with presumed or definitive ABMR (DSA positivity, C4d positivity in ptc,transplant glomerulitis). Multivariate logistic regression: GBM duplication/TG was an independent predictor of GBM-C4d positivity. Native kidneys: GBM-C4d occurred in 24/26 (92%) cases with thrombotic microangiopathy and GBM-C4d duplications, no staining was seen in minimal change disease.

**Conclusions:** The diagnostic significance of linear C4d deposits along ptc versus GBM differs. C4d along ptc marks ABMR while linear GBM-C4d is associated with structural GBM duplications in native and transplanted kidneys, independent of the etiology or antibody induced injury. In transplants GBM-C4d serves as marker for TG.

**TH-PO681**

**Predicting Outcome in Patients with Anti-GBM Glomerulonephritis Using the Histopathological Classification for ANCA-Associated Vasculitis:**

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**Background:** The renal biopsy in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) is characterized by crescent formation. No histopathological classification has been implemented for the disease. We have applied the histopathological classification for ANCA-associated vasculitis (AAV) to see whether this classification can distinguish patients regarding renal outcome.

**Methods:** We analyzed biopsies of 20 patients, diagnosed with anti-GBM GN between 1984 and 2014 at a university hospital in the Netherlands. We classified these biopsies according to the histopathological classification for AAV: sclerotic (≥50% sclerotic glomeruli), focal (≥50% normal glomeruli), crescentic (≥50% cellular crescents) or mixed (no dominant lesion) class. We collected data on serology, renal function and end-stage renal disease (ESRD) during 5-year follow-up.

**Results:** Fourteen biopsies (70%) were categorized as crescentic; three (15%) in focal class. Mean age was mixed and once (5%) as sclerotic. Mean age was 47.4 years (SD: 17.1, range: 17.0-74.9) and differed between classes (P=0.039), with the focal class having the youngest patients with a mean age of 25.4 years. Estimated glomerular filtration rate (eGFR) at time of biopsy differed between classes (P=0.001), focal class having a mean of 90.2 mL/min/1.73m², crescentic 6.9 and mixed 8 (no available data for sclerotic class).

**Conclusions:** These preliminary results show that the histopathological classification for AAV is useful for anti-GBM GN, predicting outcome in terms of eGFR at time of biopsy and at 1 year after biopsy. The focal group had more favorable outcomes regarding renal function and development of ESRD.

**TH-PO682**

**The Role of C4d Immunohistochemistry to Highlight Immune Complex Deposition in IgA Nephropathy**

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**Background:** IgA glomerulonephropathy (IgAN) is one of the most common immune complex associated nephropathies worldwide. It may develop de novo or recur in an allograft. Recently, C4d immunohistochemistry has been shown to highlight immune complex deposits in a variety of glomerular diseases. Limited conclusive data is available regarding the utility of C4d immunohistochemistry to highlight mesangial deposits in IgAN despite some authors claim to the contrary. The presence of this finding would be beneficial in cases where immunofluorescence studies are unavailable. Our study seeks to determine the ability of C4d immunohistochemistry to highlight mesangial, IgA dominant immune complex deposition.

**Methods:** A retrospective study from two institutions is performed. 24 cases (19 native and 5 allografts) from one and 36 native cases from the other of IgAN diagnosed between the years of 2005 and 2012 were selected (n=60). All cases were confirmed IgAN by immunofluorescence and electron microscopy. Parallel-embedded tissue sections from all biopsies were then stained for C4d immunohistochemistry by each respective institutional protocol. Cases from each institution were reviewed by the respective senior author for the presence, intensity and location of glomerular staining by the C4d antibody.

**Results:** All native and allograft cases of IgAN from both institutions showed complete absence of mesangial C4d immunoreactivity with some non-specific tubular epithelial staining in some cases and some low intensity, segmental capillary wall staining in others. Control tissue reacted appropriately.

**Conclusions:** Our results suggest that at least in our small cohort spanning two academic medical centers, the utility of C4d immunohistochemistry to support a diagnosis of IgAN in the native or allograft population is limited despite recent evidence of C4d deposition in immune complex associated disease. Although complement deposition with C3 is typically seen in IgAN, C4d deposits are not identified, suggesting the lack of this specific component factor in IgAN.

**TH-PO683**

**DNA Methylation as a Biomarker of Disease Status in Patients with ANCA-Associated Vasculitis**

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**Background:** ANCA-associated vasculitis (AAV) is associated with environmental exposures and age, both of which are linked to changes in DNA methylation. We tested whether DNA methylation changes in patients compared to healthy controls and if DNA methylation may be used as a biomarker of disease status.

**Methods:** AAV patients (n=67) were followed longitudinally through disease activity and remission (143 leukocyte samples), including 21 patients in long-term remission off therapy and 32 healthy individuals. DNA methylation was measured using mass spectrometry and bisulfiite sequencing at methyltransferase (MPO) and proteinase 3 (PRPTN). Expression was measured for MPO, PRPTN and DNA methyltransferase 1 (DNMT1).

**Results:** Patients with active AAV were hypomethylated compared to healthy individuals. Within paired active and remitting patients, MPO-ANCA and half of PR3-ANCA patients showed increased DNA methylation. In PR3-ANCA patients with increased methylation in remission, DNA methylation correlated with expression of MPO and PR3TN, and stable remission. DNMT1 expression in leukocytes from active and remitting patients was 0.6 fold and 0.8 fold, respectively, of healthy individuals. At MPO and PR3TN there is a positive correlation between DNA methylation and DNMT1 expression. Conc: AAV patients are characterized by dynamic changes in DNA methylation; differences in methylation during disease remission suggest these fates have an epigenetic basis.
TH-PO684
Epidemiologic Features of Anti-Glomerular Basement Membrane Disease
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Background: Anti-glomerular basement membrane (anti-GBM) disease is a rapidly progressive glomerulonephritis mediated by antianti bodies to the noncollagenous domain of the alpha-3 chain of type IV collagen. Previous reports demonstrated an association with a seasonal or environmental exposures in some cases (PMID: 4604010, 5326901). We sought to understand epidemiologic factors associated with anti-GBM disease.

Methods: Reports from consecutive cases of anti-GBM disease diagnosed at the University of Washington were retrospectively reviewed, with specific attention to epidemiologic parameters. Statistical analysis was performed on Graphpad Prism using Fisher’s exact and Mann-Whitney tests.

Results: Seventy-three (M=31; F=42) cases of anti-GBM disease were identified, with a median age of 56 years. Overall, 2 to 11 cases were seen per year (median = 6); a high incidence year was defined as > median number of cases. 60% of cases were diagnosed in a high-incidence year (p=0.07). No associations among ANCA-positivity vs. respiratory symptoms, age, sex, and/or season of presentation were identified.

Conclusions: There were quantitative and qualitative differences in epidemiologic parameters in anti-GBM disease. Unlike low incidence years, cases diagnosed in high incidence years showed a trend for increased likelihood of concurrent mesangial IgA deposition, and male gender. The findings suggest potential differences in the environmental and/or gender-based triggers in the development of anti-GBM.

TH-PO685
The Lumped System Utilized in the Japanese Histological Grade Classification of IgA Nephropathy May Produce a Score with a Broader Applicability Compared to the Split System of Oxford Classification
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Background: Japanese Histological Grade Classification (JHGC; HG1-HG4) (J Nephrol, 2013) and Oxford classification (Oxford) were compared with a focus on their ability to predict renal functional decline (RFD) and proteinuric remission (PUR).

Methods: 411 Japanese with IgAN (male 49%) were collected from 32 centres in Japan. The patients, whose median age was 36.2 years old, were prospectively followed for a median of 36 months. The average amount of initial proteinuria (PU) was 0.8 g/day. Mean eGFR was 77.9±29.6 ml/min/1.73m2 and median rate of decline in eGFR was -0.7 ml/min/m2/year.

Results: 24% and 55% of patients received steroid and RAS blockade, respectively. The ICC among 5 observers on M, E, S, and T, and HG scores were fair or good. In multivariate Cox analysis, hazard ratio (HR) of MEST in Oxford for 1.5 time’s increase of serum creatinine (sCr) was not significant, whereas HG3 and HG4 in JHGC were significant (HR of 13 and 42, respectively) even after adjustment by steroid, RAS blockade, initial PU, initial eGFR, and initial MAP (p<0.05). When comparing HG, M, E, S, and T, HG score was the only independent predictor in isolation or in comparison to varied combinations of MEST parameters. The HR for PUR (an endpoint of proteinuria as 0.3 g/day) was not significant in Oxford, whereas HG3, initial MAP and steroid were independent predictors with HR as 0.4, 0.9, and 1.7, respectively (p<0.05).

Conclusions: HG score was more effective than Oxford in predicting both RFD and PUR in the Japanese cohort consisting of earlier stage of IgAN. The inherent flexibility in a lumped approach (JHGC) as opposed to a split system (Oxford) may explain the HG score producing a more robust when being applied to diverse cohorts allowing a wider application of scoring.

TH-PO686
Prospective Cross-Sectional and Longitudinal Observational Study of Urinary Podocyte Markers and Urinary Megalin in Kidney Disease of ANCA-Associated Vasculitis
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Background: The purpose of this study is to clarify the significance of urinary podocyte markers (urinary podocyte number (U-Pod/Cre) and urinary podocalyxin (U-PCX)/Cre) and urinary megalin (A-Meg/Cre, megalin’s extracellular domain; C-Meg/Cre, full-length of megalin) in ANCA-associated vasculitis (AAV).

Methods: AAV patients (30 cases) were recruited from August 2009 to April 2014. Presence of proteinuria and/or reduced eGFR or histological renal damage was defined as kidney disease (KD)(+). U-Pod/Cre, U-PCX/Cre, A-Meg/Cre and C-meg/Cre were measured around the treatment start (M0), and at 1 (M1), 3 (M3), 6 (M6) and 12 months (M12) after treatment.

Results: At M0, urinary protein creatinine ratio (U-PCR) was significantly higher, and eGFR was significantly lower in KD(+). CRP was not different between KD(+) and KD(-) at M0. U-Pod/Cre was significantly higher in KD(+), and U-Pod/Cre, A-Meg/Cre and C-Meg/Cre were not different at M0, although there was a trend of high C-Meg/Cre in KD(+), compared with KD(-). After treatment in KD(+), CRP(from M1 on), U-PCR, urinary-NAG (U-NAG)/Cre(from M3 on) significantly improved. U-Pod/Cre and C-Meg/Cre(from M6 on) were significantly improved after treatment in KD(+), and U-PCX/Cre and A-Meg/Cre were not significantly changed. Only the correlation of C-Meg/Cre with U-NAG/Cre (p=0.028, Spearman r:0.46, 95%CI 0.04-0.74) was significant between laboratory data and urinary markers measured at M0.

Conclusions: U-Pod/Cre and C-Meg/Cre are elevated in AAV kidney disease and improve after treatment. U-Pod/Cre and C-Meg/Cre may reflect podocyte and proximal tubular injuries, respectively, in AAV.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Clinical and Histological Determinants of Renal Outcome in Lupus Nephritis

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Background: The ISN/RPS 2003 histopathological classification of lupus nephritis (LN) is based on lesions historically thought to be relevant for prognosis, but for some lesions the evidence base is lacking. Without preconceptions, we tested a wide range of histologic and clinical features to objectively identify prognostic indicators of renal outcome in patients with LN.

Methods: 42 histological and 7 clinical parameters were determined as candidate predictors of renal outcome. A cohort of patients was identified from the pathology archives of the Department of Pathology of the University Medical Center Leiden over one class of LN from 1990-2000. Renal biopsies were scored for 42 histologic parameters. eGFR and proteinuria were recorded at time of renal biopsy, as well as during 1, 5, and 10 years of follow-up. For preliminary analyses, variables were tested using univariate mixed models, in which p<0.05 for fixed effects was considered statistically significant.

Results: Interim analysis was performed on 29 patients, of whom none developed end-stage renal disease. Significant associations with eGFR were found for age (p=0.03) and eGFR (p=0.001) at time of renal biopsy, percentage of normal glomeruli (p<0.01), percentages of glomeruli with mesangial hypercellularity (p=0.05), endocapillary hypercellularity (p=0.03), endothelial swelling (p=0.03), endocapillary mononuclear cells (p=0.01), white loops (p=0.02), and cellular crescents (p=0.05), as well as the presence of an interstitial infiltrate (p=0.04). Significant associations with proteinuria were found for eGFR at time of biopsy (p=0.02), percentage of glomeruli with mesangial global sclerosis (p=0.02), presence of cellular and fibrocellular crescents (p=0.01), as well as the presence of an interstitial infiltrate (p=0.01) and tubular atrophy (p=0.02).

Conclusions: Besides histological parameters characterized of the primarily established subsets of LN, histological and clinical parameters may have prognostic significance. These and other features will be studied in an extended dataset in multivariable analyses of which the outcome may be relevant for future modifications of the LN classification.

Specificity of Full House Immunofluorescence for Systemic Lupus Erythematosus

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Background: The finding of full house immunofluorescence (IF) in combination with various histological lesions in renal biopsies of patients without overt systemic lupus erythematosus (SLE) is a diagnostic challenge. We studied the clinical course of these patients as compared to patients who did have SLE at the time of biopsy.

Methods: Patients with full house IF on renal biopsy between 1968-2014 were identified from the pathology archives at our center. Clinical records were reviewed for the presence of ACR or SLICC criteria for the classification of SLE at the time of renal biopsy and during follow-up.

Results: 149 patients with full house IF on renal biopsy were identified. At time of biopsy, 112 had SLE according to >4 ACR criteria (SLE+), 30 did not fulfill the full ACR criteria for SLE (SLE−), and 30 did not fulfill the full SLICC criteria. Of the latter 30, one was classified as SLE+ due to an interstitial infiltrate (p=0.04). Survival without end-stage renal disease regardless of immunosuppressive therapy was better in the group of patients with SLE+ compared to those in SLE− (p=0.01). No difference was noted between patients with SLE+ or SLE− in the percentage of patients with tubular atrophy (p=0.10). eGFR, serum creatinine, and proteinuria were significantly more frequent in patients classified as SLE+ than in those without SLE (p<0.01). No difference was noted between patients with SLE+ and SLE−. SLE+ patients with coexisting diseases and 70 patients with other glomerular diseases were enrolled. Anti-PLA2R antibodies in serum were assayed by direct immunofluorescence microscopy. The staining of PLA2R in glomeruli was evaluated by standard immunofluorescence microscopy.

Results: Anti-PLA2R was found only in MN patients. PLA2R-related MN rate in MN was 87.25%, the positive rate of the serum anti-PLA2R and glomerular PLA2R were 68.89% and 83.21%, respectively, respectively. PLA2R-unrelated MN patients had more coexisting diseases compared with PLA2R-related MN patients (61.11% vs 21.13%, p<0.01), but in MN patients with coexisting diseases, the rate of PLA,R-related MN is 72.97%, thus we regard that PLA,R in glomeruli or anti- PLA,R in circulation is not suitable for discrimination of IMN and SLE. Our results demonstrated that the staining of PLA2R in glomeruli or anti-PLA2R in serum and direct immunofluorescence microscopy for immunostaining of PLA2R in glomeruli was evaluated by standard immunofluorescence microscopy.

Conclusions: We confirm that anti-PLA2R antibody measured by IFA is specific detected in serum of MN patients but it is controversial as used in the differential diagnosis of IMN and as a biomarker to predict outcome of disease. The absence of predictive value may be due to the fact that you have not looked at quantitative data (would need ELISA or quantitative expression of IF data).

Endoplasmic Reticulum Stress Marker Glucose-Regulated Protein 78 Instead of Calcineurin Expression within Kidney Is Predictive of Poor Response to Cyclosporine Treatment in Idiopathic Membranous Nephropathy

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Background: Cyclosporine (CsA) is effective to achieve 60-70% remission rate in treatment of idiopathic membranous nephropathy (IMN). Little is known if Endoplasmic Reticulum stress marker glucose-regulated protein 78 (GRP78) within kidney before CsA treatment could predict post treatment outcome.

Methods: Seventy-six adult biopsy-confirmed IMN patients treated by CsA for at least 6 months from Peking Union Medical College Hospital from January 2014 to December 2015 were retrospectively reviewed. They were grouped into non-remission (NR) (n=12), partial remission(PR) (n=12), or complete remission(CR) (n=52) at the end of six month treatment of CsA with an initial CsA dosage (2.8±0.7 Mg/Kg/d). GPR78 in kidney and Calcineurin (Calxin) expression in the kidney and serum were assayed by immunohistochemistry and ELISA. Their expressions were correlated with clinical outcome.

Results: Serum CAL and kidney CAL expression in IMN patients are significantly increased compared to healthy controls, although there is no difference in either serum or kidney CAL among NR, PR or CR groups. There is a negative correlation between serum CAL activity and renal CAL expression (p=0.034). However, glomerular GPR78 expression in NR group is significantly higher than CR group (Bonferroni correction p=0.0083). There is a positive correlation between kidney CAL expression and GPR78 expression (p=0.05).

Conclusions: ER stress marker GPR78 expression in glomerular section of kidney indicates worse renal outcomes. The combination of kidney GPR78 and CAL may be potentially useful markers of LN activity and urine KIM-1 is better performance than these novel tubular biomarkers are not predictive for a clinical response to treatment of active LN.

Funding: Government Support - Non-U.S.
Selected Reaction Monitoring for Quantification of Angiotensin-II Signature Proteins in Urine

**Methods:** We demonstrated that 47 of 83 AngII-regulated genes were differentially expressed in cystic vs normal kidney tissue. We then selected 18 AngII-regulated proteins upregulated in cystic tissue and/or present in urine. We developed SRM assays for 37 peptides corresponding to 18 AngII-regulated proteins. To assess reproducibility and recovery, we spiked in bovine serum albumin (BSA), and the corresponding heavy-labeled peptides. We determined an optimal method for detection of AngII-regulated peptides. Heavy peptides corresponding to 13 identified AngII-regulated peptides were purchased and spiked into urine. Ultimately, 20ug of total protein/sample was concentrated and analyzed on triple-quadrupole mass spectrometer. We quantified AngII-regulated peptides in urine samples of 9 ADPKD and 2 healthy subjects.

**Results:** Technical replicate CVs were <6% for BSA peptides, and recovery was ~100%. Calibration curves demonstrated linearity (R²=0.99) and CVs=20% in the concentration range of 7/13 peptides in normal and ADPKD urines. Deamidated peptides accounted for 1-40% of total concentration. Peptides were quantified in all urine samples. Peptides corresponding to proteins TSP1, BST1, and LAMB2 had the highest excitation rate in urine of the only ADPKD patient with impaired GFR.

**Conclusions:** We have developed a protocol for SRM quantification of AngII-regulated proteins in urine. Seven AngII-regulated peptides were quantified in urine samples. Future studies will examine if urine excitation rate of AngII signature proteins is associated with cyst size and GFR in larger cohorts of ADPKD patients.

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**Background:** SLE and AAV are distinct auto-immune diseases with possible renal involvement. Some patients fulfill both SLE and AAV classification criteria, defining the SLE/AAV overlap syndrome. We aimed: 1) to report clinical, biological and pathological characteristics of patients with SLE/AAV overlap syndrome and a biopsy-proven glomerulonephritis (GN), 2) to evaluate the incidence of overlapping auto-antibodies and of the overlap syndrome in a cohort of patients with lupus nephritis (LN) or crescentic GN (CGN).

**Methods:** A nationwide survey was conducted to identify cases of SLE/AAV overlap syndrome. Data were collected from SLE and AAV French research groups. Inclusion criteria were diagnosis of both SLE and AAV and biopsy-proven GN between 1995 and 2014. An independent cohort of LN and CGN was used to study the prevalence of overlapping antibodies and/or overlap syndrome. Additional cases were identified through a systematic literature review.

**Results:** The national survey identified 8 cases of SLE/AAV overlap syndrome. All patients were female, median age was 40 years. AAV preceded (n=3), followed (n=3) or occurred concomitantly (n=2) to SLE. Six patients had rapidly progressive GN, and 3 had alveolar hemorrhage. All patients had antinuclear antibodies (ANA), 7 had p-ANCA anti-myeloperoxidase (MPO) antibodies. Renal biopsy showed LN or CGN. Remission was obtained in 6 patients. Literature review identified 31 additional cases with similar profile. Cohort analysis revealed ANCA positivity in 24% of LN, ANA positivity in 55% of CGN, with no correlation with pathological findings, and a prevalence of 2/110 (1.8%) for SLE/AAV overlap syndrome.

**Conclusions:** In patients with GN, SLE/AAV overlap syndrome may occur but its prevalence seems low. Most patients have an aggressive renal presentation, with usually both ANA and anti-MPO antibodies. Further studies are needed to assess shared pathogenesis and therapeutic options.
this correlation varies with the GD, age, sex, blood pressure control (BP), body mass index (BMI), albuminuria, serum creatinine, estimated glomerular filtration rate (GFR) by MDRD, proteinuria degrees (mg/24h (PD)), urine output (UO) and ACE/ARBs treatment.

Methods: Observational cross-sectional study of renal biopsies performed 2010-2014. Spearman’s coefficient and multiple linear regression was used to identify the correlation of the proteinuria determinations.

Results: 188 biopsies collected; 96 were GD. Mean age 54±18 years; 66% male; BMI 27.1±5.75. The GD was: glomerulonephritis (GN) IgA 21%, membranous (MGN) 19%, vasculitis 17%, focal segmental (FSGS) 13%, minimal change (MGN) 10%, lupus 10%, and others 10%. The GFR was categorized >60 mL/min 37.5%; 30-60 mL/min 22.9% and <30 mL/min 39% and PD was categorized <90 mL/min 8% and >90 mL/min 92%. The BP was controlled in 60.4%. Mann 240.2 mg/dl and P/Cr 2.71 (1.6-5.0). P24H and P/Cr showed significant correlations (r=0.71, P<0.001). An IgA was higher than P/Cr in an increased in P24H of 0.7/p24h/95% CI 0.59, 0.87; P<0.001. There was no correlation seen in subgroup analysis of UO<1 liter/day and vasculitis (P=0.39, P=0.13). The correlation was higher in women than men (r=0.81 vs r=0.64), if aged <65 vs >65 (r=0.85 vs r=0.50), in controlled BP (r=0.70 vs r=0.57), in GFR <60 mL/min (r=0.90) and in PD <300 mg/ml (r=0.71). In group of ACE ARB (r=0.75 vs 0.66) and with BMI group (r=0.83 vs 0.59, P=0.76). IgAgN (r=0.67), MGN (r=0.73), FSGS (r=0.78), MCGN (r=0.93) and lupus (r=0.90).

Conclusions: Excellent correlation was observed P/Cr. The P/Cr is useful in IgA, GN, MGN, FSGS and MCGN, regardless of sex, age, BP, ACE/ARBs and BMI. The correlation was greater with higher GFR and with lower PD. Proteinuria determinations in 24-hour urine in patients with UO<1 liter/day and vasculitis.

TH-PO697


Background: The aim of this research was to study the renal functional reserve (RFR) and electron microscopy (EM) in patients with subclinical lupus nephropathy, and to evaluate the changes in the urinary excretion of albumin, retinol-binding protein and electrolytes induced by amino-acids (AAs) infusion; and their relationship with the renal morphology data.

Methods: In 25 lupus patients (SLE group) and in 15 controls, on the 24-hour urine collection and on urine specimens taken after both an oral water load and an AAs infusion, glomerular filtration rate (GFR: creatinine clearance - ml/min/1.73 m²), microalbuminuria (uALB) and sodium excretion (FENa) were evaluated. The urinary retinol-binding protein (RBP) was evaluated only in the SLE group which was also divided in subgroups according to the classification of lupus nephritis (ISN/RPS 2003). Biopsies were also analyzed in order to characterize the renal ultrastructural abnormalities (EM).

Results: Both in the SLE group and controls there was a significant increase in GFR, uALB, FENa and RBP, after the AAs infusion and on urine specimens taken after both an oral water load and an AAs infusion. Under these conditions the urinary excretion of RBP was significantly lower than basal in patients with SLE and in the controls. The correlation was greater with higher GFR and with lower PD. Perform proteinuria determinations in 24-hour urine in patients with UO<1 liter/day and vasculitis.

TH-PO698

Course of PR3 Titters versus MPO Titters in ANCA Vasculitis Patients After Rituximab Therapy Vega Goedecke, Marcus Hiss, Hermann G. Haller, Annette D. Wagner. Dept of Nephrology and Hypertension, Medical School Hannover, Hannover, Germany

Background: Rituximab has been proven to be an effective therapeutic agent in moderate to severe cases of ANCA vasculitis. B cell depletion plays a major role in suppressing inflammatory processes mediated by granulocytes in ANCA vasculitis. PR3 antibodies are specific for cANCA vasculitis, whereas MPO antibodies are detectable in pANCA vasculitis.

Methods: We compared the time course of anti-PR3 titers in 25 cANCA patients with the course of anti-MPO titers in 11 pANCA patients receiving rituximab induction therapy. We compared anti-PR3 and anti-MPO titters before initiation of rituximab therapy and 5, 6 months, 12 months after starting therapy. The mean age of both groups was comparable (56 in cANCA patients vs. 58,1 years in pANCA patients). The female to male gender ratio was 13:12 in cANCA patients and 6:5 in pANCA patients.

Results: Our results show that rituximab therapy significantly lowers anti-PR3 titers in cANCA vasculitis patients after 3, 6, 12 and 24 months. In contrast, anti-MPO titers are not lowered significantly in pANCA vasculitis patients after rituximab therapy.

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

Underline represents presenting author.

TH-PO699

Comparison of Urinary Microvesicle Isolation Methods for miRNA Profiling in Nephritic Syndrome Ilse M. Roel, Thomas Laufer, Thomas Brefoert, Hannah Schroers, Johan Van der vlag, Jack F. Wetzel, Jeroen Deegens. 1Nephrology, RadboudUMC, Nijmegen, Netherlands; 1Comprehensive Biomarker Center GmbH, Heidelberg, Germany.

Background: Urinary microvesicles (uMV) are a promising source for biomarker discovery, including miRNAs (small noncoding single stranded RNAs, which regulate gene expression). UMV can be isolated by different techniques. In healthy subjects, an exosome precipitation protocol yielded the highest quantities of miRNA in uMV. The optimal isolation method of uMV for miRNA profiling in proteinuria is unknown.

Methods: Urine samples were collected from 1 normal control (NC) and 4 patients with nephritic syndrome (NS1-4). UMV were isolated by 6 different protocols: exoquest(B), Qiagen’s exoRNeasy(C), exoquick after additional 17.000g centrifugation step (D), Qiagen’s exoRNeasy after additional 17.000g centrifugation step (E), ultracentrifugation (UCF) (F). UCF was followed by size exclusion chromatography(G). The miRNA-profiles were compared with the profile of raw urine (A) to correct for contamination. We determined the expression profiles of all miRBase release v20 human miRNAs using CBC’s custom Agilent SurePrintG3 Human miRNA (8x60K) microarrays.

Results: Results are shown in the table. miRNA-analysis was unsuccessful in 5/35 samples (method B/D/G) due to insufficient amount of RNA. Method C and E resulted in highest amount of total miRNAs and in highest percentage miRNAs that were not detected in A. In method F, despite lower amount of total miRNAs, 9-56 additional miRNAs that were not present in A/C/E, were detected.

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

Underline represents presenting author.

249A
TH-PO700
Gross Hemataria of Glomerular Origin in Adults
Sami Safadi, Samih H. Nasr. 1 Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Anatomic Pathology, Mayo Clinic, Rochester, MN.

Background: Gross hemataria is a relatively uncommon presentation of glomerulonephritis. Glomerular gross hemorrhagi (GGH) is more frequent in children than adults. IgA nephropathy and Alport syndrome are the most common causes of GGH in children. The clinicopathologic characteristics of GGH in adults have not been systematically evaluated. We investigated the etiology and clinicopathologic characteristics of GGH in a large single-center cohort of adults.

Methods: Adult patients (18) with native kidney biopsy were identified from the pathology database. The electronic medical record (EMR) was searched for the symptom of gross hematuria in these patients. The EMR was then examined manually to select patients with GGH. Patients with a urological cause of hematuria were excluded. Univariate logistic regression was used to test association between age, gender, and diagnosis.

Results: Between 1993 and 2015, 101 patients with GGH were identified. 51% were male and 49% were female. Age ranged from 13 to 88 years old. Mean age at biopsy was 52 yrs. (18-89). The clinicopathologic causes of GGH were heterogeneous as shown in table 1. The most common causes were: IgA nephropathy-HSP nephritis (IgA/HSP) (36%), thin basement membrane disease (TBMND) (14%), pauci-immune crescentic GN (PICGN) (13%), and monoclonal protein related glomerular disease (amyloidosis, MIDD, PGNMID) (15%). Younger adults were more likely to have IgA/HSP (OR 3.2, p<0.01), and less likely to have PICGN (OR 0.05, p>0.01). Male patients were more likely to be older on presentation (dif 32 yrs, p<0.05). Female patients were slightly more likely to have loin pain hematuria syndrome (LPHS) and TBMND. Only 30% of patients with IgA/HSP with GGH had crescents on biopsy.

Conclusions: This is the first study to analyze GGH in adults. We show that causes of GGH in adults are very heterogeneous, but most cases are due to IgA/HSP or TBMND disease in younger adults, and PICGN in older adults.

Diagnosis
N
IgA/HSP
36
TBMND
14
PICGN
13
LPHS
5
MIDD
3
Infection-related GN
7
Proliferative Lupus Nephritis
3
Amyloidosis
3
MPGN, immune complex (IC) type
3
Fibrillary GN
3
PGNMID
3
MGN with Reinal Vein Thrombosis
3
Anti-GBM Disease
2
C3 GN
2
Proliferative GN, IgG related
1
Mesangio proliferative GN, IC type
1
Fahy Disease
1

TH-PO701
IgM Staining in Immunofluorescence Is a Risk Factor for Relapsing in Focal Segmental Glomerulosclerosis
Daiane Silva, Gisele Vigel Falendranches, Luiz H.B.C. Sette, Renata Silva, Denise Maria do nascimento Costa, Maria Silva, G.M. Cavalcante, Lucila Maria Valente. Nephrology, Univ Federal do Pernambuco, Recife, Pernambuco, Brazil.

Background: Glomerular IgM and C3 deposits are frequently found in idiopathic focal segmental glomerulosclerosis (fSGS). Some experimental studies have suggested that IgM deposits may play a role in activation of the complement system in the glomeruli. However, the clinical meaning of the IgM deposits is unclear in fSGS patients. In this study we systematically evaluated. We investigated the etiology and clinicopathologic characteristics of GGH in a large single-center cohort of adults.

Methods: Adult patients (18) with native kidney biopsy were identified from the pathology database. The electronic medical record (EMR) was searched for the symptom of gross hematuria in these patients. The EMR was then examined manually to select patients with GGH. Patients with a urological cause of hematuria were excluded. Univariate logistic regression was used to test association between age, gender, and diagnosis.

Results: Between 1993 and 2015, 101 patients with GGH were identified. 51% were male and 49% were female. Age ranged from 13 to 88 years old. Mean age at biopsy was 52 yrs. (18-89). The clinicopathologic causes of GGH were heterogeneous as shown in table 1. The most common causes were: IgA nephropathy-HSP nephritis (IgA/HSP) (36%), thin basement membrane disease (TBMND) (14%), pauci-immune crescentic GN (PICGN) (13%), and monoclonal protein related glomerular disease (amyloidosis, MIDD, PGNMID) (15%). Younger adults were more likely to have IgA/HSP (OR 3.2, p<0.01), and less likely to have PICGN (OR 0.05, p>0.01). Male patients were more likely to be older on presentation (dif 32 yrs, p<0.05). Female patients were slightly more likely to have loin pain hematuria syndrome (LPHS) and TBMND. Only 30% of patients with IgA/HSP with GGH had crescents on biopsy.

Conclusions: This is the first study to analyze GGH in adults. We show that causes of GGH in adults are very heterogeneous, but most cases are due to IgA/HSP or TBMND disease in younger adults, and PICGN in older adults.

Diagnosis
N
IgA/HSP
36
TBMND
14
PICGN
13
LPHS
5
MIDD
3
Infection-related GN
7
Proliferative Lupus Nephritis
3
Amyloidosis
3
MPGN, immune complex (IC) type
3
Fibrillary GN
3
PGNMID
3
MGN with Reinal Vein Thrombosis
3
Anti-GBM Disease
2
C3 GN
2
Proliferative GN, IgG related
1
Mesangio proliferative GN, IC type
1
Fahy Disease
1

Urinary excretion of citrate, cis-acminate, isocitrate, oxoglutarate and succinate was reduced 40-68%. Based on data from Nephrone, expression of genes for four TCA cycle enzymes was reduced in human kidney tissues with neproscerosis. One transcription factor (TFAP2C) regulating TCA genes was also significantly reduced in neproscerosis.

Conclusions: In conclusion, in non-diabetic CKD, targeted metabolomics identified differences in the urinary excretion and plasma concentrations of small molecules that are consistent with both reduced renal excretion and impaired metabolism. Reductions in TCA cycle metabolites and gene expression were also identified and suggested suppressed mitochondrial function in CKD.

Funding: NIDDK Support, Other U.S. Government Support, Pharmaceutical Company Support - Abbvie

TH-PO702
Targeted Metabolomics Reveals Reduction in TCA Cycle Metabolites in Non-Diabetic Hypertensive Chronic Kidney Disease
Stein I. Hallan,1 Maryam Akfarian,2 Leila R. Zelnick,2 Bryan R. Kestenbaum,3 Shoba Sharma,3 Rintaro Saito,3 Kumar Sharma,3,1 Ian H. De Boer,2 1Center for Renal Translational Medicine, UCSD, San Diego, CA; 2Kidney Research Inst and Div of Nephrology, Univ of Washington, Seattle, WA; 3Clinical Metabolomics Inc, La Jolla, CA.

Background: Increasing metabolic disturbances have recently been described in DKD using metabolomic analysis. Non-diabetic hypertensive CKD is common and needs to be better characterized.

Methods: Using a targeted quantitative panel of 66 organic acids, we compared plasma concentrations and urine excretion in 24/2 adults with stage 3-4 non-diabetic hypertensive CKD to those of 10 healthy controls.

Results: After correcting for multiple testing, urinary excretion of 27 metabolites and plasma concentration of 33 metabolites differed significantly (range -68% to +113%). All 27 altered urine metabolites was reduced in CKD, while 27 of 33 altered plasma metabolites were higher in CKD. Pathway analysis based on significantly altered metabolites identified seven metabolic pathways significantly altered in CKD, most strikingly the TCA cycle (6 of 20 measured metabolites significantly different, q<0.001).

Conclusions: In conclusion, our metabolomics results suggest that the TCA cycle and the metabolism related to TCA cycle are strikingly altered in non-diabetic hypertensive CKD.

Funding: NIDDK Support, Other U.S. Government Support, Pharmaceutical Company Support - Abbvie

TH-PO703
The Application of Laser Microdissection and Liquid Chromatography – Mass Spectrometry in the Diagnosis of Renal Amyloidosis
Michiko Aoki,1 Dedong Kang,2 Yusuke Kajimoto,2 Takafumi Kanemitsu,3 Kiyotaka Nagahama,4 Akira Shimizu,5 Analytic Human Pathology, Nippon Medical School, Tokyo, Japan.

Background: In our department, renal amyloidosis of kidney biopsies have been diagnosed by Congo red stained, immunofluorescence (IF) for immunoglobulin light chain (LC) and heavy (HC) chains, and immunostaining for amyloid A, transthyretin, and β2-microglobulin. Recently, it has been reported that liquid chromatography tandem mass spectrometry (LCMS/MS) is helpful for detection of the amyloid precursor proteins.

Methods: We retrospectively investigated 30 cases of renal amyloidosis, 11 cases (36.7%) of AA and 19 cases (63.3%) of AL amyloidosis, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of serum immunofixation electrophoresis (IFE) and findings of IF.

Results: We retrospectively investigated 30 cases of renal amyloidosis, 11 cases (36.7%) of AA and 19 cases (63.3%) of AL amyloidosis, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of serum immunofixation electrophoresis (IFE) and findings of IF.

Conclusions: LCMS/MS could detect the component proteins in amyloid deposits in all cases, even in the cases that had less than 5% area of amyloid deposition in glomeruli. Furthermore, among AL amyloidosis, which was diagnosed previously, we found 2 cases of AH amyloidosis and 2 cases of AAL amyloidosis. LCMS/MS is very helpful for diagnosis of amyloidosis, especially AAL and AH amyloidosis.
TH-P0704

THSD7A Staining of Membranous Glomerulopathy in Clinical Practice Reveals Cases with Dual Autoantibody Positivity

Christopher Patrick Larsen,1 Larry N. Cossey,2 Laurence H. Beck,2 John C. Lieske,3 Andrew D. Rule,4 Lars Patrick,5 Ken Kayakabe,6 Hidekazu Ikeuchi,7 Hitoshi Sugiyama,8 Michio Nagata,9 Hiroshi Sato,10 Hitoshi Yokoyama,11 Yoshisasa Nojima,12 1Dept of Medicine, Geffen School of Medicine, University of California, Los Angeles; 2Dept of Medicine, University of Alabama at Birmingham; 3Dept of Nephrology, Cleveland Clinic, OH; 4Dept of Pathology, Mayo Clinic, MN; 5Div of Nephrology, Kanazawa Medical University, Uchinada, Japan.

Background: The majority of primary membranous glomerulopathy (MG) cases are due to antibodies directed against the podocyte phospholipase A2 receptor (PLA2R) antigen. Recently, thrombospondin type-1 domain containing 7A (THSD7A) was described as a second antigenic target leading to MG. We sought to validate an immunohistochemical stain for the diagnosis of THSD7A-associated MG on renal biopsy material.

Methods: Immunohistochemical staining for THSD7A (Sigma) and PLA2R (Sigma) was performed in all cases of non-SLE associated MG diagnosed in our laboratory between December 2014 and April 2015. This included a total of 258 cases. Both stains were performed on formalin fixed paraffin embedded tissue. Serologic testing for PLA2R (ELISA, WB) and THSD7A (WB) antibodies was performed in a subset of cases to determine the specificity of positive THSD7A staining for the diagnosis of THSD7A MG.

Results: MG stained positive for THSD7A-only in 7 (2.7%) cases, PLA2R-only in 141 (54.7%) cases, and showed dual positivity for THSD7A and PLA2R in 2 (0.8%) cases. Staining was negative for both in 108 (41.8%) cases. Serologic testing was performed for antibodies to PLA2R and THSD7A in 9 cases with both serum and biopsy material available and the results are shown in Table 1.

Conclusions: Based on these findings we believe it is possible to specifically diagnose THSD7A-associated MG based on renal biopsy staining. Additionally, we confirm that only a minority (3.5%) of MG cases reflect THSD7A-associated disease. Interestingly, 2 (22%) THSD7A-positive cases showed dual positivity for PLA2R and THSD7A with serologic studies showing evidence of antibodies to both THSD7A and PLA2R antigens in these patients. These cases demonstrate the importance of using a panel based approach to subtyping MG.

Funding: NIDDK Support

TH-P0705

Clinical Characteristics Associate Differently with Single Nephron GFR Than Total GFR in Normal Adults

Aleksandar Denic,1 Lilach O. Lerman,1 John C. Lieske,2 Mariam P. Alexander,2 Harini A. Chakker,2 Emilio D. Poggio,4 Richard J. Glassock,5 Andrew D. Rule,4 Div of Nephrology, Mayo Clinic, MN; 2Dept of Pathology, Mayo Clinic, MN; 3Div of Nephrology, Mayo Clinic, AZ; 4Dept of Nephrology, Cleveland Clinic, OH; 5Dept of Medicine, Geffen School of Medicine, CA.

Background: Total GFR (GFR) is the product of mean single nephron GFR (snGFR) and the number of nephrons. Thus, associations with GFR may be attributable to associations with snGFR, nephron number, or both.

Methods: We identified 1,520 living kidney donors at Mayo Clinic and Cleveland Clinic with pre-donation contrast-contrast CT scans and iodotamalate clearance (GFR), and with kidney biopsies at the time of donation. snGFR was estimated from GFR divided by nephron number (CT bilateral cortical volume x biopsy non-sclerotic glomerular density). GFR, snGFR, and nephron number were associated with clinical and biopsy characteristics (age and sex-adjusted).

Results: Donors were 58% women, mean±SD age of 43±12.7 y, GFR of 103±20ml/min/1.73m², nephron number of 728,280±390,668 per kidney, and snGFR of 0.073±0.042 ml/min/1.73m². There was a strong decline in nephron number and modest rise in snGFR with age such that the net effect was an age-dependent decline in GFR.

Conclusions: In Japan, patients with IV-Giv-V LN were significantly associated with decreased renal function and nephrotic syndrome. In addition, the frequency of mixed proliferative and membranous type and chronic lesions was higher at the repeat biopsy, suggesting that these histological features reflect progression of the disease or refractory nature to treatment.

Funding: Government Support - Non-U.S.

TH-P0707

MicroRNA Signatures in Renal Disease: A Meta-Analysis of Tissue and Urine Datasets

Christos A. Argyropoulous, Mark L. Unruh, V. Shane Pankratz. Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: MicroRNA (miRNA) are negative regulators of gene translation and an emerging biomarker in a wide variety of diseases. Little is known about the ability of miRNA to classify patients with renal pathology.

Conclusions: In Japan, patients with IV-Giv-V LN were significantly associated with decreased renal function and nephrotic syndrome. In addition, the frequency of mixed proliferative and membranous type and chronic lesions was higher at the repeat biopsy, suggesting that these histological features reflect progression of the disease or refractory nature to treatment.

Funding: Government Support - Non-U.S.
Methods: We undertook a meta-analysis of normalized miRNA profiles from clinical samples in Gene Expression Omnibus. miRNAs in mirBase20 were scored for kidney relevance according to their experimentally or computationally ability to bind to proteins in the kidney proteome (http://www.proteintatlas.org). Elastic Net (EN) regression was then used to select short miRNA signatures according to their ability to classify diseased from healthy samples using 10-fold cross-validation.

Results: Using our systems biology approach we identified 739 miRNAs as potential kidney biomarkers out of 1689 candidates. A total of 8 studies with 178 samples were included. Of those, 2 studies in patients were lupus (N=30) were excluded due to the incompatibility of the normalization strategy with the other samples. miRNAs profiles from 31 urine samples and 117 biopsy samples were available for analysis.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Platform</th>
<th>Source</th>
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<th>Abnormal</th>
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<tbody>
<tr>
<td>GSE33771</td>
<td>Microarray (μA)</td>
<td>Renal Bx (Bx)</td>
<td>28</td>
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</tr>
<tr>
<td>GSE393052</td>
<td>μA</td>
<td>Bx</td>
<td>10</td>
<td>30 (TpA Cell Rejection), 11 (TpA AB Rejection), 4 (TAP A)</td>
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<tr>
<td>GSE29283</td>
<td>μA</td>
<td>Bx, Cortex</td>
<td>3</td>
<td>5 (Hypertension, HTN)</td>
</tr>
<tr>
<td>GSE28434</td>
<td>μA</td>
<td>Bx, Medulla</td>
<td>3</td>
<td>5 (HTN)</td>
</tr>
<tr>
<td>GSE48318</td>
<td>qPCR</td>
<td>Urine exosomes</td>
<td>2 (Normalalbuminuria, N/A)</td>
<td>2 (Microalbuminuria, MA)</td>
</tr>
<tr>
<td>doi: 10.1371/journal.pone.0054662</td>
<td>qPCR</td>
<td>Whole urine</td>
<td>10 NA</td>
<td>17 MA (within 2 years)</td>
</tr>
</tbody>
</table>

The median (IQR) AUC for individual miRNAs to classify diseased samples was 0.590(0.46-0.68) for unselected miRNAs but increased to 0.640(0.54-0.69) in the presellected ones. A short signature of 19 miRNAs achieved a superior classification performance for renal pathology (cross-validated AUC 0.96).

Conclusions: This is the first study to date examining the performance of a panel of miRNAs in classifying patients with kidney disease. A panel of miRNAs may classify patients with native and allo grant renal disease aiding the interpretation of elevated creatinine in clinical practice.

TH-PO708

Study Into the Effect of Aquaporin-2 on the Efficacy and Predicted Effect of Tolvaptan in Patients of Nephritic Syndrome | Eichi Sato, 1 Tsukasa Nakamura, 1 Mayuko Amaha, 1 Mayumi Nomura, 1 Daisuke Matsumura, 1 Akiko Fuji, 1 Yoko Ono, 1 Yoshihiko Ueda, 1 1 Dept of Pathology, Dokkyo Medical University, Koshigaya Hospital, Koshigaya, Saitama prefecture, Japan; 2 Div of Nephrology, Dept of Internal Medicine, Shinshu University Central General Hospital, Matsumoto, Chiba Prefecture, Japan.

Background: A retrospective investigation was conducted into the efficacy and adverse drug reactions of tolvaptan in the treatment of diabetic nephropathy and MCNS (Minimal Change Nephrotic Syndrome) with heart failure.

Methods: A total of 56 patients with chronic kidney disease (due diabeto nephropathy) and MCNS with heart failure who over the last 2 years and who were treated with tolvaptan. We defined effective cases as those showing a 2-fold increase in urinary volume compared to pre-administration levels or a clear improvement in edema control after 4 weeks of the therapy. The kidney function was also measured. A score of (−) is assigned when the collecting duct shows no staining; (+) weak positive, (++) responder but negative for the non-responder. In MCNS cases findings were positive for the responder but weak positive for the non-responder.

Results: Of the 56 cases, 49 were tolvaptan responders. No problematic side effects were observed. Comparison of tolvaptan responders and non-responders indicated that serum Cre levels were significantly lower in responders. We performed immunostaining for aquaporin 2 in the collecting duct. In diabetic cases, findings were positive for the responder but negative for the non-responder. In MCNS cases findings were positive for the responder but weak positive for the non-responder.

Conclusions: Diabetic nephropathy and nephrotic syndrome responders exhibited aquaporin 2 expression in collecting duct epithelial cells. No expression or weak positive expression was observed in diabetic nephropathy and in MCNS non-responders.

TH-PO709

Subclinical Anti-Smith and Anti-Ribonucleoprotein Antibodies Precede Proliferative Lupus Nephritis Diagnosis | Stephen W. Olson, 1 Lisa K. Prince, 1 Dusty J. Little, 1 Kevin C. Abbott, 1 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 2 Nephrology, Naval Medical Center San Diego, San Diego, CA; 3 NIDDK, National Inst of Health (NIH), Bethesda, MD.

Background: Lupus Nephritis (LN) manifests in approximately 50% of Systemic Lupus Erythematosus cases. Anti-Smith (SM) and Anti-Ribonucleoprotein (RNP) antibodies are associated with proliferative lupus nephritis (PLN) at diagnosis. We hypothesized that prediagnostic anti-SM and anti-RNP antibodies were more common in PLN than SLE without LN.

Methods: This case-control Department of Defense Serum Repository study compared 3 longitudinal prediagnostic quantitative anti-SM and anti-RNP antibody levels in 252A patients with biopsy-proven PLN from the Walter Reed National Military Medical Center with 21 age, sex, race, and age of serum matched SLE without LN disease controls.

Immunoassays were performed at Quest Diagnostics.

Results: More PLN patients had an anti-SM antibody level ≥4 AI than matched disease controls at any time (52% vs. 5%; p<0.001) and <2 years (47% vs. 6%, p=0.01) before diagnosis, but not >2 years before diagnosis (22% vs. 0%, p=0.11). More PLN patients had an anti-RNP antibody ≥4 AI than matched disease controls at any time (57% vs. 14%, p<0.001), <2 years (53% vs. 19%, p=0.04) and >2 years (6% vs. 0%, p=0.01) before diagnosis. Only an anti-SM antibody absolute rise over time of >4 AI prior to diagnosis was specific for PLN (30% vs. 0%; p=0.02). But, anti-RNP antibody more often preceded anti-SM antibody when there was a clear antecedent antibody (89% vs. 11%, p=0.003).

Conclusions: In a large subgroup of PLN patients, anti-RNP antibodies were consistently elevated prior to anti-SM antibodies, but not rising, years prior to diagnosis. Anti-SM antibodies predominantly elevate in the last two years prior to PLN diagnosis which supports a possible direct contribution to PLN pathogenesis. Our data suggests that SLE patients with baseline RNP antibody along with a rising anti-SM antibody levels may benefit from increased surveillance for early signs of PLN. A more prompt biopsy diagnosis would allow for proactive therapeutic intervention to preserve maximal renal function.

Funding: Other U.S. Government Support

TH-PO710

The Relationship Between Phospholipase A2 Receptor Autoantibody and Idiopathic Membranous Nephropathy | Weiying Lin, 1,2,3 Hang Li, 1,2,3 Xuemei Li, 1,2,3 Yan Qin, 1,2,3 Ying Su, 1,2,3 Yang Yu, 1,2,3 Yin Guan, 1,2,3 Yubing Wen, 1,2,3 Xuewang Li, 1,2,3 1 Dept of Nephrology, Peking Union Medical College Hospital; 2 Peking Union Medical College; 3 Chinese Academy of Medical Sciences.

Background: The value of PLA2R autoantibody is still controversial in diagnosis, activity monitoring and prognosis estimation in idiopathic membranous nephropathy (IMN). The method used is non-uniform.

Methods: A total of 233 patients with biopsy-proven IMN at Peking Union Medical College Hospital from 2012 January to 2014 March were enrolled. A control group was set up. The serum antibody tier collected at the time of renal biopsy was measured by quantitative ELISA. 14 IMN patients with detectable antibody at biopsy were followed up to retest antibody 6 months later. Besides, the diagnostic accuracy between ELISA and immunofluorescence (IF) method for IMN was compared. The consistency and difference in antibody detection between two methods were also performed.

Results: The total sensitivity of antibody was 60.0% in IMN. However, it increased to 71.3% if patients didn’t receive immuno-suppression therapy before testing. The antibody specificity was 100.0%. Hypoalbuminemia became severe (P<0.05) and the proportion of nephrotic arrange proteinuria rose gradually (P<0.05) as antibody levels increased. The antibody changes were consistent with clinical outcomes. The antibody AUC-ROC for IMN diagnosis was 0.800 by ELISA. There was no significant difference in AUC-ROC between ELISA and IF in IMN diagnosis (P>0.05). The kappa value of antibody detection consistency between ELISA and IF was 0.941±0.033. The positive rate of antibody detection wasn’t significantly different between ELISA and IF (P>0.05).

Conclusions: PLA2R autoantibody has high sensitivity, notable specificity and good diagnostic accuracy for IMN. The antibody positive rate is affected by immunosuppression therapy and disease activity. The antibody could reflect disease activity and predict outcomes. Moreover, There is no significant difference in diagnostic accuracy and antibody detection difference between ELISA and IF. The antibody detection consistency is good between ELISA and IF.

TH-PO711

Factors Related to the Glomerular Volume in Different Cortical Zones of the Human Kidney | Yusuke Okabayashi, 1 Go Kanzaki, 1 Nobuo Tsuboi, Kotaro Haruhara, Kentaro Koike, Yoischi Miyazaki, Tetsuya Kawanura, Makoto Ogura, Takashi Yokoo. 1 Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: Recent studies have shown that glomerular enlargement is a surrogate marker of low nephron number in primary hypertension and in people with lower birth weight. To date, however, information is limited regarding the diversity in the distribution of glomerular size within the cortex and associations with relative GFR. The value of PLA2R autoantibody is still controversial in diagnosis, activity monitoring and prognosis estimation in idiopathic membranous nephropathy (IMN). The method used is non-uniform.

Methods: A total of 89 autopsy kidneys without apparent renal diseases were analyzed to measure the glomerular volume (GV) in different parts of the renal cortex. The mean GV was calculated from the measured each glomerular area. Relationships between the GV and other clinicopathological features were investigated.

Results: The GV showed wide variations between the individuals and showed maximal values in the innermost cortex (p<0.033). The positive rate of antibody detection wasn’t significantly different between ELISA and IF (P>0.05).

Conclusions: PLA2R autoantibody has high sensitivity, notable specificity and good diagnostic accuracy for IMN. The antibody positive rate is affected by immunosuppression therapy and disease activity. The antibody could reflect disease activity and predict outcomes. Moreover, There is no significant difference in diagnostic accuracy and antibody detection difference between ELISA and IF. The antibody detection consistency is good between ELISA and IF.
As a whole, compared to the GV in the superficial cortex (2.7±1.0 x 10^3/mm^3), the averaged GV in the juxtamedullary cortex (3.1±0.8 x 10^3/mm^3) was significantly larger. Of note, in 27 cases (30%), the mean GV in the superficial cortex was larger than that of the juxtamedullary cortex. Such individuals with glomerular enlargement in the superficial cortex were characterized by a low glomerular density and/or large body size.

Conclusions: In each individual kidney, there are considerable variations in the distribution of the GV. Nephron number/body size and hypertension underlie the enlargement of glomeruli in superficial and juxtamedullary cortex, respectively.

TH-P0712
Highly Sensitive Method for Quantification of Iohexol Vera Jankowski, Joachim Jankowski. Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, Germany.

Background: Iohexol is used for accurate determination of the GFR in CKD patients. However, high iohexol amounts might lead to adverse effects in organisms. In order to minimize the iohexol dosage required for the GFR determination in humans, the development of a sensitive quantitation method is essential. Therefore, the objective of our preclinical study was to establish and validate a simple and robust LC-ESI-MRM method for iohexol quantification.

Methods: In order to test whether a significantly decreased amount of iohexol is sufficient for reliable quantitation, a LC-ESI-MRM mass-spectrometric approach was assessed. We analyzed the kinetic of iohexol in rats after application of different amounts of iohexol (15 mg-150 mg/kg body weight). Blood sampling was performed at different time points. Iohexol and the internal standard (iothalamic acid) were separated from serum proteins using centrifugal filtration device with a cut-off of 3 kDa. The chromatographic separation was achieved on a reversed-phase column.

Results: A linear correlation of the iohexol amount and mass-signal (MS) intensity was observed. Thus, a threshold for physiological active iohexol concentrations was determined. The Clinical and Renal Pathological Features and Presence of Anti-PLA2R Antibody in 9 Patients with Both Membranous Nephropathy and IgA Nephropathy. Xin Zhang, Weifeng Lin, Jianing Li, Yuhong Wen, Jianfeng Cai, Hang Li, Xuewei Li. Nephrology Dept, Peking Union Medical College Hospital, Beijing, China.

Background: Both membranous nephropathy (MN) and IgA nephropathy (IgAN) rank top among the primary glomerulonephropathy but they rarely coexist in the same patient. Whether they are accidentally concurrent remains controversial. Here we reported the clinical and pathological features of 9 cases with concomitant biopsy-proved MN and IgAN.

Methods: The 9 patients were admitted to our hospital for renal biopsy between 2009 and 2014, none having apparent secondary causes of renal diseases. 36 age-, sex-, and anti-PLA2R, IgG and C1q in their second renal biopsy. While data in the present study suggest silent lupus activity, the association of these histological findings with potential relapses in PNL invites to open discussion.

Funding: Government Support - Non-U.S.

TH-P0714
The Clinical and Renal Pathological Features and Presence of Anti-PLA2R Antibody in 9 Patients with Both Membranous Nephropathy and IgA Nephropathy. Xin Zhang, Weifeng Lin, Jianing Li, Yuhong Wen, Jianfeng Cai, Hang Li, Xuewei Li. Nephrology Dept, Peking Union Medical College Hospital, Beijing, China.

Background: Both membranous nephropathy (MN) and IgA nephropathy (IgAN) rank top among the primary glomerulonephropathy but they rarely coexist in the same patient. Whether they are accidentally concurrent remains controversial. Here we reported the clinical and pathological features of 9 cases with concomitant biopsy-proved MN and IgAN.

Methods: The 9 patients were admitted to our hospital for renal biopsy between 2009 and 2014, none having apparent secondary causes of renal diseases. 36 age-, sex-, and biopsy-year- matched controls with isolated IgAN or isolated primary MN, respectively, were randomly selected. Clinical features were compared across these groups. Anti-PLA2R antibody was assayed with ELISA test by using the >80% preserved serum samples in 9 cases and 36 controls with isolated MN.

Results: The clinical and pathological features of cases and controls were summarized in Table 1. Table 1 the clinical and pathological features among patients with combined IgAN and MN, isolated primary MN, and isolated IgAN.

<table>
<thead>
<tr>
<th>Group</th>
<th>Combined IgAN and MN</th>
<th>Isolated primary MN</th>
<th>Isolated IgAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>9</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>40.2±8.4</td>
<td>40.9±7.6</td>
<td>38.6±9.8</td>
</tr>
<tr>
<td>24h-Upe, g/24h</td>
<td>5.9±3.7</td>
<td>6.7±5.5</td>
<td>1.61±1.9*</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>74.4±20.2</td>
<td>75.4±17.6</td>
<td>116.5±110.9*</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>29.1±6.9</td>
<td>27.4±7.2</td>
<td>38.8±8.4*</td>
</tr>
<tr>
<td>Mesangial proliferation</td>
<td>None</td>
<td>None</td>
<td>All</td>
</tr>
<tr>
<td>Lee’s grading of IgAN</td>
<td>Grade I</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>6</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
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<td>N/A</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>MN Classification</td>
<td>Grade I</td>
<td>1</td>
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</tr>
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<td>Grade II</td>
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<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Grade III or IV</td>
<td>0</td>
<td>2</td>
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</tr>
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</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Combining MN and IgAN are more likely to mimic isolated primary MN. It was reported that various microRNAs regulated the progression of tubulointerstitial fibrosis. However, whether fibrosis-related miRNAs are excreted in urine, as well as the changes of miRNA profiles in urine exosomes of CKD patients were unknown. Although miR-192 levels in urine exosomes were markedly increased and decreased as their upregulation and their contents varied significantly from fmol/L to nmol/L. Furthermore, miRNA levels were analyzed by electron microscope, surrounded by a double-layer membrane. CD63, a major marker in exosomes was analyzed by western blot.

Background: Renal fibrosis is an inevitable outcome of chronic kidney disease (CKD). It was reported that various microRNAs regulated the progression of tubulointerstitial fibrosis. However, whether fibrosis-related miRNAs are excreted in urine, as well as the changes of miRNA profiles in urine exosomes of CKD patients were unknown.

Methods: Morning urine specimens were collected from 10 healthy donor and 16 CKD patients, whose renal biopsy showed mild to moderate tubulointerstitial fibrosis. Urine exosomes were isolated from 2ml samples using urine exosome isolation kit and observed by transmission electron microscopy. Quantification of miRNA levels in urine exosomes were determined using strep-loop qRT-PCR followed by real-time PCR. CD63 levels in exosomes were analysis by western blot.

Results: Urinary exosomes appeared as clusters of vesicles of 30-200nm in diameter under electron microscope, surrounded by a double-layer membrane. CD63, a major exosome marker associated with membranes of cellular vesicles, in exosomes isolated from some volume of urine indicated that the excretion of exosomes varied among different people. Moreover, the markedly increased CD63 levels in CKD patients suggested that the excretion rate of exosomes was probably upregulated in CKD patients with renal interstitial fibrosis. Most of previously reported fibrosis-related miRNAs, including miR-21, miR-29 family, miR-30e, miR-102 and miR-200 family were detectable in urine exosomes. However, their contents varied significantly from fmol/L to nmol/L. Furthermore, miRNA levels in urine exosomes were not associated with their levels in kidney. MiR-21 and miR-29c levels in urine exosomes were markedly increased and decreased as their upregulation and downregulation in kidney, respectively. MiR-29b, miR-30e and miR-200b levels in urine exosomes were markedly increased despite their downregulation in kidney. Although miR-192 level in urine exosomes was as large as ~10^(-9)nmol/L, its excretion was not significantly changed in CKD patients as compared with healthy control.

Conclusions: Profiling of miRNA in urine exosomes might indicate renal tubulointerstitial fibrosis in CKD patients.

Funding: Government Support - Non-U.S.

TH-P0716
Glucosuria in Normoglycemic Non-Diabetic Kidney Disease: Not Necessarily due to an Isolated Proximal Tubule Defect
Abdulrahman M. Harndah, Kameel A. Gharibaei, Samih H. Nasr, Nelson Leung. Nephrology and Hypertension, Mayo Clinic, MN.

Background: In the absence of hyperglycemia, glucosuria has been classically attributed to either a global dysfunction of the proximal tubule known as the Fanconi syndrome, or familiar renal glucosuria which includes inherited defects in the genes that encode the glucose handling kidney transporters. We have investigated the clinical observation that glucosuria is common in other kidney disease entities.

Methods: We analyzed the data for adult patients with native kidney biopsy between January 2014 and January 2015 at our institution that had concurrent urinalysis. We identified the patients who had glucosuria on urinalysis, in the absence of concurrent hyperglycemia (serum glucose > 180 mg/dL) or diabetes and were excluded from the analysis. The remaining sub-group of 44 (67 %) patients had a median age of 58 (19-81 years), 43 % were women, and 81 % were Caucasian. Median urinary glucose was 40 mg/dL (range 16-236). Concurrent serum glucose for this group showed a median of 101 mg/dL (range 54-149), with 66 % of patients having glucose less than 110 mg/dL. In this sub-group, biopsy findings included 32 (73 %) patients with glomerular disease (most commonly glomerular microangiopathy and pauci-immune crescentic glomerulonephritis), 10 (22 %) tubulointerstitial disease (most commonly acute tubulointerstitial nephritis) and 2 (4%) arteriosclerosis as the predominant features on biopsy.

Results: 186 adult patients with native kidney biopsy had concurrent urinalysis. Sixty six patients (35%) had evidence of glucosuria on urinalysis. Twenty two (33 %) of these patients had either hyperglycemia (serum glucose > 180 mg/dL) or diabetes and were excluded from the analysis. The remaining sub-group of 44 (67 %) patients had a median age of 58 (19-81 years), 43 % were women, and 81 % were Caucasian. Median urinary glucose was 40 mg/dL (range 16-236). Concurrent serum glucose for this group showed a median of 101 mg/dL (range 54-149), with 66 % of patients having glucose less than 110 mg/dL. In this sub-group, biopsy findings included 32 (73 %) patients with glomerular disease (most commonly glomerular microangiopathy and pauci-immune crescentic glomerulonephritis), 10 (22 %) tubulointerstitial disease (most commonly acute tubulointerstitial nephritis) and 2 (4%) arteriosclerosis as the predominant features on biopsy. No evidence of proximal tubule dysfunction was found amongst this group.

Conclusions: Glucosuria in the absence of hyperglycemia and diabetes, although classically associated with isolated proximal tubule dysfunction, is common in other kidney diseases and is a frequent occurrence in glomerular disease, which likely reflects a degree of secondary tubular injury. Future delineation of the pathophysiology of this observation may improve the understanding of tubular function in glomerular disease.

TH-P0717
Severe Interstitial Fibrosis Can Be a Predictor of Renal Function in Patients with Lupus Nephritis, Especially in Cases With the International Society of Nephrology/Renal Pathology Society Class IV
Daisuke Honda, Kisara Onda-Tsueshita, Isao Ohsawa, Hiroyuki Inoshita, Satoshi Horikoshi, Yasuhiko Tomine. Div of Nephrology, Dept of Internal Medicine, Juntendo Univ Faculty of Medicine, Tokyo, Japan.

Background: The ISN/RPS classification of lupus nephritis (LN) pays little attention to the interstitial injuries. We explored the association between irreversible interstitial fibrosis and renal function in patients with LN, especially in class IV cases that have not been thoroughly examined in this aspect. Methods: Forty-three patients of LN were enrolled in this study. All patients were classified into the ISN/RPS classification and were divided into 4 groups according to interstitial fibrosis extent (no, 0%; mild, 1-25%; moderate, 26-50% and severe, more than 50% fibrosis of the interstitial area, n = 8, 16, 11 and 8, respectively). All 8 patients with severe fibrosis were classified in class IV. Blood and urine analysis was evaluated at the time of renal biopsy. We compared the data according to both categorizations in all patients, and in only class IV cases (n = 23).

Results: In each class categorized with the ISN/RPS classification, renal function showed no significant difference. When all patients were classified according to interstitial fibrosis severity, their renal function at the time of renal biopsy showed no significant difference. However, renal function with severe fibrosis at the last follow-up period was significantly worse than those in the other fibrosis groups (sUN, p < 0.01; sCr, p < 0.05; and eGFR, p < 0.05). Moreover, when we examined only class IV patients, renal function in patients with severe fibrosis at the last follow-up period was significantly worse than those in the other fibrosis groups (sUN, p < 0.01; sCr, p < 0.05; and eGFR, p < 0.01). On the other hand, the serological activities of systemic lupus erythematosus (SLE) significantly improved under all categorizations.

Conclusions: We conclude that severe renal interstitial fibrosis can be a predictor of renal function in patients with LN, independent of glomerular lesions and the serological activities of SLE, especially in cases with ISN/RPS class IV.

TH-P0718
Correlating Biophysical Structure Characteristics with Diagnosis and Phenotypic Severity in Complement-Mediated Renal Disease

Background: Rare genetic variations in the C3, CFH, and CFB genes may lead to dysregulation of the alternative pathway of the human complement system, altering the innate immune response associated with complement activation. The phenotypic consequence includes the thrombotic microangiopathies (TMA) and C3 glomerulopathies (C3G).

Methods: In this study, we compared variants identified in TMA patients to variants identified in C3G patients. Each variant was analyzed in a pipeline that included structural optimization of the wild type and mutant proteins based on molecular mechanics calculations. Initially, the wild type protein structure was optimized using the polarizable AMOEBA force field and dead-end elimination techniques. Each variant was then individually introduced to the wild type structure, which was then re-optimized. Both wild type and mutant models were analyzed in molecular dynamic simulations and differences between wild type and variant free energies were calculated.

Results: Overall, for each variant we were able to obtain both: 1) qualitative data describing location and interactions; and 2) quantitative changes to protein conformation and stability relative to the wild type baseline. From these data, we were able to create a spectrum of free energy changes correlating to disease severity and enhance our interpretation of rare and novel variants, as well as identify biophysical characteristics specific to TMA and C3G.

Conclusions: These methods allow us to understand the biophysical consequences of even variant, predict the phenotypic severity of novel variants, and ultimately inform patient diagnosis.

TH-P0719
Urinary EFG is Associated with Interstitial Fibrosis and Tubular Atrophy in Proteinuric Patients
Wenjun Ju, Vij Nair, Michelle R. Smith, S.M. Bagnasco, L. Barisoni, Matthias Kretzler. 1Medicine, Univ of Michigan, Ann Arbor, MI; 2Pathology, The Johns Hopkins School of Medicine, Baltimore, MD; 3Pathology, Univ of Miami, Miami, FL.

Background: Interstitial fibrosis (IF) and tubulointerstitial atrophy (TA) are key morphologic determinants of progression and strong predictors for renal outcome. However, their broader clinical application is limited by the invasiveness of the kidney biopsy procedure. Nephrologists routinely use biomarkers of IF/TA to not only guide treatment but also to drive intervention based on disease activity.

Methods: We used a bioinformatic approach identified EFG as a predictor of kidney function, and urine EFG (uEFG) improved prediction of renal outcome by glomerular filtration rate (GFR) and albuminuria. EFG’s expression is limited to tubule epithelium and its role in epithelial cell regeneration suggests that the improved prediction might be driven by detection in urine exosomes with chronic tubulointerstitial damage (c-TID).

Conclusions: Here we investigate the correlation between uEFG and TID, reflected by the % of cortex affected by IF/TA, and whether uEFG can predict c-TID in adult patients of the NEPTUNE cohort.
Methods: Whole slide images of glass slides stained with Silver, Trichrome and PAS from formalin fixed, paraffin embedded (FFPE) tissue was scored blinded for glomerular mesangial matrix expansion. The score was calculated as the percentage of glomeruli with 2+ or more (0-100)

Results: The assays using silver staining gave a good correlation (r=0.75) with the positive control, while for the PAS stained sections the correlation was lower (r=0.60).

Conclusions: Our study shows that staining formalin-fixed, paraffin-embedded tissue is feasible and that the results are in line with a positive control. However, the results for the PAS stained sections were lower than for the silver stained sections, which might indicate that the PAS staining is less sensitive for detecting mesangial matrix expansion.

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

Underline represents presenting author.

255A
TH-PO725

Long-Term Outcome in Glomerulonephritides with Organized Micritubular Monoclonal Deposits (IMMOMID): A Case Series of 25 Patients

Le Dufour Y.1, Vincent Javouhé, Guy Touchard, Frank Bréix,1
1Nephrology, Hospital, Poitiers, France; 2Anatomopathology, Hospital, Poitiers, France; 3Hematology; hospital Saint Louis, Paris, France.

Background: Glomerulonephritis (GN) with organized micritubular monoclonal deposits (GOMMID), also referred to immunotoxid glomerulopathy, is a rare entity distinct from fibrillary GN and type I cryoglobulinemic GN. Treatment and outcome in GOMMID remain poorly described.

Methods: Twenty-five adults (17 men, median age: 61 years) from 21 nephrology departments were retrospectively studied. Inclusion criteria were: Congo Red-negative, monotypic IgG glomerular deposits, with micritubular organization (10-60 nm in external diameter) by electron microscopy (EM), without pathological criteria for cryoglobulinemic GN.

Results: Renal manifestations included: constant proteinuria (median: 6.0 g/d), nephrotic syndrome (72%), microscopic hematuria (79%), hypertension (79%), median serum creatinine: 130 µmol/L. Biopsy proven extrarenal manifestations in 2 cases (mononeuritis, nodular hydropneuritis). Eighteen patients had a serum and/or urinal monoclonal component, 12 had a lymphoproliferative disorder (chronic lymphocytic leukemia (CLL): n=6; lymphocytic B cell lymphoma n=3). Kidney biopsy showed atypical membranous GN (n=14) or membranoproliferative GN (n=11), with IgG deposits: IgG1 (n=8/15), IgG2 (n=5/15), IgG3 (n=2/15), mostly kappa (n=15/25). By EM, micritubule mean diameter was 15.6 nm. Intracytoplasmic lymphocytic micritubular inclusions were observed in n=4/11 (CLL n=3, lymphocytic B cell lymphoma n=1). Twenty-one patients received chemotherapy based on alkylating agent (n=17) and/or rituximab (n=6). Renal response occurred in 15 cases (71%), associated with hematological response in 9 evaluable cases. Eleven patients received a second line of chemotherapy. After a median follow-up of 45 months, 17 patients had a persistent renal response, 3 had reached end-stage renal disease and 5 had died.

Conclusions: GOMMID should be suspected in patients with glomerular disease in the context of CLL or lymphocytic B cell lymphoma. Early chemotherapy, adapted to the underlying B-cell clone, is associated with a favorable renal outcome in 68% of patients.

TH-PO726

PLA2R-Related Membranous Nephropathy in a Patient with Mannan-Binding lectin Deficiency

Stéphane Bally,1 Hanna Debecque,2 Chantal Dumestre,2 Franck Dumestre,2 Jean Rendu,2 Pierre M. Ronco,2 Denise Ponard,1
1Nephrology and Dialysis, CHU Chambéry, Chambéry, France; 2UMR S1155, INSERM, Paris, France; 3Immunology Laboratory, CHU Grenoble, Grenoble, France; 4Pathology Center, Hôpitaux de Lyon, Lyon, France; 5Biochemistry and Molecular Genetics laboratory, CHU Grenoble, Grenoble, France.

Background: About 75% of patients with primary membranous nephropathy (MN) have autoantibodies against phospholipase A2 receptor (PLA2R), predominantly of IgG4 subclass. C3 and C5b-9 occur in glomerular immune deposits, implicating complement activation as a putative effector mechanism. It was also shown that purified anti-PLA2R IgG4 could activate the mannose binding lectin (MBL) pathway, but the respective role of the three pathways of complement activation remains elusive. Here we report the case of a patient with PLA2R related MN and MBL deficiency who developed MN.

Methods: Kidney biopsy specimens were evaluated for staining for PLA2R, IgG subclasses, and various complement components, including C3, C1q, C4d, factor B, properdin and C5b-9. MBL concentration was assayed by ELISA and its activity was measured from C4 cleavage. Polymorphisms in exon 1 and in the promoter region for MBL2 were detected by direct sequencing.

Results: Kidney biopsy showed MN with intense staining for PLA2R, IgG4, C3, factor B, properdin and C5b-9 and weak staining for C1q, IgG1 and C4d within the subepithelial deposits. Exploration of the lectin pathway revealed a severe MBL quantitative and functional deficiency (concentration 12 µg/mL, normal range 30-3000 µg/mL; and activity < 10% normal range 35-135%). Genotyping revealed a 57 (A/C) heterozygous polymorphism in codon 57 of exon 1 associated with homozygous and heterozygous variation at -550 (L/L) and -221 (X/Y) respectively in the promoter region, suggesting that the patient harbours a monotypic IgG glomerular deposits, with microtubular organization (10-60 nm in external diameter) by electron microscopy (EM), without pathological criteria for cryoglobulinemic GN. The cause of relapse after RTX treatment seemed to be the result of the underlying B-cell clone, is associated with a favorable renal outcome in 68% of patients.
Results: Significant interstitial fibrosis and accumulation of CD68+ MØ was evident in all progressive disease groups. Most interstitial CD68+ MØ co-expressed CD163 (89-99%). By contrast, CD163 expression by glomerular CD68+ MØ varied from 20% across the progressive disease groups, indicating much greater heterogeneity of M1/M2 phenotypes in this compartment. Interstitial CD163+ M2-type MØ correlated with the degree of interstitial fibrosis in each type of progressive renal disease (all p<0.01), with proteinuria in IgAN (p=0.009), HSPN, and LN (p<0.01), and with kidney function in CAI (p=0.001). In addition, CD133+ MØ co-localized in fibrotic lesions with excess type I collagen deposition. In vitro studies showed that dexamethasone (Dex) up-regulated CD163 expression by MØ, and that Dex plus oxidized LDL increased MØ production of pro-fibrotic factors (FGF-1, FGF-2, TGF-β1, CTGF).

Conclusions: Our study identifies CD163+ M2-type MØ as the main MØ population associated with interstitial fibrosis across a range of progressive forms of kidney disease, suggesting a functional role for this MØ subset in renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO727

Increased Urinary Angiotensinogen Is Associated with Crescent Formation in Initial Stage of Henoch Schönlein Purpura Nephritis

Yanie Huang, Xiaoming Yang. Dept of Pediatrics, The First Affiliated Hospital of Henan Univ of Traditional Chinese Medicine, Zhengzhou, Henan, China.

Background: To investigate the relative factors of increased urinary angiotensinogen (uAGT) in children with Henoch Schönlein Purpura Nephritis (HSPN).

Methods: The severity of histopathological changes in HSPN is classified by the International Study of Kidney Disease in Children (ISKDC) into six categories: grade I-VI. 85 impatient children with HSPN were undertaken renal biopsy in our hospital from 2014 June to 2015 March, and their histopathological changes included grade II (mesangial proliferation, n=21) and grade III (a focal or b diffuse mesangial proliferation or sclerosis with <50% crescents, n=64). The grade III was again divided into IIIa (n=39) and IIIb (n=25) groups, IIIa25% crescent (n=52) and IIIb-25% crescent (n=12) groups. Morning urine and serum of HSPN patients were collected on the day before renal biopsy. The levels of AGT and collagen type IV (CL-IV) in urinary and serum were detected using ELISA method. The urinary microalbuminuria and IgG levels were measured using immunoturbidimetric method. All indexes mentioned above were corrected with urine creatinine ratio.

Results: The serum AGT and CL-IV concentration had no significant difference among different groups. The AGT was higher in grade III (30.13±13.69ug/gCr) than grade II (23.31±13.69ug/gCr). The urine AGT concentration was significantly different between grade IIIa (30.13±13.69ug/gCr) and grade IIIb (13.69±13.69ug/gCr) groups. The uAGT levels were higher in grade III (30.13±13.69ug/gCr), and also higher in grade IIIb (23.31±13.69ug/gCr) than gradeII (13.69±13.69ug/gCr), ±1.7 vs. complication, 10.1±3.0, respectively. The only factor predictive of a complication in the TRB was pre-TRB Hgb (p=0.001). The ROC curve analysis revealed an area under curve of 0.68 (0.55-0.81) and 0.68 [0.57-0.80] predicting positive T and S scores from IgG autoantibody levels. Gd-IgA1 levels were not associated with any histological pattern.

Conclusions: IgG autoantibody levels correlated with GOS and predicted positive S and T scores according to Oxford classification in IgAN.

TH-PO731

Comparison of Native and Transplant Percutaneous Renal Biopsy: Safety and Diagnostic Yield


Background: No prospective studies exist which directly compare the safety and adequacy of the percutaneous native (NRB) and transplant (TRB) renal biopsy. We report a large single-center prospective series comparing the success and complication rate of NRB and TRB over a twenty year period.

Methods: From 01/1995 to 04/2015, 1,705 adult pts underwent NRB (N=767) or TRB (N=938) by a Nephrology attending or fellow. Data were collected prospectively in all biopsies. Real-time US guidance and automated needles were used for all biopsies. NRB was performed with either a 14 or 16 gauge needle while TRB was with a 16 gauge needle. All NRB pts were observed in the hospital for at least 24 hours and TRB pts for at least 3 days. Complications were defined by the need for an intervention (i.e. transfusion, surgery or embolization), readmission, or death.

Results: In the time period of reported, the TRB pts were younger (47±17 vs. 50±14 years, p<0.001) and more often female (62 vs. 48%, p<0.0001) compared to TRB. TRB pts had higher blood pressure (systolic BP: 140±22 vs. 133±18 mmHg, p<0.0001), higher serum creatinine (3.1±1.8 vs. 2.3±2.2 mg/dl, p<0.0001), increased aPTT (28±4 vs. 27±3 seconds, p<0.0001), and lower platelet count as well as lower Hgb (11±2.6 vs. 11±1.7 g/dl, p<0.0001) compared to NRB. A fellow performed the biopsy in 91% of NRB compared to 63% of TRB (p<0.0001). Adequate tissue for diagnosis was obtained in 99% of NRB and TRB (p=0.71). Total number of glomeruli on light and immunofluorescence microscopy was 33±17 for TRB and 31±13 for NRB (p=0.11). The only factor predictive of a complication in the NRB was the presence of high grade disease (no complication, 11.2±1.7 vs. complication, 10.1±1.7 g/dl, p<0.0001). Compared to TRB pts, NRB pts had a greater drop in Hgb after PRB (0.97±1.7 vs. 0.73±1.3 g/dl, p<0.0001), had more complications (6.5 vs. 3.9%, p<0.02) and/or transfusions (5.2 vs. 3.3%, p=0.045).

Conclusions: The NRB and TRB remain successful and safe procedures. There are more complications with NRB compared to TRB despite TRB having more risk factors. Differences in technique, operator (fellow or attending), or needle size may explain this variability.
Serum Immunoglobulin E Level Is Associated with Renal Progression in Immunoglobulin A Nephropathy

Shin yeong Jeong, Jie sug Kim, Sang hee Lee, Se yun Kim, Yu ho Lee, Kyung-wn Jeong, Tae won Lee, Ji hoong Lee, Yang gyun Kim, Young moo Moon, Chn-gyoo Ihm. Dept of Nephrology, Kyung Hee Univ Medical Center, Seoul, Korea.

Background: Studies reported that serum Immunoglobulin E (IgE) levels are associated with progression in IgAN and suggested IgE levels as a prognostic indicator in IgAN. The aim of this study is to explore the association between plasma IgE levels of IgAN patients and renal outcome.

Methods: This study is an observational study of IgAN patients undergoing kidney biopsy between 1995 and 2012. We collected the data of patient’s demographics and serum IgE levels from routine laboratory examination results. We retrospectively analyzed the correlation between serum IgE level and clinical parameters and pathologic findings. We defined renal progression if patient meets the following criteria: 1) negative value of delta estimated glomerular filtration rate (eGFR) (ml/min/1.73m2/months) and 2) a rise in serum creatinine (SCr) of >0.3 mg/dL.

Results: A total of 117 patients were included. The mean level of initial eGFR and serum IgE were 84.79±37.3ml/min/1.73m2 and 304±607IU/mL. The duration in glomerular stages using the H. S. Lee grading was as follows: grade 1, 28 patients (23.9%); grade II, 62 patients (53%); grade III, 19 patients (16.2%); grade IV, 6 patients; grade V, 1 patient. Of the 117 patients, twenty-two (22%) had renal progression. Serum IgE level was significantly high in high progression group compared to nonprogressive group (590±1247 vs. 238±290, p=0.014). Gender (76% vs 50%, p=0.011) and history of gross hematuria (9% vs 29%, p=0.024) were significant difference between high and low IgE group. But no significant differences were seen for delta SCr, delta eGFR, delta proteinuria, and serum IgE were 84.79±37.3ml/min/1.73m2 and 304±607IU/mL.

Conclusions: These results suggested that serum IgE level is probably associated with renal progression in IgAN patients. Further studies are needed to elucidate immunopathogenesis of the increased IgE level in IgAN.

Novel Monoclonal Antibody KM55 Specifically Detected Glomerular Galactose-Deficient IgA1 in Patients with IgA Nephropathy

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Background: Galactose-deficient IgA1 (Gd-IgA1) and immunoglobulins were performed with KM55 and anti-immunoglobulin polyclonal antibodies in paraffin embedded sections of renal biopsy specimens from patients with IgAN (n=16), and other renal diseases (n=19), such as lupus nephritis and membranous nephritis. Area of glomerular deposits (Gd-IgA1 and immunoglobulins) were semi-quantitated by spectral imaging using Nuance software.

Results: Glomerular Gd-IgA1 was specifically detected in all patients with IgAN, but not in those with other renal diseases. Gd-IgA1 could not be detected even in patients with lupus nephritis, whose glomerular IgA was positive. In patients with IgAN, immunofluorescence with KM55 revealed diffuse and global glomerular staining of Gd-IgA1. Moreover, double staining of Gd-IgA1 and IgA showed that Gd-IgA1 was localized predominantly in the mesangial region; however the localization of IgA was similar to that of Gd-IgA1 but was more broadly observed.

Conclusions: This is the first observation to clearly reveal that Gd-IgA1 could be specifically detected in glomeruli of IgAN, strongly supporting the pathophysiological function of Gd-IgA1 in patients with IgAN. Further studies are necessary to clarify the underlying mechanisms of Gd-IgA1 deposition and its contribution to renal injuries in IgAN. Novel monoclonal antibody KM55 against galactose-deficient IgA1 could be a powerful tool to detect nephritogenic IgA in patients with IgAN.

Cryoglobulinemic Glomerulonephritis: A Single-Center Experience

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Background: Cryoglobulinemic glomerulonephritis (CryoGN) is a recognized form of glomerulonephritis. However, the clinical characteristics are not well-established due to lack of large studies with biopsy and serological confirmation. We present our experience with 42 cases of serologically and biopsy-proven CryoGN.

Methods: We conducted a retrospective search for patients with cryoglobulinemia and kidney biopsy and identified patients with CryoGN.

Results: From 2000 to 2014, we identified 569 patients with cryoglobulinemia. Of the 71 patients who underwent kidney biopsy for kidney dysfunction, 43 (59%) had CryoGN, the remaining included other pathology, including interstitial nephritis, lupus nephritis, fibriobulin GN and amyloidosis. Median age of CryoGN patients was 59 yrs; male/female ratio, 23:19. Median eGFR by MDRD equation was 41ml/min/1.73m2 at onset. 88% had nephritic syndrome and rest had nephrotic syndrome. 74% had Type II, 19% Type I and 7% Type III cryoglobulinemia. Hypocomplementememia was present in 83%, 76% had skin involvement, 16% had joint symptoms, 14% had nephropathy and 1% had pulmonary involvement. 4 patients required dialysis. Etiology of cryoglobulinemia was a hematological disorder in 40% (of which 88% lymphoproliferative and 12% MGRS) and hepatitis C in 26% patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
80% patients received immunosuppression for treatment, 54% receiving Rituximab. Median duration of follow up was 18 months. Median overall survival was 36.4 months. At 6 months, median gFR improved to 48ml/min.17.73m2.

Conclusions: Though CryoGN is the most common pathology in cryoglobulinemia, a wide array of other lesions is seen. Most patients with CryoGN have skin lesions while other systemic features of cryoglobulinemia are rare. In this study hematological disorders were the commonest etiology for CryoGN followed by hepatic C infection.

TH-PO737

The Clinicopathological Impact of Medullary Ray Injury on Early Stage Renal Allografts


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Background: Interstitial fibrosis and tubular atrophy (IF/TA) constitute an important cause of renal graft loss. Previously, we examined medullary ray injury (MRI) inducing IF/TA via non-immunological mechanisms, classifying the etiology of MRI into calcineurin inhibitor (CNI) toxicity (32.8%), vesicoureteral reflux (50%), and urinary tract infection (8.6%) (Pathol Int. 2010;60:744–9). However, we did not examine the influence of the etiology on the long-term renal allograft prognosis, since the timing of the biopsies differed among the cases. Herein, we focused on MRI observed in protocol biopsies within 3 months, examining the influence on the renal allograft prognosis.

Methods: Retrospectively, we divided 53 protocol biopsies within 3 months into two groups with (n=34) and without (n=19) MRI. The MRI+ cases with isometric vacuolization and ash in the Banff classification were classified as CNI toxicity (MRI+CNI); the cases with Tamm-Horsfall protein casts in the interstitium and thyroid-like appearance were classified as urinary tract system abnormalities (MRI+UT); and the remaining cases as others. We compared the annual change in serum creatinine (scr) levels over 3 years and the extent of fibrosis (cr/c) at the 1-year biopsies. Cases with rejection were excluded.

Results: The cr/c levels were higher in both the MRI+ group than the MRI− group at 3 years (p=0.024). Examining three MRI+ subgroups, only MRI+UT had significantly high cr/c levels compared to the MRI− group (p=0.019). The observation of IF/TA in the base-line and 1-year biopsies in the MRI+ group indicated the significant development of IF/TA.

Conclusions: Cases developing MRI within 3 months after kidney transplantation were significantly more likely to develop IF/TA at the 1-year biopsies. These cases had higher cr/c levels at 3 years. In the cases with MRI in the base-line biopsies, interventions might preserve kidney graft function over the long-term.

TH-PO738

Diagnostic Gene Signature from Urinary Extracellular Vesicles Can Be Used as Biomarker for Non-Invasive Diagnosis of Clear Cell Renal Cell Carcinoma

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Background: Clear cell renal cell carcinoma (ccRCC) is one of the most common malignancies and due to its intimate association with urine, it appears well suited for studies to identify non-invasive biomarker in this material. The extracellular vesicles (EV) can be isolated in urine. They transport proteins and nucleic acids that reflect the physiopathological status of renal cells. The purpose of this study has been to analyze the transcripts in the urinary EV from ccRCC patients and to specific transcripts for preventive diagnosis of ccRCC.

Methods: We enrolled 12 patients with a diagnosis of ccRCC undergoing unilateral nephrectomy. We collected pre-intervention urine. A group of healthy volunteers (n=11) were evaluated. Illumina HumanHT-12 v4 BeadChip was used for microarray analyses. Then, by differential centrifugation, total RNA was extracted, quantified and qualitatively assessed in pathways involved in the pathogenesis of cancer as glutathione or arsenate mediated reactions. The dysregulated genes were validated by qRT-PCR in independent cohorts of 12 patients evaluated. The qRT-PCR validated a number of genes modulated in ccRCC patients and we investigated whether the functions of these genes could be related to ccRCC through the pathways analysis. The qRT-PCR validated a number of potential diagnostic biomarkers that could be used to distinguish ccRCC patients at an early stage from healthy individuals. Some potential biomarkers were already present in pathways involved in the pathogenesis of cancer as glutathione or arsenate mediated detoxification instead other biomarkers were new.

Conclusions: Using this approach, we have identified a signature of four transcripts that could be used as biomarkers for non-invasive diagnosis of ccRCC.

TH-PO739

Initial Clinical Trial Results of a Real-Time Point-of-Care Glomerular Filtration Rate Measurement Utilizing a Novel Fluorescent Tracer Agent

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Background: A first-in-human clinical study with MB-102, a fluorescent tracer agent engineered to have photophysical and clearance properties for use as a real-time point-of-care measure of glomerular filtration rate (GFR) is reported. The clearance of this agent can be monitored noninvasively by transdermal fluorescence.

Methods: Blood samples were taken over a period of 12 hours post simultaneous administration of MB-102 and iohexol to assess pharmacokinetic parameters including clearance on 32 subjects recruited to have normal renal function. Urine samples were collected concurrently to assess percent injected dose recovered in the urine. A prototype noninvasive fluorescence detection device was employed to simultaneously measure the transdermal fluorescence from MB-102 to assess correlation with the plasma pharmacokinetics.

Results: The plasma pharmacokinetics displayed the expected 2 compartment model of a vascular-tissue equilibrium phase followed by renal excretion only. The GFR measured from the MB-102 plasma pharmacokinetics matched the GFR measured from iohexol.

The % injected dose of MB-102 appearing in the urine (99±17.7%) matched that of iohexol. The MB-102 time-dependence of the transdermal fluorescence monitored by the prototype device matched that of the plasma (r2=0.98). No significant adverse events were reported.

Conclusions: MB-102 was shown to be a GFR tracer agent in humans from the plasma pharmacokinetic match and the % injected dose in urine match to iohexol. The transdermal fluorescence pharmacokinetics mirrored that of the plasma pharmacokinetics thus demonstrating that the validity of this noninvasive GFR measurement.

Funding: Pharmaceutical Company Support - MediBeacon, LLC.

TH-PO740

Analysis of Exogenous Near Infrared Fluorescent Markers for the Transcutaneous Measurement of Glomerular Filtration Rate

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Background: Recently, we developed approaches for the transcutaneous measurement of GFR in animals. Using fluorescent markers allows GFR assessment without blood and/or urine sampling. Therefore, there is considerable interest in the development of exogenous fluorescence markers for real-time and accurate measurement of GFR via transcutaneous fluorescent methods using new dye conjugates.

Methods: A near infrared (NIR) cyanine was synthesized by a five-step synthetic procedure. This dye was used to label (2-hydroxypropyl)-β-cyclodextrin. The chemical structure was fully confirmed by H-NMR, 13C-NMR, and HRMS spectra. Optical properties were characterized by UV-2450 spectrophotometer and fluorescence spectrometer. The percent plasma protein binding (PPB) was determined by equilibrium dialysis of fluorescent marker solutions incubated with rat plasma using a two-chamber dialysis set-up. Elimination half-life was determined in combination with a miniaturized new electronic device for
the transcutaneous fluorescence detection in freely moving rats. Recovery rate in urine was measured in conscious rats after intravenous injection using metabolic cages. Mean ± S.D are given.

Results: The NIR marker was synthesized in a high yield. It exhibits good water solubility with concentrations reaching more than 200 mg/mL with a molecular weight ranging from 1.3 to 2700 Da. In addition, it is associated with low plasma PPI 4% ± 10%, which is clearly lower than that of isothalamate (9.5%). The excitation and emission are 705 nm and 790 nm respectively providing low background and high tissue penetration for in vivo application. The noninvasive real-time monitoring of clearance resulted in a half-life of 4.4 ± 0.6 min and 34.9 ± 6.8 min without and with probenecid treatment, respectively. A high urinary recovery of the marker with 99 ± 7.3% of the dose given was observed within 24 h.

Conclusions: We identified the marker with a high potential as exogenous fluorescent tracer for GFR measurement. A patent has been filed.

Funding: Government Support - Non-U.S.

TH-PO741

Phospholipase A2 Receptor Antibodies in Membranous Nephropathy: Biopsy, Serum and Urine Findings


Background: The major target antigen in Membranous Nephropathy (MN) is the phospholipase A2 receptor (PLA2R), its exact role is not yet fully understood. In this retrospective study we examined the presence of PLA2R in biopsy tissue, PLA2R antibodies in serum and urine of patients with MN, and aimed to identify associated clinical variables. Of 128 MN patients, 44 were identified from 2008 - 2014. 74 with idiopathic MN (iMN); 12 secondary MN; 9 recurrent MN post transplantation; 25 class V lupus MN (LMN). 27 controls with other GN were also used. Immunofluorescence (IF) for PLA2R was performed on paraffin embedded biopsies and ELISA (EUROIMMUN) for the detection of PLA2R antibodies in serum and urine.

Results: In the iMN group 35/74 (47%) biopsies stained positive, 30 (40%) negative and 9 (12%) borderline. Circulating PLA2R antibodies were detected in sera from 30/74 (40%) patients within 6 months from biopsy, all of whom had positive or borderline staining on biopsy. In the secondary MN group 5/12 stained positive, 1 had a detectable PLA2R antibody. In the transplant cohort 3/9 stained positive; 1 had a positive serum. Of 25 class V LMN, 3 stained positive and 1 had a positive serum antibody. There was no correlation between staining or the level of PLA2R antibody with proteinuria or creatinine at the time of biopsy; however a longitudinal study to assess the variations of PLA2R levels with clinical outcomes is in progress. The presence of PLA2R antibodies in urine of patients with active disease is interesting although further studies are required to determine whether this is due to nonspecific proteinuria.

Conclusions: Our data suggest that IF for PLA2R in biopsy tissue is more sensitive than serum testing for the presence of PLA2R antibodies. This cross sectional study did not demonstrate a correlation between PLA2R antibodies and proteinuria or creatinine at the time of biopsy; however a longitudinal study to assess the variations of PLA2R levels with clinical outcomes is in progress. The presence of PLA2R antibodies in urine of patients with active disease is interesting although further studies are required to determine whether this is due to nonspecific proteinuria.

Funding: GlaxoSmithKline plc

TH-PO742

Belimumab in Idiopathic Membranous Nephropathy: An Interim Analysis of Exploratory Biomarkers Including Anti-PLA2R Autoantibodies

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Background: Belimumab, a B-lymphocyte stimulator (BLyS)-specific inhibitor has been shown to reduce anti-phospholipase A2 receptor (PLA2R) autoantibodies and anti-PLA2R autoantibodies in serum and urine of patients with MN and proteinuria>1 g/day, of which 21 had typical granular deposition along the basement membrane (iMN cases); the 6 other had mesangial deposits without a diagnosed secondary cause of MN. Serum anti-PLA2R was assessed by ELISA (euroimmun, Germany).

Results: 21/108 patients had anti-PLA2R >9 RU/mL, all of them had iMN. Among patients with MN and proteinuria>1 g/day, 19/27 had anti-PLA2R >9 RU/mL. The area under the ROC curve (AU-ROC) of anti-PLA2R was 0.87 (95%, CI: 0.78-0.96) when cases of MN and proteinuria>1 g/day were compared vs. other cases. At a cutoff of 9 RU/mL, sensitivity and specificity were 70% and 99% respectively. When we predefined cases of iMN presence of mesangial deposits as probably not idiopathic, the AU-ROC was 0.95 (95%, CI: 0.87-1.00). In this analysis, at the cutoff of 9 RU/mL, the sensitivity and specificity were 91% and 99% respectively. All clinically diagnosed MN that had mesangial immune complex deposition were negative for Anti-PLA2R.

Conclusions: Anti-PLA2R levels had an excellent diagnostic performance to detect iMN. Anti-PLA2R >9 RU/mL may be sufficient to diagnose iMN precluding the need of a renal biopsy.

TH-PO743

Diagnostic Performance of M-Type Phospholipase A2 Receptors Autoantibodies (Anti-PLA2R) for the Differentiation of Idiopathic Membranous Nephropathy (iMN) without Mesangial Immunocomplexes in Kidney Biopsy

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Background: The presence of mesangial immune complexes in membranous nephropathy without an apparent cause constitutes a controversial element and has been considered a potential indicator of an unidentified secondary cause. The value of anti-PLA2R for diagnosis of iMN and for this specific purpose has not been assessed. Objective: Assess the diagnostic performance of anti-PLA2R to differentiate iMN (without mesangial deposits) and MN with presence of mesangial deposits as well as from other glomerulonephritides (GM).

Methods: We prospectively enrolled 108 cases with biopsy proven GM: 40 iMN, 33 systemic lupus erythematosus (23 with proteinuria >1 g/day), and other. In 27 MN, we found proteinuria>1 g/day, of which 21 had typical granular deposition along the basement membrane (iMN cases); the 6 other had mesangial deposits without a diagnosed secondary cause of MN. Serum anti-PLA2R was assessed by ELISA (euroimmun, Germany).

Results: 21/108 patients had anti-PLA2R >9 RU/mL, all of them had iMN. Among patients with MN and proteinuria>1 g/day, 19/27 had anti-PLA2R >9 RU/mL. The area under the ROC curve (AU-ROC) of anti-PLA2R was 0.87 (95%, CI: 0.78-0.96) when cases of MN and proteinuria>1 g/day were compared vs. other cases. At a cutoff of 9 RU/mL, sensitivity and specificity were 70% and 99% respectively. When we predefined cases of iMN presence of mesangial deposits as probably not idiopathic, the AU-ROC was 0.95 (95%, CI: 0.87-1.00). In this analysis, at the cutoff of 9 RU/mL, the sensitivity and specificity were 91% and 99% respectively. All clinically diagnosed MN that had mesangial immune complex deposition were negative for Anti-PLA2R.

Conclusions: Anti-PLA2R levels had an excellent diagnostic performance to detect iMN. Anti-PLA2R >9 RU/mL may be sufficient to diagnose iMN precluding the need of a renal biopsy.

TH-PO744

Declining Renal Function in Idiopathic Membranous Nephropathy: A Report from Two Tertiary London Renal Units

Sanjana Gupta,1 Kieran Mccafferty,2 Horia Stanescu,1 Stephen H. Powis,1 Alan D. Salama,1 John Connolly,2 Stephen B. Walsh,1 Robert Kleta,1 Muhammad M. Yaqoob,2 Neil Ashman.1 "UCL Centre for Nephrology; Royal London Hospital.

Background: Idiopathic Membranous Nephropathy (iMN) is a major cause of nephrotic syndrome in adults. Renal function may deteriorate (progressor) or be preserved (non-progression).

Methods: We performed a retrospective analysis of patients with biopsy proven iMN between 2000-2015.

Results: We identified 188 patients with biopsy proven iMN.

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<tr>
<th>Ethnicity (White / Black / Asian / Unknown) %</th>
<th>Male %</th>
<th>Renal replacement therapy %</th>
<th>Spontaneous remission %</th>
<th>Renal replacement therapy %</th>
<th>Median age</th>
<th>Diuresis (95%CI)</th>
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<td>48 / 17 / 24 / 11</td>
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<td>58 (44-71)</td>
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20% of patients were progressors (increase in sCr >50%, no RRT). There was no statistical difference between sCr (101 ± 6 vs 92 ± 9 μmol/L), sAlb (25.2 ± 1.3 vs 26.2 ± 0.8 mmol/L, μmol/L) or PCR (893 ± 87 vs 895 ± 94, μmol/L) at diagnosis between progressors and non-progression, respectively. Progressors were more likely to be Asian (36% vs 21%, p=0.058) and non-progressors black (32% vs 20%, p=0.058). Of the 37 patients that spontaneously remitted, 5% relapsed. 65% of patients were treated with immunosuppressives. 60% received prednisolone, the most used first line agent was cyclophosphamide 35%, then azathioprine 34% and calcineurin inhibitors (CNI) 23%. There was a significant difference between treatment between progressors and non-progressors; progressors were treated with CNI (38% vs 15%, p=0.04). Rituximab was used 3 times. The complication rate from immunosuppression was 25%. The most common was diabetes from steroid therapy at 10%. Infection occurred in 2% and drug specific complications in 7%. Thromboembolism rate from nephropathy was low at 14%.

Conclusions: At diagnosis there was no significant difference in sCr, sAlb or PCR between progressors and non-progressors. Progressor patients with iMN may benefit from aggressive immunosuppression, but this must be balanced with risks. It is important to identify progressor patients; there is an unmet need for a biomarker to do this.
Interstitial lymphocyte infiltration and EGC formation may be pathologically related to prednisone (1 mg/kg/d) and/or immunosuppressant (cyclophosphamide or cyclosporine), IgG1 (55%), IgG3 (50%) but not IgG2. Most patients showed clinical improvement on Pathologically, 17 (40.5%) cases had atypical MN, featured by mesangial electron-dense and hypocomplementemia were present in 26.8% and 20.5% patients respectively. 

TH-0746
42 Cases of Primary Sjögren Syndrome with Membranous Nephropathy: Clinical Pathophysiologic Features and Ectopic Germinal Center Formation
Menyou Zhou, Yubing Wen, Jing Wang, Xiaoxiao Shi, Yang Yu, Han Li, Mingxi Li, Xuemei Li, Xuewang Lee, Limeng Chen. Dept of Nephrology, Peking University Medical College Hospital, Beijing, China.

Background: To study the clinical pathophysiologic features of primary Sjögren Syndrome (pSS) with membranous nephropathy (MN) from a single hospital center. Pathogenesis including the formation of ectopic germinal center (EGC) was explored.

Methods: From 1990 to 2014 in Peking University Medical College Hospital, all pSS patients who underwent renal biopsy with a diagnosis of MN were reviewed. CD21 immunohistochmetry study was used to characterize EGC formation.

Results: Among 154 pSS patients with a renal biopsy, 94 (61%) were diagnosed with glomerulonephritis, and 60 (45%) cases of MN. The majority were female (76.2%) with an age of 52.3±15.0 years. At the time of renal biopsy, the patients presented with microscopic hematuria (80.9%), proteinuria (4.57±3.11g/24h), hypalbuminemia (26.5±7.3 g/L) with normal eGFR (92.8±26.3 mL/min). Hypergammoglobulinemia and hypocomplementemia were present in 26.8% and 20.5% patients respectively. Pathologically, 17 (40.5%) cases had atypical MN, featured by mesangial electron-dense deposit or Cq staining. On immunofluorescence study, C3 was positive in 43.9% cases and C4q staining positive in 34.1%. IgG subtype staining showed positive of IgG4 (95%), IgG1 (55%), IgG3 (50%) but not IgG2. Most patients showed clinical improvement on prednisone (1mg/kg/d) and/or immunosuppressant (cyclophosphamide or cyclosporine), while 2 patients had progression of CKD with persistent or recurrent proteinuria. CD21 staining on 36 available biopsy samples revealed the presence of EGC in 11 (31.4%) cases, and EGCs were notably abutting or surrounding the glomeruli in 7 cases. Grading of individual lymphoid infiltration revealed the percentage of GO (absent), GI (scattered), G2 (focal) and G3 (EGC formation) to be 5.7%, 34.3%, 26.8% and 31.4%, respectively, which was negatively correlated with eGFR (p<0.008) and positively correlated with glomerulosclerosis index (p=0.001).

Conclusions: MN is the most common type of glomerulonephritis among pSS patients. Interstitial lymphocyte infiltration and EGC formation may be pathologically related to glomerular damage.

Funding: Government Support - Non-U.S.

TH-0747
In Primary Membranous Nephropathy, Relapse After Partial Remission Is Predicted by Serum Albumin Level
Taewoo Lee, Vimal K. Deredueil, Daniel C. Cattran, Ronald J. Falk, Heather N. Reich, Patrick H. Nachman. "UNC Kidney Center, Chapel Hill, NC; Toronto General Hospital, Toronto, ON, Canada.

Background: In primary membranous nephropathy (MN), partial remission (PR), defined as reduction of proteinuria attaining <3.5 g/day with stable eGFR, is associated with decreased risk of ESKD, compared to No Remission. However, PR is associated with greater risk of relapse (46%,median 8 months) compared to complete remission (proteinuria<0.3g/day) (25%,median 25 months). Relapses are associated with increased risk of ESKD. We investigated the risk factors of relapse among patients who achieve PR by 18 months, thus simulating the setting of a clinical trial.

Methods: From the Glomerular Disease Collaborative Network cohort, we identified 135 patients who had a minimum of 24 months of follow up from biopsy. Patients who reached PR at 18 months were included for the analysis. Patients with a relapse (proteinuria

TH-0748
Clinical Significance and Risk Factor of Relapse in Proteinuria in Primary Membranous Nephropathy
Taewoo Lee, Vimal K. Deredueil, Carol J. Poulton, Ronald J. Falk, Daniel C. Cattran, Heather N. Reich, Patrick H. Nachman. "UNC Kidney Center, NC; Toronto General Hospital, ON, Canada.

Background: Achieving complete remission (CR) of proteinuria (<0.3 g/day) in primary membranous nephropathy (MN), is associated with excellent long-term renal outcome. Patients achieving partial remission (PR), defined as >50% reduction in proteinuria to <3.5 g/day with stable renal function, also show favorable prognosis compared to patients with no remission (NR). Relapses are associated with increased risk of ESKD. We investigated the risk factors of relapse in patients who have achieved a PR at any point.

Methods: To identify variables associated with relapse we studied 466 patients with primary MN registered in the Glomerular Disease Collaborative Network. 293 patients with at least 12 months of follow up were included. Time-to-event analysis from the time of PR to relapse was performed to evaluate risk factors for development of relapse. We incorporated various changes of remission status (PR, CR, and NR) during follow-up as time-dependent variable along with baseline patient characteristics.

Results: Of 293 patients, 213/283 (75%) achieved PR and 80 (17%) had NR. Among patients with PR, 95 patients (45%) reached CR, and 118 (55%) remained in PR until the last follow-up or relapse. A total of 63 relapses were observed (48 from PR and 15 from CR). By univariate analysis, older age, male sex, higher baseline proteinuria, PR vs CR and lower serum albumin (sAlb) at PR were significantly associated with increased risk of relapse. Higher sAlb at PR was associated with a lower risk of relapse (HR, 0.49 [95% CI, 0.289-0.831]) adjusted for age, sex, proteinuria at baseline, and immunosuppressive therapy. 34% of patients with sAlb £3.5g/dl at PR had a relapse (median time to relapse 7.4 months ) compared to 20% relapsers among patients with sAlb >3.5g/dl (median time 21.8 months, p=0.001).

Conclusions: A serum albumin level > 3.5 g/dl when patient achieve first PR is associated with a lower subsequent risk of relapse. We suggest that incorporating a normalized serum albumin level into the definition of PR would improve its predictive value of subsequent outcome.

TH-0749
Clinical Implication of BAFF and APRIL in Membranous Nephropathy
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Background: BAFF and APRIL have a role in B cell development. Additionally, these are related with several autoimmune diseases. However, the clinical implication of BAFF and APRIL remains unresolved in patients with membranous nephropathy (MN).

Methods: 84 patients with primary MN were recruited, and their plasma BAFF and APRIL levels at the time of diagnosis were compared with the data on patients with secondary MN (n=13) and healthy individuals (n=111). The time to complete remission was used as primary outcomes and the hazard ratios (HRs) by plasma BAFF and APRIL levels were calculated after adjustment of multiple variables.

Results: The plasma BAFF levels in primary MN (0.94 ± 0.26 ng/mL) were significantly higher than those of healthy individuals (0.54 ± 0.16 ng/mL) and lower than of secondary MN (1.59 ± 1.09 ng/mL). For the APRIL, subgroups revealed that 32 (38.1%) patients (n=51) had undetectable plasma level. The APRIL levels of primary MN (0.73 ± 2.50 ng/mL) were similar to the levels of healthy individuals (0.54 ± 0.16 ng/mL), but lower than the secondary MN (8.07 ± 5.66 ng/mL). The BAFF levels were positively associated with the auto-PLA2, antibody titers, but the APRIL levels were not. The cumulative rates of complete remission were significantly different between APRIL groups (undetectable, low level, and high level) (Figure 1), in contrast to the similar remission rates between the BAFF tertile groups. Patients with high plasma APRIL attained the complete remission sooner than patients with undetectable level: adjusted HR, 0.29 (0.089-0.921); P=0.036.
The Clinical and Prognostic Significance of Segmental Glomerulosclerosis Among Patients with Idiopathic Membranous Nephropathy

**Background:** Idiopathic membranous nephropathy (IMN) is a main cause of nephrotic syndrome in adults. In this study, we attempt to examine the relationship between segmental glomerular sclerosis in IMN and progression towards chronic kidney disease.

**Methods:** The study included 89 patients with IMN, followed over sixteen years, to evaluate the prognostic significance of glomerular segmental sclerosis in terms of renal survival. In the two groups (one with and one without segmental sclerosis), we analyze the various factors that are prognostic in IMN (eg. serum creatinine, proteinuria, etc.) and the histologic parameters.

**Results:** Segmental glomerulosclerosis was noted in 41 (46.1%) of 89 cases with IMN, representing cases from 57 (64.0%) males and 32 (36.0%) females. The prevalence of interstitial fibrosis and tubular atrophy did not contrast substantially between the two respective groups (3.3 ± 7.8 versus 1.2 ± 3.3, p=0.137). Only IgM positivity among the sclerotic group, compared to the non-sclerotic group was statistically significant (48.8% versus 25.0%, p=0.02). The median serum creatinine was significantly different among the two groups of 101 µmol/l in cases with sclerosis vs. 92 µmol/l among cases without sclerosis, p=0.059. The baseline proteinuria recorded was 2.2 gm and 2.9 gm per day in the two respective groups, p value=0.9. At last follow up, the median serum creatinine was similar among the two groups, (median 90 µmol/l in both groups, p value=0.9). At last follow up, the median serum creatinine was similar among the two groups, p value=0.9.

**Conclusions:** Our study revealed that segmental glomerulosclerosis was not associated with the severity of interstitial fibrosis. Although baseline serum creatinine was higher in patients with glomerulosclerosis at the time of biopsy, there was no impact on longterm outcome of the patients. Further studies are needed to outline the therapeutic regimen in IMN with segmental glomerulosclerosis.

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

**Underline represents presenting author.**

**262A**
Methods: 99 biopsy-proven iMN patients were collected from Huashan hospital and People's hospital of Wuzi in past 5 years. The iMN with positive PLA2R immunohistochemistry in kidney biopsies were designated as PLA2R associated MN. 79 of the 99 IMN patients were PLA,R-associated IMN and 13 were non-PLA,R-associated IMN. 49 patients were treated with prednisone plus CTX, and fifty with prednisone plus CNIs. 95% of the patients were on ACEI/ARB. The patients were followed for 15 months.

Results: The baseline characteristics between the PLA2R-associated and non-PLA2R-associated iMN was demonstrated in Table 1 (left part). In patients with non-PLA,R-associated MN, the remission rate at 3-month was significantly higher than that in PLA,R-associated group (table 1 right part). Relapses were observed in 8 patients of PLA,R-associated group and none of non-PLA,R-associated group.

<table>
<thead>
<tr>
<th>PLA2R (+) (n=78)</th>
<th>PLA2R (-) (n=13)</th>
<th>P</th>
<th>PLA2R (+) (n=78)</th>
<th>PLA2R (-) (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX (g/L)</td>
<td>14.6 (8.3)</td>
<td>0.002</td>
<td>13.3 (11.0)</td>
<td>22.0 (15.5)</td>
<td>0.059</td>
</tr>
<tr>
<td>urinary protein (g/24h)</td>
<td>2.0 (1.7)</td>
<td>0.005</td>
<td>1.5 (1.2)</td>
<td>2.0 (1.5)</td>
<td>0.276</td>
</tr>
<tr>
<td>albumin (g/L)</td>
<td>3.2 (1.7)</td>
<td>0.196</td>
<td>4.0 (2.0)</td>
<td>3.5 (1.0)</td>
<td>0.926</td>
</tr>
<tr>
<td>creatinine (mmol/L)</td>
<td>1.0 (0.5)</td>
<td>0.048</td>
<td>1.2 (0.6)</td>
<td>1.3 (0.8)</td>
<td>0.048</td>
</tr>
<tr>
<td>cholesterol (mmol/L)</td>
<td>5.4 (3.0)</td>
<td>0.011</td>
<td>5.6 (3.0)</td>
<td>5.5 (2.0)</td>
<td>0.328</td>
</tr>
</tbody>
</table>

Conclusions: The non-PLA,R-associated IMN responded quicker to the immunosuppressive therapy compared with PLA,R-associated IMN, and relapses were more frequent in PLA,R-associated IMN. Non-PLA,R-associated IMN may have a better response to immunosuppressive therapy.

**Funding:** Government Support - Non-U.S.

**TH-PO755**

**Pathogenesis of Membranous Nephropathy:**

**Funding:** Government Support - Non-U.S.

**TH-PO756**

**PLA2R Autoantibodies and Glomerular PLA2R Deposit in Membranous Nephropathy: How to Evaluate the Roles They Played?**

**Background:** Higher Glomerular PLA2R-Antigen deposit (GAg) rates compared with the serum Phospholipase A2 receptor-Antibody (SAb) positive rates were reported. However, the exact roles played by this two biomarkers remained unknown.

**Methods:** A total of 572 patients diagnosed IMN were included. Both SAb and GAg were detected. Fifty-two IMN patients received repeat renal biopsy were also included.

**Results:** In the 572 patients, 401 (70.1%) were SAb positive (SAb+) while 171 (29.9%) were SAb negative (SAb-). In SAb+ patients, the glomerular PLA2R-Antigen deposition (GAg+) was observed in 99.1% (397/401). Interestingly, the GAg+ was observed in 68.4% (117/171) SAb- patients. Patients with SAb manifested more severe proteinuria (3.9 g/24h vs 2.8 g/24h, P=0.001) and lower eGFR (104 ml/min.1.73m2 vs 110 ml/min.1.73m2, P=0.002) than patients without SAb. Further comparison between patients with SAb+/GAg+ and SAb-/GAg- showed a similar profile (more severe clinical manifestation in patients with SAb).

**Conclusions:** The GAg deposit can be detected in a large proportion of SAb negative patients, which can be explained by the lag of GAg disappearance in the follow up. The SAb was more tightly correlated to disease activity, treatment response and prognosis than the GAg. We recommend adopting GAg deposit detection as a supplement to SAb in IMN diagnosing and keeping on monitoring SAb in the follow up.

**Funding:** Government Support - Non-U.S.
TH-PO758

Comparison of Outcomes Between Individuals with Pure and Mixed Lupus Nephritis: A Retrospective Study Nosyalva Enofé,¹ Anju A. Oommen,¹ Jason Cobb,¹ Jose E. Navarrete,¹ Demilade Adelesinwo,² Oluwatobiloba A. Osikoya,² Helene B. Fevrier,¹ Alton Brad Farris,² Laura Plantinga,³ Titilayo O. Borji,¹ Dept of Nephrology, Emory Univ School of Medicine, Atlanta, GA; ²Morehouse School of Medicine, Atlanta, GA; ³Lee Univ; Cleveland, TN; ⁴Dept of Epidemiology, Rollins School of Public Health, Emory Univ, Atlanta, GA; ⁵Dept of Pathology and Laboratory Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: Lupus nephritis (LN) is divided into six classes (ISN/RPS Class I to VI) but can occur as a mixture of two classes. Pure proliferative LN (PPLN) comprises Class III or Class IV only while mixed proliferative and membranous LN (MPLN) comprises combinations of Class III & V or Class IV & V. Our aims were to compare individuals with biopsy-proven PPLN vs. MPLN in terms of clinical presentation and outcomes of complete or partial remission at 2 years and end-stage renal disease (ESRD) and clinical predictors of outcomes.

Methods: A retrospective review of all adult (>18) LN patients (n=278; PPLN (n=60) and MPLN (n=96)) identified from a native renal biopsy registry at a hospital network performed January 2000-December 2011. We assessed associations of LN category (MPLN vs. PPLN) with: time to remission (defined as ≥ 25% improvement in eGFR if baseline abnormal and urine protein creatinine ratio <0.5) and ESRD (defined using ICD-9 diagnosis code - 583.6 or the onset of chronic renal dialysis) using multivariable Cox proportional hazards analysis.

Results: The population was predominantly female (84.0%) and African American (71.8%), with a mean age of 33.4. Over follow-up (median, 1.5 years), using the PPLN group as the reference group, we did not find any associations between MPLN and time to remission (HR=0.13, 95% CI = 0.01-1.36) or ESRD (HR=0.30, 95% CI = 0.07-1.26). Baseline eGFR was significantly associated with time to remission (HR = 0.90, 95% CI = 0.84 - 0.98).

Conclusions: We found no significant differences in remission or progression to ESRD between patients with PPLN and MPLN. We, however, demonstrated that higher baseline eGFR at presentation were important factors in achieving remission in individuals with LN.

TH-PO759

Pure Class V Lupus Nephritis: Towards a Better Understanding of Lupus Membranous Nephropathy Compared to its Proliferative Counterparts Fernanda Pavan Schobor, Keisha L. Gibson, Taewoo Lee, Caroline J. Poulton, Mary Anne Dooley, William Franklin Pendergraft. UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC.

Background: Class V lupus nephritis, also known as lupus membranous nephropathy, accounts for approximately 10-20% of patients with lupus nephritis. There is not a consensus on the best treatment for isolated class V lupus nephritis, so providers often turn to the literature to extrapolate treatment approaches and outcomes. Here we compare clinical data between patients with lupus membranous, proliferative lupus nephritis and IMN.

Methods: Clinical and treatment data for lupus membranous patients were extracted from electronic medical records starting at the time of diagnosis until date of chart review. Results: Patients with lupus membranous resembled the lupus nephritis population more than the IMN population as they were more likely to be African American women in the fourth decade of life. At presentation, lupus membranous patients had preserved kidney function but significant proteinuria, much like patients with IMN. Almost all of these patients (94%) received immunosuppression. At mean follow up of 7.1 years, the mean serum creatinine remained 1.1 mg/dl, but proteinuria improved to a mean of 1.6 gram/day.

Conclusions: This cohort represents one of the largest of its kind in the literature to date. Necrotizing lesions are more characteristic of pauci-immune ANCA vasculitides, but have been described in patients with lupus nephritis as well. This rare variant is an understudied glomerular disease that portends a poor prognosis with an increased risk of progression to ESKD. There is a need for prospective multi-center treatment studies to determine durable therapeutic avenues.

TH-PO760

Necrotizing Glomerular Lesions Portend a Worse Prognosis for Patients with Lupus Nephritis Fernanda Pavan Schobor,¹ Keisha L. Gibson,¹ Mary Anne Dooley,¹ Elizabeth R. Blyth,¹ Caroline J. Poulton,¹ Harsharan Kaur Singh,² Volker Nickelet,³ William Franklin Pendergraft.¹ ¹UNC Kidney Center; ²UNC Chapel Hill, Chapel Hill, NC; ³UNC Pathology; UNC Chapel Hill, Chapel Hill, NC.

Background: Necrotizing glomerular lesions on kidney biopsy are uncommonly found in patients with lupus nephritis (LN) and are similar in appearance to those lesions found in patients with ANCA glomerulonephritis. The presence of these lesions portends a worse prognosis and has been reported previously to be more common in patients of African descent. Here we describe the clinical and histologic features of 48 patients with lupus nephritis and necrotizing glomerular lesions and their native kidney biopsy.

Methods: Patients with lupus nephritis who had necrotizing and crescentic lesions were identified from the UNC Division of Nephropathology database. Clinical, histologic, treatment, and long-term outcome data were obtained from the electronic medical record.

Results: Demographic and histologic data are shown in the following table. Most notably, these patients were predominantly African American women with class IV lupus nephritis high overall disease activity.

<table>
<thead>
<tr>
<th>Female:Male (%)</th>
<th>Tuft Necrosis (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>41 (87%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>African American</td>
<td>32 (67%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Age</td>
<td>34 ± 12</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.64 ± 1.3</td>
</tr>
<tr>
<td>Proteinuria (gm)</td>
<td>3.71 ± 3.1</td>
</tr>
</tbody>
</table>

TH-PO761


Background: Lupus nephritis histological hallmark, mostly in proliferative classes, is a “full house” (FII) pattern of immunoglobulin deposition and complement. However, Haas showed that membranous lupus nephritis (MLN) depicted this pattern only in 65% of the patients. The importance of FH deposition in MLN disease is still a matter of debate. It remains to be determined association between immunoglobulin deposition with clinical disease aggressiveness or transformation into proliferative forms.

Methods: All MLN patients submitted to kidney biopsies from July 1999 to August 2007 were included and biopsy tissue was studied by light microscopy and immunofluorescence. Patients were classified according to immunoglobulin glomerular capillary wall deposition in rich (rIF), with two or more deposited immunoglobulins, and poor (pIF) with a single and exclusive IgG deposition. Clinical and laboratorial data were collected at baseline, after one year and at the end of follow-up. Treatment was decided based on literature protocols.

Results: We included 15 patients in pIF group and 46 in rIF. At baseline, groups were similar regarding age, complement level, ANA, anti-DNA and proteinuria. Interestingly, PIF was significantly associated with a lower eGFR at baseline that persisted after one year follow-up. At the end, the pIF showed a not significant tendency to lower eGFR.
NO difference in age, eGFR and hemoglobin levels at baseline (see into segmental (S) and global (G). Data comparing renal outcomes between these two Society classification of lupus nephritis proposes a subclassification of proliferative forms M. Malheiros, Luis Yu, Cristiane B. Dias, Lect


Background: The International Society of Nephrologists and Renal Pathology Society classification of lupus nephritis proposes a subclassification of proliferative forms into segmental (S) and global (G). Data comparing renal outcomes between these two subclasses is controversial and pathogenesis also seems to differ (Barzilay J, 2005). We aimed to compare histopathology with clinical correlations.

Methods: Seventy-one biopsy-proven patients with proliferative (classes III or IV) lupus nephritis data were retrospectively analyzed. Twenty-nine of them were classified as global and 42 as segmental. All procedures were performed in one single center between 2004 and 2014.

Results: All patients received induction therapy with steroids plus either intravenous cyclophosphamide has been standard care for inducing remission and TMA were predictors for ESRD.

Results:

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Global</th>
<th>Segmental</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>29</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>31.8±12</td>
<td>31.5±9</td>
<td>0.03</td>
</tr>
<tr>
<td>Hb (mg/dL)</td>
<td>10.9±1.4</td>
<td>11±1.1</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>55.2±26</td>
<td>63.9±27</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up features

| Follow-up (y) | 3.63 | 3.62 | 0.2 |
| MDRD Final (ml/min/1.73m²) | 59.6±37.6 | 78.9±28.4 | 0.02 |
| MDRD Delta per year | +1.8±2.3 | +5.2±2.9 | 0.2 |

Conclusions: In global compared to focal proliferative lupus nephritis patients: male sex prevailed and renal function decreased on 3.6 years follow-up in spite of similar MDRD on baseline. Prospective studies are necessary to determine if histological pattern is relevant to guide the clinician’s therapy choice.


Background: To observe the discrepancy between class III and class III+V, between class IV and class IV+V, and between subclass IV-S and IV-G on clinicopathological features and renal outcomes and explore the pathological lesions associated with poor renal outcomes in patients with different classes.

Methods: The records of all adult patients with biopsy-proven proliferative lupus nephritis followed for at least 1 year were reviewed. All patients were pathologically classified according to the 2003 ISN/RPS classification of lupus nephritis and each pathological lesion was semiquantitatively scored.

Results: Patients with class III+V (class IV+V) presented with more severe proteinuria and chronic pathological lesions and milder acute pathological lesions than patients with class III (class IV); patients with subclass IV-G presented with more severe hypertension, proteinuria and hypocomplementemia, lower ANCA positivity rate, more severe glomerular cell proliferation and hyaline deposit, and milder fibrinoid necrosis and crescent than patients with subclass IV-S. The renal outcomes between patients with class III and class III+V, between class IV and class IV+V, and between subclass IV-S and subclass IV-G were not different respectively. Global glomerulosclerosis, cellular crescent, fibrous crescent, glomerular cell proliferation, tubular acute injury, interstitial inflammation and TMA were predictors for ESRD.

Results:

<table>
<thead>
<tr>
<th>Background features</th>
<th>Global</th>
<th>Segmental</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>33±10</td>
<td>34±12</td>
<td></td>
</tr>
<tr>
<td>MDRD Baseline</td>
<td>96±34</td>
<td>78±40</td>
<td>0.04</td>
</tr>
<tr>
<td>MDRD after 1 year</td>
<td>103±32</td>
<td>76±40</td>
<td>0.01</td>
</tr>
<tr>
<td>MDRD Final</td>
<td>80±39</td>
<td>63±33</td>
<td>ns</td>
</tr>
<tr>
<td>PTN Baseline (g/day)</td>
<td>4.6±3.6</td>
<td>4.4±5.7</td>
<td>ns</td>
</tr>
<tr>
<td>PTN Final (g/day)</td>
<td>1.2±1.8</td>
<td>2.1±3.8</td>
<td>ns</td>
</tr>
<tr>
<td>C3 (mg/dL)</td>
<td>85±32</td>
<td>96±52</td>
<td></td>
</tr>
<tr>
<td>Hematocrit Baseline</td>
<td>39%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>ACLiGt Baseline</td>
<td>54%</td>
<td>71%</td>
<td>ns</td>
</tr>
<tr>
<td>ACLiGM Baseline</td>
<td>43%</td>
<td>64%</td>
<td>ns</td>
</tr>
<tr>
<td>Mesangial Hypertcellularity</td>
<td>70%</td>
<td>53%</td>
<td>ns</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pred</td>
<td>22%</td>
<td>50%</td>
<td>ns</td>
</tr>
<tr>
<td>Double</td>
<td>78%</td>
<td>50%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Conclusions: We found 25% of MLN patients with only one deposited immunoglobulin. The poor IF group compared to rich IF showed lower MDRD at baseline and even after one year. Studies are needed to elucidate the role of different patterns of deposits in the pathogenesis of MLN.

TH-PO764 Ability of Spot Urine Protein/Creatinine Ratio (Spot PCR) to Correctly Identify the Proteinuria Endpoints of Complete Remission (CR), Partial Remission (PR), and Treatment Failure (TF) as Determined by 24 Hour Urine PCR (24 PCR): Experience of the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study (ACCESS) Brad H. Rovin,1 Lee A. Hebert,4 Div of Nephrology, OSUWMC, Columbus, OH; 1Div of Nephrology, OSUWMC, Columbus, OH; 4Div of Nephrology, OSUWMC, Columbus, OH. The present work is the first to rigorously test this hypothesis. ACCESS is a prospective randomized phase 2 trial of Abatacept or placebo added to the Euro-Lupus regimen of cyclophosphamide and prednisone. The error rate of spot PCR in identifying ACCESS proteinuria endpoints is high (defined by 24 PCR) was 23%. Proteinuria endpoints in LN trials are broad targets and Concordant 120, Discordant 35. P < 0.001 (null hypothesis that concordance is 95% is rejected). A unique feature of ACCESS was concurrent testing for spot PCR (monthly) and 24 PCR (each three months). ACCESS proteinuria endpoints were CR, PR, and TF assessed at 6 months and 12 months of follow-up (Arth Rheum Dis, 69, 2006, 3906, 2014). So, it is likely that using spot PCR rather than 24 PCR to guide management increases the risk of management error. So, it is likely that using spot PCR rather than 24 PCR to guide management increases the risk of management error. So, it is likely that using spot PCR rather than 24 PCR to guide management increases the risk of management error.

Results: At 6 month follow up, spot and 24 PCR were concordant in 36 CR, 25 PR, 10 TF, and discordant in 10 CR, 11PR, and 8 TF. At 12 month follow up, spot and 24 PCR were concordant in 36 CR, 11 PR, and 2 TF, and discordant in 4 CR, 2 PR, 0 TF. Tats: Concordant 120, Discordant 35. P < 0.001 (null hypothesis that concordance is 95% is rejected).

Conclusions: The error rate of spot PCR in identifying ACCESS proteinuria endpoints (defined by 24 PCR) was 23%. Proteinuria endpoints in LN trials are broad targets and mainly involve low level proteinuria. This minimizes the impact of spot PCR variability.

Funding: NIDDK Support

TH-PO765 Induction Treatments for Proliferative Lupus Nephritis: A Network Meta-Analysis Suetsenia Palmer,1 David J. Tunnillifice,2 Allisong Tong,2 Dimitris Mavridis,1 Jonathan C. Craig,3 Marcello Tonelli,4 David W. Johnson,5 Giovanni F.M. Strippoli,6,8 ’Univ of Otago Christchurch; 2 Univ of Sydney; ‘Univ of Ioannina; ‘Univ of Calgary; ‘Univ of Queensland; ‘Univ of Bari.

Background: Intra-venous cyclophosphamide has been standard care for inducing remission among patients with proliferative lupus nephritis (class III and IV). More recently, several agents have been tried, however, given the numerous treatment options and head-to-head trials, there is uncertainty about the comparative effectiveness of all available treatment options.

Conclusions: In global compared to focal proliferative lupus nephritis patients: male sex prevailed and renal function decreased on 3.6 years follow-up in spite of similar MDRD on baseline. Prospective studies are necessary to determine if histological pattern is relevant to guide the clinician’s therapy choice.
Methods: Immunosuppressive treatments to induce remission of kidney disease among patients with proliferative lupus nephritis (LN) have been evaluated using network meta-analysis of parallel-group randomized controlled trials. Outcomes were complete disease remission, treatment failure, all-cause mortality, end-stage kidney disease, major infection, alopecia, ovarian failure and malignancy. Effect sizes for treatments were calculated using random-effect meta-analysis and compared to intravenous cyclophosphamide (referent). Trials were critically appraised using Cochrane risk of bias.

Results: 47 studies involving 3510 patients were eligible. Mycophenolate mofetil was superior to intravenous cyclophosphamide for inducing disease remission (network odds ratio [NOR]: 7.7, 95% CI: 3.2-18, p<0.001), and resulted in CI of treated arms at follow-up of 0.26-0.87, and allopurinol (0.22, 0.13-0.39). Mycophenolate mofetil had uncertain risks of death (OR 1.14, 0.49-2.63), major infection (1.30, 0.88-1.92) and ovarian failure (0.48, 0.11-2.08) versus intravenous cyclophosphamide. Comparative effects of other treatments including rituximab and calcium inhibitors in combination were uncertain. Information for end-stage kidney disease and malignancy endpoints for all treatments was sparse. Treatment effects were generally consistent within networks. Methodological reporting in trials was frequently unclear.

Conclusions: Mycophenolate mofetil is more effective than intravenous cyclophosphamide for induction treatment of proliferative lupus nephritis.

TH-PO766
A Systematic Review on Tacrolimus Treatment in Lupus Nephritis
Timoke Krasia,1 Edwin Brendewold, Tom Huizinga, Tom J. Rabelink, Yoe Kie Onno Teng.1 Nephrology, LUMC, Leiden, Netherlands;2 Rheumatology, LUMC, Leiden, Netherlands.

Background: Recently, 2 large randomized controlled trials (RCTs) have been published on the efficacy of tacrolimus (TAC) in Asian LN patients. Both trials used different treatment regimens and efficacy was not consistent between the trials. Therefore, the role of TAC in the treatment of LN remains unclear. Thus, we performed a systematic review on TAC treatment for LN.

Methods: We searched multiple databases for all human studies investigating TAC treatment in LN. Then studies were selected on clinical relevance and results were analysed on renal response and adverse events.

Results: We found 26 clinical studies from which data were extracted from all controlled studies: 6 RCTs and 3 case-control studies involving a total of 888 patients. As induction treatment, TAC with steroids resulted in 82% responders of which 56% complete responders (CR). Induction with steroids, mycophenolate MMF (TAC) resulted in 85% responders, of which 46% CR. Data from 1 RCT performed with TAC in combination with steroids as maintenance treatment, resulted in 100% responders of which 56% CR. Generally, control patients receiving induction treatment with cyclophosphamide achieved 66% response of which 29% CR. Those receiving induction treatment with MMF achieved 76% response of which 53% CR. Overall infections were observed in 20% of TAC-treated patients compared to 26% of control patients treated with cyclophosphamide and 29% in MMF treated control patients. A rise in serum creatinine was observed in 5% of all TAC-treated patients compared to 2% in the cyclophosphamide control group and 0% in the MMF control group.

Conclusions: This systematic review suggests that TAC-based treatments can achieve comparable renal responses in LN as conventional regimens. Currently, limitations of the available studies are the heterogeneity of TAC-based regimens, lack of studies in non-Asian LN patients and lack of long-term safety data. Altogether, these data warrant further RCTs on TAC treatment in LN. At this time, TAC can only be advised as second-line treatment in difficult LN patients, such as therapy-refractory patients (especially if severe proteinuria is present) and in preparation or during pregnancy.

TH-PO767
Predicting Chronic Kidney Disease (CKD) in Lupus Nephritis (LN) Ana Malvar,1 Valeria Gabriela Alberton,1 Bruno Jorge Lococo,1 Haikady Nagaraja,2 Brad H. Rovin.3 Hospital Fernandez, Buenos Aires, Argentina;3 Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: Early identification of LN patients likely to develop CKD may permit therapy to be adjusted and CKD to be avoided. Clinical and histologic parameters measured after induction treatment in LN patients were associated with long-term CKD in a cohort of LN patients to define predictors of new CKD.

Methods: Patients (n=69) with biopsy-proven class III/IV LN were induced with steroids and MMF (53%) or cyclophosphamide (46%) for 6 months, and had repeat kidney biopsy (biopsy 2, 6.6±0.7 months), and were put on maintenance therapy. Long-term (median 73 months) follow-up was available on 87% of the cohort. Multivariate linear regression was used to develop a predictive model for future serum creatinine (SCr) based on clinical and histologic variables obtained after induction.

Results: The impact of maintenance therapy in CKD at last follow-up among patients who did or did not achieve a complete clinical renal response after induction (19% vs 18.4%, respectively). Among patients with complete histologic renal remission after induction, 36% had a final SCr of 1.3-2.9 mg/dl. There was no relationship between the NIH activity index at biopsy 2 and long-term kidney function. However, the median number (range of 4-8) of patients who did not develop CKD (p<0.02). Regression analysis showed a significant linear correlation between CI ≥ 4 at biopsy 2 and log(SCr) at long-term follow-up (R=0.36, p<0.0001). In multivariate analysis CI and SCr at biopsy 2 were independent predictors of long-term SCr (R=0.48, p<0.0001). For a given level of SCr at biopsy 2, a 1 unit increase of CI in the range of 4-8 corresponded to a 20% increase in last SCr.

Conclusions: Neither clinical nor histologic remission after induction predicts long-term SCr, but complete histologic remission in LN at biopsy suggests a higher risk of CKD. The combination of SCr and chronicity index (CI) at biopsy accounts for 48% of the long-term variability of renal function in those patients who reach a threshold level (CI=4) of chronic kidney damage.

Funding: NIDDK Support

TH-PO768
Clinical and Histologic Remission in Class IVG and IVS Lupus Nephritis (LN) After Induction Therapy Ana Malvar,1 Bruno Jorge Lococo,2 Valeria Gabriela Alberton,1 Diego Morales,3 Brad H. Rovin.2 Hospital Fernandez, Buenos Aires, Argentina;3 Ohio State Univ Wexner Medical Center, Columbus, OH.

Background: The ISN/RPS classification of LN distinguishes class IV with predominantly segmental lesions (IVS) from class IV with global (IVG) lesions. It has been suggested that IVG may have a lower remission rate than IVS, possibly because it more like a vasculitis than IVG. However several studies found no significant difference in long-term kidney survival between these subclasses. We examined differences in histologic and clinical remissions between IVG and IVS in our LN cohort with serial kidney biopsies.

Methods: SLLE patients (n=43) were biopsied at first presentation of kidney involvement (Bx1) and again at 6 months after completing induction therapy (Bx2). Class IVG and IS patients were treated identically with steroids plus MMF or cyclophosphamide. NIH activity (AI) and chronicity (CI) indices, proteinuria and serum creatinine (SCr) were compared. Complete clinical response (CCR) was defined as normal SCr and proteinuria < 500 mg/dl.

Complete histologic remission was defined as an AI<0 at Bx2.

Conclusions: Clinical outcomes and histologic data are shown in the Table. All patients were ANCA negative. Final SCr and proteinuria were determined after a mean follow-up of 54±7 months. Only 4 patients were lost to long-term follow-up.

TH-PO769

Background: A complete remission (CR) in severe lupus nephritis (SLN) is associated with a favorable long-term outcome. Numerous factors including level of serum creatinine (SCr) at baseline have been shown to impact on CR rate and outcome. We assess the impact of SCr on CR rate and outcome in SLN.

Methods: We evaluated the 86 adult patients in the prospective, controlled trial of plasmapheresis in SLN and compared them based on SCr level at baseline (≤1.0, 1.01-1.5, 1.51-2.0, 2.01-3.0 and >3.0 mg/dl; n= 22, 23, 16, 12, 13 respectively). The CR rate (defined by a serum creatinine (SCr) of ≤1.4 mg/dl and UPro of 0.33 g/d) and long-term outcomes (stable renal function, dialysis and death) were compared. Patients were followed for 121±64 mo.

Results: Baseline clinical features (age, gender, race and UPro) were similar among the groups. All pts had ISN/RPS class IV lesions and while the activity index was similar (73±16 vs 71±15, respectively, the chronicity index (CI) 2.3±3 vs 3±5 vs 5±5, respectively). P (0.007) was significantly higher with increasing levels of SCr. At follow-up, CR rates (80% vs 52% vs 19% vs 25% vs 0%, respectively, P <0.0001) were significantly higher and occurred in a shorter period of time (6 vs 12 vs 23 vs 18 mo, respectively, P <0.0003) in pts with lower levels of SCr. Patients with a baseline SCr of 1.0 mg/dl were >16 times as likely (odds ratio, 16.2; 95% confidence interval, 4.2-61.5) to attain a CR and >6 times as likely (odds ratio, 6.1; 95% confidence interval, 1.9-18.6) to have stable renal function at last follow-up compared to pts with a SCr >1.0 mg/dl. The 15-yr renal survival (76% vs 57% vs 48% vs 25% vs 8%, respectively, P <0.0001) and patient survival without ESRD (76% vs 40% vs 24% vs 25% vs 8%, respectively, P <0.0001) was greatest in the patients with a SCr of 1.0 mg/dl at baseline.

Conclusions: The CR rate and outcome in SLN are significantly affected by baseline serum creatinine. The CR rate is highest and long-term prognosis most favorable in pts with a baseline SCr ≤1.0 mg/dl; the group with the least amount of chronic disease on biopsy. This emphasizes the importance of early diagnosis and treatment in pts with SLN.
TH-PO770

Urine Adiponectin Isoforms and Kidney Lesions in Lupus Nephritis (LN)

Biomarker Consortium, Huimeng Qi, Lining Wang

Background: Human adiponectin isoforms exert different effects on inflammation. Urine adiponectin is increased at LN flare, but the relationship between adiponectin isoforms and kidney lesions in LN has not been studied.

Methods: Urine and plasma total and high molecular weight (HMW) adiponectin isoforms were measured by specific ELISAs in samples from 39 normal controls and 97 biopsy-diagnosed LN patients. Urine adiponectin levels were normalized and log-transformed, and then examined for associations with histologic lesions on kidney biopsy by ANOVA, nonparametric Wilcoxon ranked-sum testing and multiple linear regression analysis.

Results: The HMW to total adiponectin ratio was increased in plasma (r=0.022) and urine (p=0.0004) of LN patients compared to controls. Total and HMW adiponectin levels were highly correlated within the plasma (R=0.91, p < 0.0001) and urine (R=0.64, p < 0.0001) in LN, but between plasma and urine only HMW adiponectin showed a correlation, and this was milder (R=0.21, p=0.037). Urine adiponectin levels increased with the severity of S NP/PS class. The highest total and HMW urine adiponectin levels were found in patients who had combined class III or IV + V LN. Using urine HMW adiponectin levels to differentiate between control and LN patients, and between single and combined LN classes, receiver-operating characteristic analysis showed areas under the curve of 0.96 and 0.85, respectively. Urine HMW adiponectin was significantly increased when glomerular proliferation, cellular crescents or interstitial inflammation were present on the biopsy, and the HMW adiponectin correlated with the biopsy activity index (R=0.31, p < 0.0001), but not chronicity index. Using HMW adiponectin plus urine hemopexin plus serum creatinine, an equation to predict biopsy chronicity index was constructed with R²=0.46.

Conclusions: Urine adiponectin isoforms increase with the severity of active kidney lesions in LN. The increase in urine adiponectin is not simply a reflection of changes in systemic adiponectin, and may be due to intra-renal processing.

Funding: NIDDK Support

TH-PO771

Significance of Serum Cystatin C as a Biomarker for Clinical Practice in Patients with Lupus Nephritis

Hua Zhou, Di Lu, Hairong Tang, Lizi Li, Huimeng Qi, Linig Wang

Nephrology Dept, 1st Hospital of China Medical Univ, Shenyang, China

Background: Serum Cystatin C (sCysC) as a novel biomarker of renal function has been studied in many primary glomerular diseases. However, sCysC was barely reported in lupus nephritis (LN). We aim to compare the changes of sCysC and traditional biomarkers in LN patients who had combined class III or IV + V LN. Using urine HMW adiponectin levels to differentiate between control and LN patients, and between single and combined LN classes, receiver-operating characteristic analysis showed areas under the curve of 0.96 and 0.85, respectively. Urine HMW adiponectin was significantly increased when glomerular proliferation, cellular crescents or interstitial inflammation were present on the biopsy, and the HMW adiponectin correlated with the biopsy activity index (R=0.31, p < 0.0001), but not chronicity index. Using HMW adiponectin plus urine hemopexin plus serum creatinine, an equation to predict biopsy chronicity index was constructed with R²=0.46.

Conclusions: Urine adiponectin isoforms increase with the severity of active kidney lesions in LN. The increase in urine adiponectin is not simply a reflection of changes in systemic adiponectin, and may be due to intra-renal processing.

Funding: NIDDK Support

TH-PO772

Neutrophil Modular Blood Transcriptional Signature Is Associated with Lupus Nephritis and Its Severity in SLE

Noemie Jourde-chiche, Bertrand Gondouin, Stephane Burty, Laurent Daniel, Bertrand Dussol, Laurent Chiche

Background: Lupus nephritis (LN) is a severe complication of SLE. The aim of this study was to assess the link between blood transcriptional signatures and LN, comparatively with other pathological conditions associated with renal injury.

Methods: 102 patients were included: 62 SLE patients, 40 controls with various conditions (10 with crescentic GN due to ANCA-associated vasculitis (AAV), 15 with severe bacterial sepsis, 15 with non-proliferative glomerular diseases), and their matched healthy controls. SLE samples were split in those at the time of: a biopsy-proven active LN (group 1, n=24); an extra-renal flare (group 2, n=11); a clinically quiescent visit (group 3, n=34). Microarray data were generated using Illumina beadchips and analyzed using modular repertoire analyses.

Results: Modular repertoire analysis in SLE patients revealed, in addition to the activation of IFN-related modules, a strong upregulation of M5.15, a module of 24 transcripts annotated “neutrophil”. There was no correlation between M5.15 and SLEDAI, anti-dsDNA level or IFN modules activity. M5.15 was strongly associated with active LN (p=0.009), but not with non-renal manifestations. The neutrophil modular signature was present in 67%, 18% and 47% of patients from group 1, 2 and 3 respectively. In group 2 and 3, its presence was associated with a past history of LN or the occurrence of LN during the follow-up. M5.15 was correlated with acute renal failure (p=0.03) and serum albumin (r=-0.14). AAV and sepsis patients shared the neutrophil signature observed in SLE, but displayed no IFN signature, while those with non-proliferative GN had none of these signatures.

Conclusions: Modular repertoire analysis demonstrates that neutrophil signature is correlated with occurrence and severity of LN in SLE. This result could allow the design of new biomarkers in LN.

TH-PO773

Anticoagulation and Longterm Outcomes in Patients with Renal Artery Stenosis and Antiphospholipid Syndrome

Alina L. Casian, Shirish Sangle, Sotiria Manoustitopoulos, David N. Cruze, Lupus Unit, Guy’s Hospital, London, United Kingdom

Background: Our previous data showed renal artery stenosis (RAS) is more prevalent in antiphospholipid syndrome (APS)(26%) compared to the general hypertensive population(8%), and anticoagulation with INR=3 was associated with initial reduction of chronic kidney disease (CKD) and hypertension.

Methods: We identified 37 patients with RAS and APS fulfilling Sapporo criteria: anticardiolipin IgG/IgM titer>40 units or >99 th percentile (or >1 lupus anticoagulant) on >2 occasions >=6 weeks apart AND vascular thrombosis (or pregnancy morbidity). RAS was diagnosed by magnetic resonance angiography(MRA).

Results: 15 patients had APS alone and 22 APS associated with autoimmune conditions (13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had ESRD or death, suggesting a non-thrombotic pathogenic process underlying RAS.

Conclusions: Modular repertoire analysis demonstrates that neutrophil signature is correlated with occurrence and severity of LN in SLE. This result could allow the design of new biomarkers in LN.

Funding: NIDDK Support

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**Underline represents presenting author.**

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RAS, e.g. minimal hyperplasia. Treatment of associated vascular risk factors and autoimmune disease is paramount. Anticardiolipin antibodies and renal MRA are useful for screening hyperplastic lupus patients.

TH-PO774

A Prospective Study to Investigate Mycophenolic Acid Pharmacokinetics and Its Clinical Correlations in Lupus Nephritis Patients

Desmond Y.H. Yang, Chun-Hay Tam, Sunny Sze Ho Wong, Maggie Kam Man Ma, Susan Yang, Dan Tai Mac Chan.

1 Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong; 2 Medicine and Geriatrics, United Christian Hospital, Hong Kong, Hong Kong.

Background: The dosing regimen of mycophenolate mofetil (MMF) in the treatment of lupus nephritis (LN) is adopted from the kidney transplant experience. The role of therapeutic drug monitoring of mycophenolic acid (MPA) level in managing LN remains undefined.

Methods: We prospectively studied LN patients on maintenance treatment with prednisolone and MMF. Blood MPA level at 1, 2, 4, 8, 10 and 12 hours (i.e. C1, C2, C4, C8, C10 and C12) after MMF administration was measured with an enzymatic assay upon enrollment and repeated at 6-month intervals for 24 months, and at occurrence of clinically significant events, to investigate their clinical correlations.

Results: 51 patients were included, with prednisolone and MMF dose of 6.2±1.8mg/d and 1284±493mg/d respectively at baseline. C1, C2 and C12 MPA levels were 9.8±8.7mg/L, 8.6±6.2mg/L, 1.9±1.4mg/L during disease remission. C1, C2 and C12 MPA levels correlated with AUC(12)[r = 0.52, 0.85 and 0.77; p<0.004, <0.001 and <0.001 respectively]. C12 correlated inversely with hemoglobin, white cell and platelet counts [r = -0.359, -0.226, -0.20; p<0.001, 0.010 and 0.024 respectively]. There was no association between C12 and anti-dsDNA, serum creatinine or 24-hr urine protein excretion (r=0.53, 0.37 and 0.37 respectively). C1 and C2 showed no association with clinical or serological parameters.

Clinically significant events included infection in 2 patients, gastrointestinal upset in 3 patients, and renal flare in 5 patients. C12 MPA level at the time of these events were 1.7±1.9mg/L, 2.6±1.7mg/L and 1.5±0.9mg/L respectively.

Conclusions: C12 MPA level showed good correlation with drug exposure, and may be associated with renal flare and haematological side-effects but not infection.

Funding: Private Foundation Support

TH-PO775

Long-Term Prospective Study of Tacrolimus-Based Treatment in Lupus Nephritis Patients

Kazanori Karasawa, Keiko Uchida, Yukari Asamiya, Takahito Moriyama, Mitsuyo Itabashi, Takashi Takei, Kosaku Nitta, Dept Medicine, Kidney Center, Tokyo Women’s Medical Univ, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan.

Background: This study aimed to examine whether long-term maintenance treatment with tacrolimus for patients with lupus nephritis (LN) is effective and safe.

Methods: A total of 27 adult patients with LN after induction therapy were enrolled. Tacrolimus was initiated at a dose of 3 mg/day. Patients treated with other immunosuppressive agents were also switched to tacrolimus. Prednisolone doses were tapered during the period and their data were analyzed. The mean urinary protein/creatinine ratio significantly decreased from a baseline of 1.54 at 5 years (p = 0.016), while mean eGFR levels were unchanged throughout the 5 years of follow-up (4.7±4.1 ml/min/1.73m²).

Complications including acute myeloblastic leukemia, or their personal intention to become pregnant or discontinue medication. A total of 23 patients (mean age 52.6±11.8 years and mean duration of LN 15.6±8.7 years) were treated with tacrolimus throughout a 5-year period and their data were analyzed. The mean urinary protein/creatinine ratio significantly decreased from a baseline of 1.12±1.47 to 0.33±0.78 at 1 year (p = 0.005) and 0.40±1.54 at 5 years (p = 0.016), while mean eGFR levels were unchanged throughout the 5 years of tacrolimus treatment. The mean LNDAI was significantly decreased from a baseline of 3.54±2.53 to 1.96±1.40 at 1 year (p = 0.021) and 2.08±1.44 at 5 years (p = 0.022). Similarly, the mean prednisolone dose significantly decreased from a baseline of 0.35±0.21 mg/kg/day to 0.22±0.15 mg/kg/day at 1 year (p = 0.022) and 0.17±0.09 mg/kg/day at 5 years (p = 0.001). The mean blood concentration of tacrolimus was 4.0±2.3 ng/ml. Only one patient experienced a disease flare, and there were no deaths during the study period.

Conclusions: Our results suggest that tacrolimus can be potentially effective for the treatment of LN; moreover, the current dosage appeared to be generally well-tolerated for long-term maintenance treatment in patients with LN.

TH-PO776

Comparison of Kidney Function and Mortality of Mexican Children versus Adults with Lupus Nephritis


Background: Childhood-onset lupus nephritis (CLN; onset before 16 years of age) has been associated with a more aggressive disease course compared to adulthood-onset lupus nephritis (ALN). Kidney factors such as LN Class and Activity and Chronicity Indexes are related to renal prognosis. No information is available in our setting. Aim: To compare kidney function and mortality of CLN vs ALN.

Methods: Retrospective cohort study. Medical records of patients with LN biopsy proven performed Jan/2005 – Dec/2012 were reviewed. Clinical, kidney function and sociodemographical variables were recorded. Kidney biopsy findings, LN class, Activity and Chronicity Indexes, and patient status (alive/deceased) were also analyzed.

Results: There were 53 patients with CLN and 188 with ALN, with a follow-up of 24±23 vs 43±22 months, and age 12±2 vs 32±11 years, respectively. Main results are shown in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CLN</th>
<th>ALN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria g/day</td>
<td>0.5 (0.2-1.4)</td>
<td>0.2 (0.6-4.3)</td>
</tr>
<tr>
<td>CrCl (ml/min/1.73m²)</td>
<td>85±42</td>
<td>80±29</td>
</tr>
<tr>
<td>Activity Index</td>
<td>4±3</td>
<td>8±3</td>
</tr>
<tr>
<td>Chronicity Index</td>
<td>1±0</td>
<td>3±2*</td>
</tr>
<tr>
<td>LN Class</td>
<td>23 (12)</td>
<td>42 (22)</td>
</tr>
</tbody>
</table>

Conclusions: Patients with CLN had higher mortality and those with ALN had lower CrCl at the end of follow-up. Children died mainly due to infectious causes which might be related to the immunosuppression used because of the high prevalence of class IV LN.

TH-PO777

Determining Long-Term Outcomes in Lupus Nephritis Through Molecular Analysis of Serial Kidney Biopsies

Samar Parikh, Ana Malva, Huijuan Song, Jianying Zhang, Lianbo Yu, Brad H. Rovin, Div of Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH; 2 Nephrology, Hospital Fernandez, Buenos Aires, Argentina.

Background: Most patients with proliferative lupus nephritis (LN) achieve a partial remission (PR) after induction therapy. With time some patients will attain complete remission (CR) while others will not improve. We tested whether gene expression in serial kidney biopsies could identify markers of long-term kidney outcome in patients who achieved a PR after induction.

Methods: The expression of 511 immune response genes was evaluated for 9 pairs of proliferative LN biopsies. A kidney biopsy was done at flare (bx1) and after induction therapy was completed (bx2). All patients achieved a clinical PR prior to bx2. At 3 year follow-up 4 patients were in CR and 5 patients did not improve or worsened (NR). Gene expression was analyzed by real-time PCR. The genes were selected based on their expression differences between bx1 and bx2.

Conclusions: Future studies will focus on validation of these markers and further characterization of the biology of these patients to more accurately predict long-term outcomes after induction therapy.

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expression profiles were compared at bx1 and bx2 between these CR and NR patients. Transcripts were considered differentially expressed only if they met both criteria of at least a 1.5-fold change (FC) and p-value < 0.01.

**Results:** At flare, 2 transcripts were differentially expressed between CR and NR. IL-28a, a type 3 interferon gene was decreased 2.6-fold (p = 0.006) and mannose-binding lectin serum peptide 1 (MASP1), a member of the complement lectin-pathway, was decreased 1.8-fold (p = 0.009) in CR versus NR. From bx1 to bx2, 8 genes were differentially expressed in the CR group. Expression of adhesion molecule VCAM1 and macrophage regulator CEBPB was decreased while expression of TGF-β activator SMAD3, inhibitor of TLR signaling, TOLLIP, and inhibitor of NFκB signaling, TRAF4 was increased. In NR, from bx1 to bx2, 9 genes were differentially expressed. Expression of the type 3 interferon, IL28b and the TNF-receptor TNRFSF13b (TACI) was decreased while expression of complement C2 and CFNB and the TNF cytokine TNFSF8 was increased.

**Conclusions:** This gene characterization of kidney biopsies at LN flare along with the change in expression after treatment identifies differentially-expressed genes among patients who eventually have or do not have a CR. Some of these genes may be candidate biomarkers of long-term renal outcomes in LN.

**Funding:** Other NIH Support - NINDS U01: DK096927, Pharmaceutical Company Support - Mallinckrodt/Questcor Fellowship Grant: 00033990

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**TH-PO778**

**Evaluation of Healthcare Resource Utilization and Costs by Immunosuppressant Pattern of Use in Lupus Nephritis**

**Shih-Yin Chen, Ning Wu, Ji-Ting, Fei Shih. Biogen.**

**Background:** US-based treatment guidelines recommend 6 months of immunosuppressant (IS) therapy before continuing or switching regimens for class IV/V lupus nephritis (LN) patients. Literature suggested that management of LN is costly, but published data on how costs and healthcare resource utilization (HRU) may vary by IS pattern of use are limited.

**Methods:** We identified LN patients initiating cyclophosphamide (CYC) or mycophenolate mofetil (MMF) in 2010-2013 from a US commercial/Medicaid claims database. All-cause costs and HRU during the year post-IS initiation were examined. Comparison was made between the following four groups based on their IS utilization:
1. Patients who remained on the same IS throughout IS continuously for at least 7 or up to 12 months (reference group),
2. Patients who switched/ discontinued IS at 6 months (305 patients),
3. Patients who switched/discontinued IS after 6 months (N=223),
4. Patients who switched/discontinued IS after 6 months, but then stayed on the same IS through 7-12 months. Identifying safe and efficacious therapies early for LN patients may have economic implications. Future study supplemented with clinical markers may help understand the economic impact of achieving early renal response is warranted.

**Funding:** Pharmaceutical Company Support - Biogen

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**TH-PO779**

**Retrospective Analysis of 65 Pregnancies in Patients with Lupus Nephritis in France**

**Jean-charles Puthet,1 Noemie Jourdier-chiche,2 Dominique Chauveau,3 Eric Daugas,4 Laurent Juillard.1 1Hôpital Edward Herriot - Hospices Civils de Lyon, France; 2Hôpital La Conception - CHU Marseille, France; 3Hôpital Rangueil - CHU Toulouse, France; 4Hôpital Bichat - APHP, on behalf of the French Cooperative Group on Lupus Nephritis, France.**

**Background:** Lupus nephritis (LN) mostly affects women of childbearing age. Despite the improvement in care over the last decades, pregnant women with LN are still at high-risk of maternal and foetal complications.

**Objective:** To understand the economic impact of achieving early renal response is warranted.

**Methods:** The aim of this study is to outline retrospectively the care and pregnancy progress of 65 pregnancies carried out after 2004, at the postpartum between 2004 and 2014, in patients with LN diagnosed before or during pregnancy.

**Results:** Data was collected from 65 pregnancies in 44 patients across nine French hospitals centres. LN was revealed by pregnancy in five cases. A preparation phase preceded the pregnancy in 90% of the cases, and complete remission from the disease was obtained for more than 24 months in 74% of them. Corticosteroids and hydroxycorticoamine were generally continued (68% and 73% respectively). Azathioprine and aspirin were administered in 37% and 65% of pregnancies. Maternal complications occurred in 40% of cases, with a 38% rate of premature birth. 68% of pregnant women with LN flares during these pregnancies were: the presence of positive anti-native DNA antibodies (p < 0.0001), low C4 (p = 0.004), the absence of complete remission of LN at conception (p < 0.001), or inactivity of LN inferior to 12 months (p = 0.003). Preeclampsia occurred more frequently with the deterioration of kidney function or an increase in proteinuria at conception (p = 0.011 and p = 0.001). The perinatal death rate was calculated at 6.8%. We observed 25% premature births and 15% intrauterine growth retardation (IUGR).

**Conclusions:** We found encouraging results. The incidence of maternal and foetal complications during pregnancy was reduced compared to previous European studies including lupus patients. Risk factors of major maternal complications are best characterized.

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**TH-PO780**

**Nephrotic Syndrome and Pregnancy**

**C. De Castro,1 J. Ashley Jefferson,2 Thomas R. Easterling,3 Div. of Nephrology, Dept. of Medicine, Univ of Washington School of Medicine; 2Dept of Obstetrics and Gynecology, Univ of Washington School of Medicine, Seattle, WA.**

**Background:** In the absence of hypertension or renal insufficiency, some consider the perinatal outcomes in pregnant women with nephrotic syndrome to be good. However, the diagnosis and management of both maternal and fetal well-being is challenging.

**Methods:** We describe the presentation, management, and maternal and fetal outcomes of 31 pregnancies in 24 women with biopsy proven nephrotic syndrome during pregnancy. We included demographical data, laboratory findings, antenatal and postnatal management, the relationship between the numbers of organ involvement and several fibrotic markers in Japanese patients with IgG4-Related Disease.

**Results:** There were 24 subjects (9 primiparas) with 31 pregnancies and 32 offming. Mean age was 27.6 years (range 16-39 years) and mean gestational age at presentation was 18.7 weeks (range 5-40 weeks). Labs revealed a mean creatinine 0.85mg/dl (range 0.4-1.4mg/dl), mean serum albumin 1.97g/dl (range <1.3-2.2g/dl), and mean proteinuria 0.86g/day (range 3.6-32g). UltraCOM cardiac output measurements were available for 18 pregnancies. Mean cardiac output at presentation was markedly elevated at 8.38L/min. 14 of 31 pregnancies were known to have kidney disease before pregnancy. Nephrotic syndrome was newly diagnosed in 16 patients. Biopsy was performed during pregnancy in 10 subjects (median age of gestation 20-5 weeks (range 2-27 weeks) changing management in 70%. 6 were biopsied postpartum. Biopsy diagnoses were FSGS(11), IgAN(3), lupus nephritis(3), membranous nephropathy(3), and 1 case each of Fibrillary GN, MPGN, C3GN, and minimal change disease. Maternal complications included preeclampsia(10/31), acute kidney injury(3/31) and cellulitis(3/31). Mean age of gestation at delivery was 35.4 weeks (range 25-40 weeks). 17 delivered via cesarean section. Fetal complications included birth weight <2500g(18), IUGR(3), and 10 were admitted to NICU.

**Conclusions:** Pregnant women with nephrotic syndrome are at high-risk for developing maternal and foetal complications despite the absence of significant hypertension or renal insufficiency.

**TH-PO781**

**The Relationship Between Serum Cholinesterase, Number of Organ Involvement and Fibrotic Markers in Japanese Patients with IgG4-Related Disease**

**Hirofumi Nishikawa, Yoshinori Taniguchi, Tatsuki Matsumoto, Kazu Hamada-Ode, Yosiko Shinamura, Koji Ogata, Kosuke Inoue, Taro Horino, Shimpei Fujimoto, Yoshio Terada. Kochi Univ, Japan.**

**Background:** To evaluate the relationship between cholinesterase, number of organ involvement and serum fibrotic markers in Japanese patients with IgG4-related disease (IgG4-RD) including kidney involvement.

**Methods:** The clinical setting, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=20) were assessed. Several laboratory data of IgG4-RD with multiple organs’ involvement (IRDMO) (n=10), IgG4-RD with limited organ’s involvement (IRDL0) (n=10), ANCA-associated vasculitis (AAV) (n=10) and the pregnancy in 90% of cases were comparatively examined. Furthermore, we studied the relationship between the numbers of organ involvement (NOI) and several fibrotic markers (ELF score and serum Dkk-1) in IgG4-RD group.

**Results:** Serum cholinesterase (CHE) levels were significantly lower in IRDMO group than in AAV and SJS group, were considered significant of NE-RD and LN group. Serum albumin and IgG levels were significantly lower and CRP levels were significantly higher in AAV group, compared with IgG4-RD and SJS group. There were no significant differences in these levels between IRDMO and SJS. In total IgG4-Related Disease (IRDMO, IRDL0, SJS, SJS group), serum CHE levels inversely correlated with NOI, CRP levels positively correlated with NOI, Dkk-1 and without inhibitors, levels in IRDMO were significantly lower than IRDL0 and healthy subjects (p < 0.05).

**Conclusions:** The ELF score and serum Dkk-1 level might be a clinically useful indicators of active fibrosis and the extent of disease in Japanese patients with IgG4-RD. Notably, serum CHE levels could predict these phenomena.

**TH-PO782**

**Serum Cholinesterase, Number of Organ Involvement and Fibrotic Markers in Japanese Patients with IgG4-Related Disease**

**Hirofumi Nishikawa, Yoshinori Taniguchi, Tatsuki Matsumoto, Kazu Hamada-Ode, Yosiko Shinamura, Koji Ogata, Kosuke Inoue, Taro Horino, Shimpei Fujimoto, Yoshio Terada. Kochi Univ, Japan.**
TH-PO782
Crescentic IgA Nephropathy – A Prospective Study Krishan L. Gupta, Prabhakar Doddi, 1 Rittambha Nanda, 2 Raja Ramachandran, 1 1 Nephrology, PGIMER, Chandigarh, India; 2 Pathology, PGIMER, Chandigarh, India.

Background: Crescentic IgA nephropathy (cIgAN) carries a very poor prognosis and the initial creatinine at presentation predicts long-term outcome. The present prospective study was carried out to evaluate the clinicopathological correlation and outcome of cIgAN.

Methods: We enrolled 21 IgAN patients, 14 recurrent tonsillitis (RT) patients without urinary abnormalities and 20 children with tonsillar hyperplasia (TH) who had been performed tonsillectomy. Genomic DNA from tonsillar crypts of each patient was extracted, and V4 regions of the 16S ribosomal RNA (rRNA) gene were amplified and analyzed using a high-throughput multiplexed sequencing approach. Differences of the genus composition among three groups were statistically analyzed by PERMANOVA, and visualized by principal component analysis (PCA).

Results: Our data suggested that bacterial diversity of cIgAN was different from that of TH. However, there was no bacterial genus that differs significantly in the frequency of between IgAN and RT. The PCA did not separate IgAN from RT, although it was discriminated from TH. In addition, we compared the bacterial composition between IgAN patients with higher and lower serum IgA levels; however, no difference in composition of microbiome between the two groups was observed.

Conclusions: Similar pattern of bacteria are present in tonsillar crypts of both IgAN and RT, suggesting that the host responsiveness to these bacteria is important in the development of IgAN.

TH-PO783
Comprehensive Microbiome Analysis of Tonsillar Crypts in IgA Nephropathy Hirofumi Watanabe, Shin Goto, Masafumi Tsuchida, Ichichi Narita. Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background: IgA nephropathy (IgAN) is the most prevalent primary chronic glomerular disease, in which the mucosal immune response, especially elicited in the tonsil or intestine, has been estimated to be involved with the development of the disease. To explore the relationship between IgAN and bacterial flora in the tonsils, we conducted a comprehensive microbiome analysis.

Methods: We enrolled 21 IgAN patients, 14 recurrent tonsillitis (RT) patients without urinary abnormalities and 20 children with tonsillar hyperplasia (TH) who had been performed tonsillectomy. Genomic DNA from tonsillar crypts of each patient was extracted, and V4 regions of the 16S ribosomal RNA (rRNA) gene were amplified and analyzed using a high-throughput multiplexed sequencing approach. Differences of the genus composition among three groups were statistically analyzed by PERMANOVA, and visualized by principal component analysis (PCA).

Results: Our data suggested that bacterial diversity of cIgAN was different from that of TH. However, there was no bacterial genus that differs significantly in the frequency of between IgAN and RT. The PCA did not separate IgAN from RT, although it was discriminated from TH. In addition, we compared the bacterial composition between IgAN patients with higher and lower serum IgA levels; however, no difference in composition of microbiome between the two groups was observed.

Conclusions: Similar pattern of bacteria are present in tonsillar crypts of both IgAN and RT, suggesting that the host responsiveness to these bacteria is important in the development of IgAN.

TH-PO784
Urinary N-Acetyl-d-Glucosaminidase Level Is Associated with Tubulointerstitial Fibrosis and Therapeutic Response in Immunoglobulin A Nephropathy Yousuke Yamada, Makoto Harada, Akinori Yamaguchi, Koji Hashimoto, Makoto Higuchi, Yuji Kamijo. Dept of Nephrology, Shinshu Univ School of Medicine, Matsumoto, Nagano, Japan.

Background: Therapeutic response in Immunoglobulin A nephropathy (IgAN) patients has been shown to be affected by the severity of chronic renal failure, such as tubulointerstitial fibrosis. Urinary N-acetyl-d-glucosaminidase (U-NAG) is a known biomarker of tubulointerstitial injury. The present study aimed to clarify if U-NAG level was associated with the severity of tubulointerstitial fibrosis and whether it could predict the therapeutic response to ST.

Methods: Among the 81 IgAN patients who were diagnosed by kidney biopsy and treated with ST between March 2005 and April 2015 at Shinshu University Hospital, the U-NAG data of 77 patients were investigated for relationships between clinical and histological data. To search for associations between U-NAG level and clinical remission (CR) rate, we examined 39 of the above 77 patients who were observed for 3 years following ST.

Results: Measurement may also aid in the prediction of therapeutic response to ST in IgAN.

TH-PO785
Beneficial Effect of Immunosuppressive Therapy for IgA Nephropathy with Moderately Impaired Renal Function Kyung sun Park, 1 Jongha Park, 2 Jong Soo Lee, 1 Hyun Chul Chung, 2 1 Div of Nephrology, Dept of Internal Medicine, Dongguk Medical Center, Ulsan, Korea; 2 Div of Nephrology, Dept of Internal Medicine, Ulsan Univ Hospital, Ulsan, Korea.

Background: A variety of treatment has been attempted to slow progression of IgA nephropathy (IgAN) such as renin-angiotensin system inhibitors and adding corticosteroid for patients with impaired renal function. We compared clinical outcomes of IgAN patients who were treated with vs. without immunosuppressive therapy (IST), and explored identified risk factors associated with progression of renal dysfunction.

Methods: Patients who were diagnosed as IgAN between 2001 and 2014 were screened. Among the 81 patients who had initial estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m² and had followed up for at least 12 months were included in this analysis.

Results: A total of 92 patients were analyzed. 39 patients received IST (Group 1) and 53 did not (Group 2). Median follow-up (59 vs. 77 months) and mean age (46.6 vs. 47.4 years) were not significantly different. In Group 1, serum creatinine was increased (93 vs. 136 mg/dL, P<0.01), serum creatinine (1.66 vs. 1.45 mg/dL, P<0.003), and median amount of proteinuria (2033 vs. 1115 mg/day, P<0.001) were significantly higher, but mean cGFR (43.7 vs. 50.1 mL/min/1.73 m², P<0.001) and serum albumin (3.5 vs. 4.0 g/dL, P<0.009) were lower than Group 2. Three patient of Group 1 and 7 of Group 2 progressed to end-stage renal disease (ESRD). ESRD-free survival was comparable between two groups (P=0.639).

Conclusions: IST may have a beneficial effect for slowing progression of IgAN with moderately impaired renal function.

TH-PO786
Longitudinal Study of a Kindred with Familial IgA Nephropathy Reveals Stable Serum Levels of Galactose-Deficient IgA1 in a Kindred with Familial IgA Nephropathy Reveals Stable Serum Levels of Galactose-Deficient IgA1 Hiroyuki Park, 1,2 Yoshimi Ueda, 1,2 Zina Moldoveanu, 3 Stacy D. Hall, 1 Karen Hart, 1 Krzysztof Kiryluk, 1 Ali G. Gharavi, 3 Dana Rizk, 3 Bruce A. Julian, 3 Jan Novak, 1 1 Univ of Alabama at Birmingham, Birmingham, AL; 2 The Jikei Univ School of Medicine, Tokyo, Japan; 3 Columbia Univ College of Physicians and Surgeons, New York, NY.

Background: Patients with IgA nephropathy (IgAN) have elevated levels of circulating galactose-deficient IgA1 (Gd-IgA1). Familial form of IgAN has been reported among people of all ancestries. Serum Gd-IgA1 levels are heritable in patients with familial and sporadic IgAN. Moreover, 50% of first-degree relatives of patients with familial IgAN have high serum Gd-IgA1 levels (>50th percentile of healthy controls) without clinical signs of IgAN. This kindred had a longitudinal study of a large kindred with familial IgAN.

Methods: Pedigree includes 4 men with biopsy-proven IgAN. Members recruited in 2005 and 2014 included 2 IgAN patients, 13 relatives, and 7 genetically unrelated marry-ins. Serum Gd-IgA1 was measured using lectin ELISA and expressed relative to a standard serum Gd-IgA1 in U/100 ng of serum IgA. Spot urine sample was obtained for urinalysis and Gd-IgA1 in serum samples was determined.

Results: Change in serum Gd-IgA1 level was stable within families and in marry-ins (P=0.179 compared to baseline).

Conclusions: Serum Gd-IgA1 levels are stable within families and in marry-ins. Gd-IgA1 measurement may also aid in the prediction of therapeutic response to ST in IgAN.
Conclusions: Serum IgG-IgA levels in 22 individuals in this multiplex IgAN pedigree were stable over a 9-year period. No blood relative developed IgAN or exhibited a urinary abnormality during the 9-year follow-up period.

Funding: NIDDK Support, Private Foundation Support

TH-PO787
Childhood IgA Nephropathy with Nephrotic Syndrome (NS-IgAN) at Onset

Yuko Koike,1 Akihiro Shimizu,1 Nobuo Tsutobi,1 Keita Hiranuma,1 Makoto Ogura,2 Sayuri Shirai,1 Yoshinori Yasuda,1 Takashi Yasuda,1 Shoihi Maruyama,1 Tetsuya Kawamura,1 Seiichi Matsuo,2 Takashi Yoko,1 Ashikaga Red Cross Hospital,1 Hoshino Ashikaga,1,2

Background: Recently, in Japan, IgA nephropathy (IgAN) has been often treated by tonsillectomy. In this report, we investigated the clinical outcomes and factors affecting renal outcome of childhood NS-IgAN.

Methods: We retrospectively analyzed 1267 patients with IgAN biopsied between 1979 and 2010. Propensity scores were calculated using logistic regression. Associations between RASB and ESRD were examined using a Cox regression model adjusted by inverse probability of treatment weighted.

Results: During follow-up (median 5.1 years), 130 patients developed ESRD. With Cox regression adjusted by inverse probability of treatment weighted, RASB use was significantly associated with a lower risk of ESRD (hazard ratio, 0.57; 95% confidence interval [CI] 0.30-0.50, p<0.001). Among the 357 cases of NS- and other IgAN, the association was weaker (hazard ratio, 0.65; 95% CI 0.40-0.50, p<0.001). Among patients with IgAN using propensity score approaches.

Conclusions: In keeping with KDIGO recommendations, our results did not suggest improvement in renal prognosis by steroid therapy alone for IgAN with eGFR<50mL/min. However, IgAN patients referred to nephrologists often have reduced eGFR at the time of referral. Therefore, we evaluated the KDIGO guidelines to assess, and further develop their clinical significance for treatment of IgAN with reduced eGFR by a large multicenter cohort study in Japan.

TH-PO791
The Effect of Renin-Angiotensin System Blockade on the Incidence of End-Stage Renal Disease in IgA Nephropathy

Exhibition

Ritsuko Katafuchi,1 Kentaro Kitani,1 Yoshinari Nishiyama,1 Tetsuya Tsuruya,1 Takahito Uehata,1 Kenjiro Endo,1,2

Background: The impact of renin-angiotensin system blockade (RASB) on the incidence of end-stage renal disease (ESRD) remains unclear in IgA nephropathy (IgAN). This study assessed associations between RASB and ESRD in IgAN using propensity score-based methods.

Methods: We retrospectively analyzed 1267 patients with IgAN biopsied between 1979 and 2010. Propensity scores were calculated using logistic regression. Associations between RASB and ESRD were examined using a Cox regression model adjusted by inverse probability of treatment weighted, regression, stratification and matching.

Results: During follow-up (median 5.1 years), 130 patients developed ESRD. With Cox regression adjusted by inverse probability of treatment weighted, RASB use was significantly associated with a lower risk of ESRD (hazard ratio, 0.57; 95% confidence interval 0.41–0.79). Significant associations were observed for other propensity score-based methods.

Conclusions: In keeping with KDIGO recommendations, our results did not suggest improvement in renal prognosis by steroid therapy alone for IgAN with eGFR<50mL/min. However, IgAN patients referred to nephrologists often have reduced eGFR at the time of referral. Therefore, we evaluated the KDIGO guidelines to assess, and further develop their clinical significance for treatment of IgAN with reduced eGFR by a large multicenter cohort study in Japan.

TH-PO788
Predictive Factors of Spontaneous Remission in Patients with Immunoglobulin A Nephropathy

Hironobu Mukaiyama,1,2 Taketsugu Hama,1,2 Wook Kang,1,2

Background: Immunoglobulin A nephropathy (IgAN) is commonly considered as a lifelong disease, incidences of spontaneous remission (SR) have been occasionally reported. We investigate the incidence as well as the clinical predictors of SR in IgAN.

Methods: Medical records of biopsy-proven IgAN in Severance hospital from 2006 to 2014 were reviewed. SR was defined as complete remission reached without any corticosteroid therapy or combination therapy with tonsillectomy demonstrated significantly improved renal survival compared with no steroid therapy (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.50-0.93, p=0.015). Like KDIGO recommendations, multivariate analysis adjusted for other confounders showed that median level of proteinuria was a strong predictor of SR (HR 0.76, 95% CI 0.63-0.92, p=0.005). During a median follow up of 4 years, 70 patients (34.8%) reached primary outcome.

Conclusions: We conclude that treating the contributive factors to CR in multivariate analysis will tend to significant improvement in renal survival compared to no steroid therapy (HR 0.25; 95% CI 0.06-0.70, p<0.05).

TH-PO790
Evaluation of KDIGO Clinical Practice Guidelines for IgA Nephropathy by Japanese Multicenter Large Cohort Study

Kouko Watanabe,1 Kentaro Koike,1 Akihiro Shimizu,1 Nobuo Tsutobi,1 Keita Hiranuma,1 Makoto Ogura,2 Sayuri Shirai,1 Yoshinori Yasuda,1 Takashi Yasuda,1 Shoihi Maruyama,1 Tetsuya Kawamura,1 Seiichi Matsuo,2 Takashi Yoko,1 Ashikaga Red Cross Hospital,1 Hoshino Ashikaga,1,2

Results: Among the 84 patients with NS- and other IgAN, the association was weaker (hazard ratio, 0.65; 95% CI 0.40-0.50, p<0.001). Among patients with IgAN using propensity score approaches.

Conclusions: In keeping with KDIGO recommendations, our results did not suggest improvement in renal prognosis by steroid therapy alone for IgAN with eGFR<50mL/min. However, IgAN patients referred to nephrologists often have reduced eGFR at the time of referral. Therefore, we evaluated the KDIGO guidelines to assess, and further develop their clinical significance for treatment of IgAN with reduced eGFR by a large multicenter cohort study in Japan.

TH-PO789
Comparison of the Effect of Oral Steroid and Tonsillectomy Combined with Steroid Pulse Therapy for IgA Nephropathy

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Results: Recently, in Japan, IgA nephropathy (IgAN) has been often treated by tonsillectomy combined with steroid pulse therapy (TSP) instead of traditional oral steroid therapy (oPSL). However, there are few reports described about the comparison of them.
approaches. In stratified analysis, a beneficial association between RASB and ESRD was observed in patients with history of hypertension, reduced estimated glomerular filtration rate (<60 mL/min/1.73 m²), mesangial proliferation and segmental glomerulosclerosis (P for interaction <0.05), and tended to be greater in patients with proteinuria (>1.0 g/24 h), extracapillary proliferation, and receiving methyldopa/isoniazide pulse therapy (P for interaction <0.10).

Conclusions: Treatment with RASB was associated with a lower incidence of ESRD in the real-world practice of IgAN.

TH-PO794
Remission of Urinary Protein at 2 Years After Diagnosis with Normal Renal Function and Remission of Urinary Protein at 1 Year After Diagnosis with Decreased Renal Function as an Accurate Prognostic Marker in IgA Nephropathy Takayuki Fujii,1 Junichi Hoshino,2 Joichi Usui,1 Satoshi Suzuki,1 Yoshifumi Ubara,1 Kunihito Yamagata.1 1Seirei Sakura Citizens Hospital, Sakura, Japan; 2Tosanoumun Hospital, Tokyo, Japan; 3Unit of Toksuka, Toksuka, Japan.

Background: Level of proteinuria (UP) has a strong association with poor renal prognosis in IgA nephropathy. Recent studies reported that the level of UP, especially, remission of UP(CR) defined as less than 0.3 g/d, during the follow-up was a more accurate prognostic factor than at diagnosis. In this multicenter study, we evaluated which post-diagnosis measurement point achieving CR strongly associated with the renal prognosis.

Methods: 1,077 patients diagnosed with IgA nephropathy between March 1991 and December 2013, and could be followed-up for at least 3 years or reached end-stage kidney disease (ESKD) were enrolled. We performed a retrospective cohort study among 2 divided groups: 638 with eGFR<60 mL/min/1.73 m² (A) and 439 with eGFR<60 mL/min/1.73 m² (B). The endpoint of this study was a 50% decrease in eGFR or ESKD. The annual daily UP level until 3 years after diagnosis was categorized into 2 grades: <0.3 g/d and >0.3 g/d and its association with the renal prognosis was investigated. The hazard ratio of the endpoint adjusted with clinical and pathological findings and treatment was examined.

Results: Regarding CR as a reference, UP<0.3 g/d was not a significant poor prognostic factor at diagnosis, but at 1 year, especially at 2 years, it became a significant factor in group A. On the other hand, in group B, UP<0.3 g/d was already shown to be a significant factor at diagnosis and the strongest factor at 1 year.

Conclusions: CR within 2 years after diagnosis with normal renal function and CR within 1 year after diagnosis with decreased renal were the most accurate predictors for a favorable outcome in IgA nephropathy.

TH-PO795
Copetin, a Surrogate Marker for AVP, Is Associated with Disease Severity and Progression in IgA Nephropathy Patients Debbie Zittema,1 Jan A.J.G. van den Brand,2 Jack F. Wetzel,3 Ron T. Gansvoort,1 1Nephrology, Univ Medical Center Groningen, Groningen, Netherlands; 2Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: The disease course of IgA Nephropathy (IgAN) is difficult to predict. Copetin, a surrogate marker for AVP, has been described to cause kidney damage in various renal diseases. We investigated therefore the associations of copetin with disease severity and progression in IgAN.

Methods: Included were 60 biopsy proven IgAN patients from the Radboud UMC Nijmegen, of whom urine and blood samples were available. Urinary excretion of α1M, KIM-1, NGAL and plasma copeptin was measured at baseline. Survival analyses were performed for the composite outcome death, end stage renal disease (ESRD), doubling of serum creatinine, start of immunosuppressive therapy and the individual components.

Results: In IgAN patients (male: 72%, age: 42±13 year, eGFR: 48±21 mL/min/1.73m², copetin: 9.4±5.18 pmol/L) copetin was associated at baseline with proteinuria (St. β=0.34, p=0.01) and with start of immunosuppressive therapy (p=0.04) using a log rank test. When patients who started immunosuppressive therapy during follow up (n=14) were excluded, copetin (as continuous variable) was furthermore associated with the incidence of ESRD (p=0.01, HR=1.09; i.e. a 9% increase in risk of ESRD per 1 pmol/L increase in copetin), doubling of serum creatinine (p=0.004, HR=1.07) and the composite outcome (p=0.003, HR=1.07) in Cox regression models, adjusting for proteinuria and sex. After additional adjustment for eGFR, which is debatable as eGFR decline could be part of the causal pathway between copetin and outcomes, the survival analyses lost significance.

Conclusions: Copetin is a promising disease severity marker in IgAN with additive predictive value for future kidney function loss over proteinuria, but not over eGFR, the strongest predictor of disease progression in this study.

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TH-PO796

Clinical Outcomes of Nephrotic Syndrome in IgA Nephropathy

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TH-PO797

Comparative Outcomes in Primary Glomerulonephritis Among a Large Diverse United States Population

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TH-PO798

A Specific Transcriptomic Profile Characterizes Peripheral Blood Mononuclear Cells (PBMCs) from Uremic Patients (pts) Treated With On Line Hemodiafiltration (OL-HDF) Compared to Those Treated With Bicarbonate Dialysis (BHD)

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Background: Recent studies suggest that OL-HDF can reduce the progression of dialysis-related cardiovascular diseases, but the molecular mechanisms underlying this improvement are not yet known. The aim of our study was to identify, through a high-throughput approach, differences in gene expression profiles of PBMCs from pts undergoing OL-HDF compared to BHD.

Methods: The transcriptomic profile was evaluated in PBMCs isolated from 10 pts regularly dialyzed with OL-HDF (convective volume 22 L) and 10 pts treated with BHD using microarray analysis (Agilent Technologies). The results were evaluated by statistical (ANOVA) tests and functional pathway analysis (Ingenuity Pathway Analysis).

Results: We observed that 868 genes were differentially expressed in the comparison between OL-HDF and BHD (fold change>1.5). Thirty-seven functional gene networks were identified and atherosclerosis signaling was the top canonical pathway associated with BHD (p=2.45x10^-10). Among the downregulated genes in OL-HDF there were PDGF (FC=-2.13) and Clusterin (FC=-2.14), involved in vascular injury and Mononucone Oxidase A (MAO-A, FC=-2.43), an important source of oxidative stress and a major contributing factor to the development of ventricular hypertrophy and heart failure. Interestingly, Apolipoprotein E (APOE) gene, an anti-oxidant/ inflammatory protein, was upregulated (FC=+1.7) by OL-HDF. qPCR, performed in an independent testing-group [15 BHD, 15 OL-HDF] confirmed that PDGF, Clusterin and MAO-A were down-expressed in OL-HDF (p =0.01), whereas APOE resulted higher expressed (p<0.01).

Conclusions: The OL-HDF can contribute to cardiovascular risk reduction through the modulation of pathways involved in the progression of atherosclerotic disease. This observation could open new perspectives in the prevention of cardiovascular risk in dialysis pts.

TH-PO799

Twice-Weekly versus Thrice-Weekly Hemodialysis in Patients with or without Residual Kidney Function

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Background: Residual kidney function (RFK) accounts for large solute removal and significantly contributes to survival benefits in hemodialysis (HD) patients. However, there are no reliable outcome data suggesting that the frequency of HD might be safely reduced in patients with substantial RFK.

Methods: A total of 685 patients receiving more than 3 months HD therapy were included from the CRC registry for ESRD. The presence of RFK was defined as more than 100 ml/day of urine volume, and patients were classified into twice-weekly HD with RFK (n=113), thrice-weekly HD with RFK (n=137) and thrice-weekly HD without RFK (n=435).

Results: The baseline RFK was significantly higher in twice-weekly HD patients with RFK than in thrice-weekly HD patients with RFK (P<0.002). In multivariable analyses, compared with thrice-weekly HD patients without RFK, thrice-weekly HD patients with RFK were associated with lower risk for all-cause mortality (HR 0.65; 95% CI 0.39-1.04; P=0.04). For hospitalization of cardiovascular events, thrice-weekly HD treatment with RFK did not reduce the risk of mortality (HR 0.65; 95% CI 0.22-1.87). For hospitalization of cardiovascular events, thrice-weekly HD treatment with RFK was independently associated with lower risk, (HR 0.40; 95% CI 0.16-0.98), but twice-weekly HD patients with RFK were not associated (HR 0.89; 95% CI 0.38-1.71).

Conclusions: Twice-weekly HD patients with RFK have similar outcome compared to thrice-weekly HD patients without RFK. However, thrice-weekly HD patients with RFK were more advantageous for mortality and CVE than those without RFK.

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

Underline represents presenting author.

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Conclusions: Among a large racially/ethnically diverse United States population, FSGS was the most prevalent GN and was associated with the highest rate of progression to ESRD among all race/ethnic groups (36% overall) followed by membranous GN (12%), minimal change disease (10%) and MCD (7%).

Methods: Retrospective longitudinal cohort study in the period 1/1/2000 through 12/31/2013 among patients within Kaiser Permanente Southern California. Patients who had biopsy proven primary GN were characterized and followed until they reached the outcomes of ESRD or mortality. ESRD was defined as receiving dialysis or renal transplant.

Results: 2,849 patients were identified with biopsy proven GN. The mean age of the cohort was 47 yrs with 48% females, 37% Hispanics, 30% whites, 17% blacks, and 12% Asians. Focal segmental glomerulosclerosis (FSGS) was the most common GN among all race/ethnic groups (36% overall) followed by membranous GN (12%), minimal change disease (MCD) (12%), IgA nephropathy (IgAN) (10%), and others (31%). The mean follow up was 3.8 yrs. ESRD occurred in 26% (704 required dialysis and 38 had a renal transplant). Mortality occurred in 18%. ESRD occurred among 35% of FSGS, 19% among IgAN, 12% among MGN, 10% among MCD, and 29% among other GN's.
TH-PO800
Comparison of Outcomes Between Incremental and Abrupt Initiation of Hemodialysis: A Propensity-Matched Analysis of a Prospective Cohort Study in Korea

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Background: When patients are diagnosed as end-stage renal disease (ESRD) and initiate hemodialysis (HD), thrice-weekly HD is a very common format. Recent report suggested possible benefit from beginning HD therapy less than three times weekly and incremental increase of dialysis dose, but there are not sufficient data. We compared outcomes of thrice-weekly and incremental HD.

Methods: A cohort of 1273 patients who were diagnosed as having ESRD and initiated hemodialysis from 2008 to 2014 were prospectively enrolled. The patients were classified into the abrupt initiation group (3 sessions/week) or the incremental initiation group (1-2 sessions/week). We compared HRQOL evaluated by KDQOL-SF and Beck’s depression inventory (BDI) score at 3 months and 12 months after HD, and residual renal function by daily urine volume at 12 months after HD and all-cause mortality between the groups.

Results: Before propensity score matching, the abrupt group tends to be younger and showed smaller daily urine volume, higher modified Charlson comorbidity index (mCCI), and higher serum blood urea nitrogen and creatinine level compared to incremental group. A total of 432 patients (288 for abrupt and 144 for incremental group) were selected by propensity score matching. HRQOL tends to be better in incremental group for every domain of KDQOL-SF and BDI, but none of them showed significant difference at 3 months. At 12 months after HD, only cognitive functioning domain was better in incremental group. Daily urine volume at 12 months after HD was similar in two groups. All-cause mortality was comparable between two groups before and after propensity score matching.

Conclusions: Incremental initiation of HD showed comparable results with abrupt group regarding HRQOL, residual renal function and all-cause mortality. Incremental HD might be considered as another format of initiating HD for selected ESRD patients.

TH-PO801
Predictors of Substantial Residual Kidney Function in the First Year of Hemodialysis Treatment
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Background: Residual kidney function (RFK) plays a critical role in dialysis adequacy, quality of life, and survival in hemodialysis (HD) patients. Therefore, identifying predictors related to preservation of RFK may contribute to improving patient management and developing novel strategy for preserving RFK.

Methods: In a longitudinal cohort of 18,091 patients who initiated conventional HD over four years (1/2007-12/2010), we examined the association of baseline characteristics during the first 3 months of their dialysis treatment with RKF [renal urea clearance (KRU) or ≥600 mL/day of UV as outcomes with 2-level adjustments for case-mix variables and laboratory measurements in addition to baseline RFK values.

Results: Patients were 62-14 years old, 37% female, 29% non-Hispanic Black, and 67% diabetic. Median KRU and UV were 2.95 (IQR, 1.63-4.64) mL/min/1.73m2 and 800 (IQR, 500-1,300) mL/day, respectively. High γδ lymphocyte, higher serum concentrations of albumin and calcium, and lower serum concentrations of creatinine and phosphorus were consistently associated with better preserved RFK indices irrespective of models. A history of congestive heart failure was an independent predictor for loss of RFK.

Conclusions: Better nutritional and CKD-MBD indices were associated with preserved RFK while a history of congestive heart failure were associated with loss of RFK at 1 year of hemodialysis initiation in this large national cohort. Additional studies to preserve RFK in dialysis patients are needed.

TH-PO802
Clinical Determinants of Ultrafiltration Rates in Hemodialysis
Adam K. Horeish, Jeffrey M. Rimmer. Univ of VT Med Ctr, Bulington, VT.

Background: High rates of ultrafiltration (UFR) are associated with adverse events. Approaches to reduce UFR other than fluid restriction alone are needed.

Methods: We examined characteristics associated with ultrafiltration rates (UFR) in patients dialyzed at UVMMC. Ultrafiltration rates (volume removed/pre-dialysis weight/treatment time) were followed electronically. Charts of 213 patients treated in October 2015 were examined with IRB approval. Patient characteristics and laboratory values were determined for 177 patients receiving three treatments during each of 4 consecutive weeks. These include average weight (PWI), treatment duration (RT), and inter-dialytic weight gain (WtG); age, gender, dialysis vintage, sequence (TTTS vs MW), treating unit, diabetes, heart failure, prescribed diuretics, difference between serum and dialysate sodium (DifNa), percent urea reduction (PRU), absolute urea reduction, serum potassium, albumin, hemoglobin and pre and post dialysis blood pressure. The relation of weight, weight gain and treatment length were examined with descriptive statistics. Other potential explanatory variables were explored with multivariable regression models using both average UFR and average UFR for first weekly treatment as dependent variables.

Results: The range and median for PWT, RXT, and WtG respectively are 41.6 to 226, 81 Kg, 3 to 5.5, 4 hrs; and 0.63 to 8.38, 2.69 kg. When the values of PW, RXT and WtG are below the median, 48.4%, 44.8% and 19.1% of patients respectively have a UFR > 10 mL/kg/hr and 15.6%, 23.9% and 48.9% if above the median. Variables significantly associated with UFR by regression are enumerated in table 1.

Variables not listed did not reach significance.

Conclusions: The large effect of low PWt requires long RXT to avoid high UFR with moderate WtG. Other prescribed variables that could be used to modify UFR include TTTS vs MFV schedule, DifNa and possibly diuretic use.

TH-PO803
Study on Hemodialysis (HD) Time and Prognosis in Maintenance HD Patients: The Q-Cohort Study
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Background: HD time has been recognized as an important factor of dialysis adequacy. However, there have been few reports on studying the associations between HD time and prognosis in maintenance HD patients. We present some findings from a prospective cohort study, the Q-cohort Study, which was set up to explore the risk factors for mortality in Japanese HD patients. In this present study, we examined the associations between HD time and mortality in Japanese HD patients.

Methods: A prospective multicenter cohort study (Q-Cohort Study) was conducted between December 2006 and December 2010. A total of 3,459 Japanese HD patients were prospectively followed for 4 years. We examined the association of HD time and prognosis using a Cox proportional hazards model. Propensity scores were calculated using logistic regression.

Results: During follow-up period, 566 patients died from any causes. Patients with HD of 5 hours or more (n = 2,144) showed significantly lower mortality risk for all cause death at hazard ratio = 0.82 (95% confidence interval: 0.68 to 0.99) compared with those with HD of less than 5 hours (n = 1,315) after adjusting for confounding risk factors. This association remained significant using a propensity score-based approach. We stratified the study, the Q-cohort Study, which was set up to explore the risk factors for mortality in Japanese HD patients.

Methods: In a longitudinal cohort of 18,091 patients who initiated conventional HD over four years (1/2007-12/2010), we examined the association of baseline characteristics during the first 3 months of their dialysis treatment with RKF [renal urea clearance (KRU) or ≥600 mL/day of UV as outcomes with 2-level adjustments for case-mix variables and laboratory measurements in addition to baseline RFK values.

Results: Patients were 62-14 years old, 37% female, 29% non-Hispanic Black, and 67% diabetic. Median KRU and UV were 2.95 (IQR, 1.63-4.64) mL/min/1.73m2 and 800 (IQR, 500-1,300) mL/day, respectively. High γδ lymphocyte, higher serum concentrations of albumin and calcium, and lower serum concentrations of creatinine and phosphorus were consistently associated with better preserved RFK indices irrespective of models. A history of congestive heart failure was an independent predictor for loss of RFK.

Conclusions: Better nutritional and CKD-MBD indices were associated with preserved RFK while a history of congestive heart failure were associated with loss of RFK at 1 year of hemodialysis initiation in this large national cohort. Additional studies to preserve RFK in dialysis patients are needed.

Variables not listed did not reach significance.

Conclusions: The large effect of low PWt requires long RXT to avoid high UFR with moderate WtG. Other prescribed variables that could be used to modify UFR include TTTS vs MFV schedule, DifNa and possibly diuretic use.

TH-PO803
Study on Hemodialysis (HD) Time and Prognosis in Maintenance HD Patients: The Q-Cohort Study
Kiichiro Fujisaki,1 Shigeru Tanaka,2 Masatomo Taniguchi,3 Kazuhiro Tsunya,4 Hideki N. Hirakata,5 Takanari Kitazono. 1Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; 2Div of Nephrology, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.

Background: HD time has been recognized as an important factor of dialysis adequacy. However, there have been few reports on studying the associations between HD time and prognosis in maintenance HD patients. We present some findings from a prospective cohort study, the Q-cohort Study, which was set up to explore the risk factors for mortality in Japanese HD patients. In this present study, we examined the associations between HD time and mortality in Japanese HD patients.

Methods: A prospective multicenter cohort study (Q-Cohort Study) was conducted between December 2006 and December 2010. A total of 3,459 Japanese HD patients were prospectively followed for 4 years. We examined the association of HD time and prognosis using a Cox proportional hazards model. Propensity scores were calculated using logistic regression.

Results: During follow-up period, 566 patients died from any causes. Patients with HD of 5 hours or more (n = 2,144) showed significantly lower mortality risk for all cause death at hazard ratio = 0.82 (95% confidence interval: 0.68 to 0.99) compared with those with HD of less than 5 hours (n = 1,315) after adjusting for confounding risk factors. This association remained significant using a propensity score-based approach. We stratified the analysis by patient age in 10-year increments, this finding remaining significant only in patients aged 60 years or older than 80 years.

Conclusions: Our results suggest that HD time of 5 hours or more improves all-cause mortality especially in older HD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO804

Salt Taste Sensitivity, Sodium Intake, and Fluid Status in Hemodialysis


1 Univ of MI; 2 Renal Research Inst.

Background: Dietary Sodium intake (SI) contributes to volume status and blood pressure (BP) control in hemodialysis (HD) patients. Salt taste sensitivity (STS) may drive sodium intake, and has not been systematically studied in HD. We sought to assess the relationship between STS, SI, fluid status (as determined by bioelectrical impedance spectroscopy (BIS)) and pre-dialysis BP in HD patients.

Methods: As part of an ongoing randomized trial involving a low sodium diet, adults receiving outpatient HD were assessed for STS using commercial taste strips impregnated with 0.1-6% sodium chloride (NaCl); mean SI was estimated from 3-day food diaries. Total Body Water (TBW) and Extracellular Volume (ECV) were estimated using whole-body and segmental (calf-resistance) BIS, respectively.

Results: Baseline data on 33 enrolled patients (16 male, 17 black, 13 white, mean age 52±15yr) were analyzed. Mean monthly pre-HD systolic BP was 151±16 mmHg. Mean SI was 2.5±g/day (range: 1.1-5.2). Mean estimated SI was 0.8±g/day higher in patients without STS compared to those with STS (1.6±% NaCl (p=0.06). Higher SI correlated with higher calf ECV (r=0.38, p=0.04), whole-body-BIS TBW (r=0.65, p=0.0005) and ECV (r=0.34, p=0.09). Mean Calf ECV was significantly lower in those with STS vs those without STS at 1.6% (0.19 ± 0.23 L; p=0.04). There was no correlation between SI and pre-dialysis BP (in-center routine or standardized).

Conclusion: Salt taste sensitivity and measures of hydration status by bioelectrical impedance spectroscopy are correlated with sodium intake in hemodialysis. The findings suggest that patients with low salt taste sensitivity may be particularly at risk for fluid excess. Future research should examine mechanisms of Salt taste sensitivity and its role in management of hemodialysis patients.

Funding: Private Foundation Support

TH-PO805

Arrhythmic Risk in Patients with Type II Diabetes on Hemodialysis: Preliminary Results from the Monitoring in Dialysis (MiD) Clinical Study

Prabir Chaudhury, Don E. Williamson, James A. Tumlin, David M. Charytan, Kowdile chandrasekar Prakash, Vijay K. Khre; 1 Univ of Cincinnati; 2 Nephrology Associates; 3 Univ of Tennessee; 4 Brigham and Womens Hospital, Boston; 5 Apollo Hospitals-Chennai; 6 Medanta-Medicity.

Background: 40% of the overall ESRD population has diabetes and these patients are considered to be at increased risk of cardiac events. The goal of this analysis was to describe the pattern of both clinically significant events and documented arrhythmias in a subset of patients with Type II diabetes from the Monitoring in Dialysis (MiD) study.

Methods: The MiD study is a prospective, multi-center, observational study designed to characterize the type and frequency of documented and adjudicated arrhythmias in hemodialysis patients during a 6-month period, using an implanted continuous cardiac monitoring device (Medtronic Remote XT or Revel LINQ). All documented arrhythmias and clinically significant co-morbidities (CSA) defined as bradycardia ≥40 bpm for ≥2 sec, asystole ≥3 sec, sustained ventricular tachycardia ≥130 bpm for ≥30 sec and symptomatic arrhythmias during this period were then correlated temporally to the dialysis cycle (first, second or third dialysis session of the week; during or after hemodialysis; how long after hemodialysis).

Results: Type II Diabetes was present in 39/66 (59%) of the MiD patients. The mean age was 62 (36-76) years, 72% male, mean years on HD 2.8 (1-15), 36% with a history of cardiac arrhythmias with a mean follow-up of 8.6 months (range 0.6-13.9). Arrhythmic risk in the Type II diabetic patients was similar to the previously reported data on the entire study population, with the highest incidence of documented arrhythmias occurring in the 12 hour period starting with each dialysis session (particularly in the 8 hours after the end of the session). The incidence then decreased, followed by a gradual rise during the rest of the interdialytic period. Interestingly, the incidence of CSA in the 12 hour period starting with each dialysis session of the week was much greater than in the overall study population.

Conclusions: The increase in the incidence of CSA in diabetic ESRD patients suggests that these patients could be a target population for the use of the Reveal implant.

Funding: Pharmaceutical Company Support - Medtronic

TH-PO806

Individualising Fluid Restriction Based on Target Weight Can Prevent a High Ultrafiltration Rate

Emily Sec, John W. MacD. Agar. Nephrology, Univ Hospital, Geelong, VIC, Australia.

Background: Fluid restriction (FR) in haemodialysis patients has traditionally been advised by residual urine output and an arbitrarily defined oral intake, commonly 750ml/day. Surprisingly, little attention has been paid to individualising FR according to target post-dialysis weight (TW), despite the logical argument that smaller patients require less fluid. Excessive inter-dialytic weight gain (IDWG), when calculated as a percentage of TW (IDWG%), results in a high ultrafiltration rate (UFR) if session length (t) is constant ([UFR(ml/kg/hr) = IDWG(ml) + TW(kg) ÷ (thr)]). Since a high UFR has been linked to a poor clinical outcome, these patients must be identified and targeted. We aim to determine if a high IDWG% can be predicted from TW and then be used to individualise FR.

Methods: Data were prospectively collected from 14,112 sessions in 139 patients undergoing in-centre thrice-weekly haemodialysis between Jan-Dec 2014. Mean age was 68.9yr, 56% were male. Mean TW and IDWG% were calculated every 6 weeks. Results were divided into IDWG% cohorts, within each of which an average TW was calculated.

Results: Mean IDWG% was 2.30% (range 0.1-6.4). IDWG% was inversely proportional to TW (r=−0.78).

From this data, we devised a formula that calculates an individualised FR based on the desired UFR (dUFR), the session duration (t), TW, and interval days between sessions (n). As [IDWG% = FR x n] and [IDWG% = dUFR x t x TW]; therefore [FR(ml) = dUFR x t x TW ÷ n x residual urine output]

Conclusions: Patients with low TW are most at risk of high IDWG% and, consequently, a high UFR. A high UFR leads to rapid intravascular volume contraction which triggers post-dialytic thirst and reinforces the inevitable cycle of further high IDWG%. As TW provides a readily accessible clinical end-point that predicts at-risk patients, we propose that FR be individualised according to TW to enable patients to remain below the desired UFR.

TH-PO807

Ultrafiltration Rate Should Be Independently Targeted as a Marker of Haemodialysis Adequacy

Emily Sec, John W. MacD. Agar. Dept of Nephrology, Univ Hospital, Geelong, VIC, Australia.

Background: For 30 years, solute clearance has been the key determinant of dialysis adequacy. This emphasis has marginalised the critical contribution of safe rates of fluid removal to “adequate” dialysis. Ultrafiltration rate (UFR) has been proposed as an easily measurable marker of volume management (Agar 2015 HDI) and several studies have demonstrated a correlation between high UFR and poor clinical outcomes. Despite this association, UFR is not routinely targeted and the proportion of patients who meet percentage reduction in urea (PRU) but not UFR targets is unclear. While a “safe” UFR may be yet to be conclusively defined, current literature supports an escalating clinical risk beyond a UFR of 10ml/hr/kg and an absolute risk above 1.5ml/hr/kg.

Results: Data were prospectively collected from patients undergoing in-centre thrice-weekly conventional haemodialysis over a 12-month study period (Jan-Dec 2014). PRU and mean UFR were calculated every 6 weeks. UFR <10ml/hr/kg was defined as “volume-adequate” and PRU >65% was considered “solute-adequate”.

Results: 720 episodes were collected from 115 patients. The mean age was 68.9yr and 56% were male. 73% of episodes met both adequacy targets (PRU+UFR+), 10% met the UFR but not the PRU target (PRU-UFR+), 16% met the PRU but not the UFR target (PRU+UFR-). 1% met neither (PRU-UFR-). In patients who met the PRU target 18% did not meet the UFR target.
Conclusions: Adequacy of solute removal does not equate to adequacy of volume removal. When a solute marker is used as the sole determinant of dialysis adequacy, a significant number of patients undergo “volume-inequivalent” dialysis. These patients were more likely to be female and have a lower post-dialysis weight. Given the potentially substantial clinical implications, we propose that UFR be independently targeted allowing composite solute and volume markers to together define truly “adequate” dialysis.

TH-PO808
Fluid Management with Technology-Assisted Probing Peter B. De Oreo,1 Mary kay Deck,2 Anne M. Brunfield.3 1Medical Affairs, Centers for Dialysis Care 1, Shaker Heights, OH; 2Systems, Intelomed 2, Wexford, PA; 3Clinical Services, Intelomed 1, Wexford, PA.

Background: Intradialytic hypotension (IDH) is associated with mortality. Rapid fluid removal is associated with cardiovascular (CV) morbidity and mortality. Decreased pulse pressure during HD is associated with improved outcomes. A focused intervention approach assisted by monitoring technology was used to assess fluid management as defined by 1) achievement of post weight within 1 kg around dry weight, 2) avoidance of IDH (SBP<90), 3) decrease in pulse pressure (PP) from pre-post dialysis.

Methods: 24 patients (16 controls, 8 intervention) were included. Control data: 18 treatments (txs) prior to protocol along with 18 txs during active monitoring and guided probing. The protocol required setting goal to <2 KG < dry weight OR < .2 KG last post weight with small goal changes early in treatment, set of defined actions based on CV physiologic monitoring via CV Insight™ (CVI) [Intelomed, Wexford, PA] and relative plasma volume (RPV) via Crit-Line III® [Fresenius, Kayville, UT]. Interventions were employed based on monitoring data, with a goal to increase UF tolerance without increasing IDH events.

Results: Intervention patients demonstrated significant improvement in all three fluid management parameters during the protocol compared to preceding txs.

<table>
<thead>
<tr>
<th></th>
<th>PW/DW-1 KG*</th>
<th>PW/DW-1 KG*</th>
<th>SBP&lt;90</th>
<th>Pre RP</th>
<th>Post RP</th>
<th>UFR</th>
<th>PW/DW*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seerline</td>
<td>.09 ± 1.02</td>
<td>.26 ± 0.2</td>
<td>.07 ± 0.1</td>
<td>7.1 ± 1.3</td>
<td>58 ± 1.2</td>
<td>5.7 ± 0.1</td>
<td>.01 ± 0.001</td>
</tr>
<tr>
<td>Protocol</td>
<td>.36 ± 0.04</td>
<td>.15 ± 0.04</td>
<td>.01 ± 0.02</td>
<td>66 ± 1.6</td>
<td>53 ± 1.6</td>
<td>7.4 ± 0.1</td>
<td>.02 ± 0.001</td>
</tr>
</tbody>
</table>

*p <0.001; p<0.05*

Conclusions: Although reducing DNa to < 140 mEq/L may have only a modest impact on IDW and predialysis SBP it has the potential to significantly decrease mortality.

TH-PO810
Comparison of Ordered versus Measured Dialysate Sodium Concentrations Ambreen Gul,1 Dana Miskulin,2 Leonard A. Armit,1 Siriram Narsipur,3 Susan Paine,1 Ronald Schrader,1 Philip Zager.1,2 1DCI, Albuquerque, NM; 2UNM, Albuquerque, NM 3Tufts, Boston, MA; 4SUNY, Stony Brook, NY; 5SUNY, Syracuse, NY.

Background: There is controversy regarding the optimal dialysate sodium concentration (DNa). Many investigators have urged the use of DNa of 134 to 138 mEq/L, while others have cautioned that low DNa may be associated with increased hospitalization and mortality. Unfortunately, throughout this debate, little attention has been paid to how closely delivered DNa matches ordered DNa.

Methods: We studied 333 hemodialysis (HD) patients at 4 DCI facilities. We sampled dialysate from the arterial dialyzer port prior to the start of HD for measurement of DNa. Units 1 and 2 used Fresenius 2008 K machines and Fresenius Granuflo® Dry Acid and Naturalyte®, mixed onsite from dry concentrates. Units 3 and 4 used Gambro Phoenix machines and pre-mixed acid concentrates obtained from Rockwell and bicarbonate cartridges from Baxter or Gambro. The online clearance feature was off.

Results: Measured DNa was usually higher than ordered DNa. The magnitude of difference varied by clinic (p <0.0001).

Conclusions: Intradialytic hypotension (IDH) is associated with mortality. Rapid fluid removal is associated with cardiovascular (CV) morbidity and mortality. Decreased pulse pressure during HD is associated with improved outcomes. A focused intervention approach assisted by monitoring technology was used to assess fluid management as defined by 1) achievement of post weight within 1 kg around dry weight, 2) avoidance of IDH (SBP<90), 3) decrease in pulse pressure (PP) from pre-post dialysis.

Results: Intervention patients also demonstrated significant improvement in IDH compared to Control patients that dialyzed without guided probing.

Conclusions: A focused effort to improve fluid management through technology guided probing supported by CVI measures of cardiovascular stress and RPV, was successfully executed by chair-side staff. Optimizing fluid removal goals while simultaneously avoiding IDH events illustrates the benefit of patient monitoring.

Funding: Pharmaceutical Company Support - Intelomed

TH-PO809
Increased Mortality Associated with Higher Dialysate Sodium Concentrations Is Not Due Solely to Higher Interdialytic Weight Gains and Blood Pressure Ambreen Gul,1 Ronald Schrader,1 Susan Paine,1 Philip Zager.1,2 1DCI, Albuquerque, NM 2UNM, Albuquerque, NM.

Background: There is ongoing controversy regarding the optimal DNa. Many investigators have urged the use of DNa of 134 to 138 mEq/L, to limit interdialytic weight gain (IDWG) and improve control of hypertension. In contrast, others have cautioned that low DNa may be associated with increased hospitalization and mortality.

Methods: We conducted a retrospective observational study of 26,000 chronic hemodialysis (HD) patients treated in facilities operated by Dialysis Clinic Inc. from 2009-2013 to assess the relationships of DNa to IDWG and predialysis systolic BP (SBP) and their effect on mortality. We fit a time-varying Cox proportional hazards regression model for mortality, which included all incident and prevalent patients. There were over 630,000 patient-months of follow-up. Multiple data values for each patient were aggregated by month. Predictor variables in addition to DNa included demographics, monthly lab values, and session-level data including IDWG and pred- and post-dialysis BP. Individual clinic effects were fit as random effects. Time-varying predictors were lagged by 2 months.

Results: Higher DNa concentrations were associated with modest increases in IDWG and predialysis SBP [figure]. Moreover, neither predialysis SBP ≥ 150 mm Hg or IDWG < 4.2% of estimated dry weight were associated with increased mortality.

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

276A
Least squares mean differences (95% CI) were larger at Clinics 1 [-3.27 (-4.02, -2.53) mEq/L] and 2 [-3.77 (-4.49, -3.05) mEq/L] vs. with Clinics 3 [-1.44 (-2.16, -0.78) mEq/L] and 4 [-1.78 (-2.47, -1.10) mEq/L]. The percentages of measured DNA concentrations within ±2 mEq/L of the ordered DNAs at Clinics 1, 2, 3 and 4 were 47, 25, 71 and 77%, respectively.

**Conclusions:** Measured DNA concentrations were often significantly higher than ordered DNA in facilities using Fresenius machines and dialysate concentrates mixed onsite. Routine measurement of DNA should be incorporated into facilities’ QAPI programs. Future studies looking at clinical outcomes associated with differences in prescribed DNA should include measurements of delivered DNA concentrations.

**Funding:** Clinical Revenue Support

**TH-PO811**

**Successful Use of Bivalirudin Protocol to Prevent Extracorporeal Thrombosis in Hemodialysis Patients with Heparin Induced Thrombocytopenia**

Abdullah Hamad, Fadwa S. Al-Ali, Hoda Tollia, Rania Abdelzahim Ibrahim, Mohamed Elsayed. *Nephrology, Fahad Bin Jassim Kidney Center, Hamad General Hospital, Doha, Qatar.*

**Background:** Heparin Induced Thrombocytopenia (HIT) has been reported in hemodialysis (HD) patients with a variable prevalence of 1-13%. There have been few reports using Lepirudin, Argatroban and Danaparoid in the management of extracorporeal thrombosis (ECT) during dialysis in these patients as heparin is contraindicated. We are reporting use of Bivalirudin to prevent ECT.

**Methods:** Our Study was done in Fahad Bin Jassim Kidney Center in Doha, Qatar (a large outpatient HD clinic of 300 patients). All patients diagnosed with HIT were included.

HIT was diagnosed by ELISA method.

**Results:** 8 patients had confirmed positive HIT AB, 2 were receiving warfarin for atrial fibrillation with no ECT events and were excluded. One patient had a negative repeat test for HIT AB with no ECT events so he was excluded too. 5 patients with HIT AB and recurrent ECT events during dialysis were included. 3 patients had fistula and 2 had permanent catheter. A protocol was developed to start and adjust Bivalirudin based on activated partial thromboplastin time (APTT) value. Table 1 summarizes patients dosing and adjustment on protocol.

**Bivalirudin Infusion Protocol for HIT in Hemodialysis Patients**

1. Initial Infusion Rate 0.625mg/kg/hr
2. Baseline aPTT should be checked and then 2 hours after infusion initiated
3. aPTT should be checked 2 hours after infusion every session until a PTT in therapeutic range with no further change then every once per week
4. APTT for bleeding versus thrombosis must be evaluated to determine safe and effective dose in high risk of bleeding
5. aPTT adjust at 1.5–2.5 X normal range
6. aPTT adjust to 2.0–2.5 X normal range

**Bivalirudin Infusion Protocol for HIT in Hemodialysis Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dialysis access type</th>
<th>Duration on Bivalirudin</th>
<th>Starting dose</th>
<th>Final dose</th>
<th>Adjustment of dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>fistula</td>
<td>5 months</td>
<td>1.8 mg/hour</td>
<td>3.4 mg/hour</td>
<td>6 times</td>
</tr>
<tr>
<td>2</td>
<td>fistula</td>
<td>4 months</td>
<td>1.6 mg/hour</td>
<td>2.1 mg/hour</td>
<td>2 times</td>
</tr>
<tr>
<td>3</td>
<td>permcath</td>
<td>2 months</td>
<td>2 mg/hour</td>
<td>4 mg/hour</td>
<td>4 times</td>
</tr>
<tr>
<td>4</td>
<td>fistula</td>
<td>4 months</td>
<td>1.5 mg/hour</td>
<td>1.8 mg/hour</td>
<td>1 time</td>
</tr>
<tr>
<td>5</td>
<td>permcath</td>
<td>8 months</td>
<td>1.7 mg/hour</td>
<td>3 mg/hour</td>
<td>3 times</td>
</tr>
</tbody>
</table>

**Conclusions:** We are reporting a successful use of Bivalirudin protocol to prevent ECT in HD patients with HIT. It provided a simple dosing initiation with easy adjustment on protocol.

**Funding:** Clinical Revenue Support

**TH-PO813**

**The Correlation of BNP and hANP in Hemodialysis Patients and Their Prediction Ability of Life Prognosis**

Koji Takemura, Fumitaka Fujino, Yoshihiro Miyauchi, Takashi Watanabe. *Nephrology, Asahi General Hospital, Asahi, Chiba, Japan.*

**Background:** B-type natriuretic peptide (BNP) and human atrial natriuretic peptide (hANP) have been reported to be useful for assessment of the volume status, cardiovascular risk, or life prognosis in hemodialysis patients. However, correlation or superiority of the two parameters are not clear. The aims of this study were to assess whether BNP and hANP have correlation, and whether they are predictive.

**Methods:** Two hundred and twenty-eight hemodialysis patients at one hospital were assessed in March 2012. BNP and hANP were measured at the end of hemodialysis. And we observed the patients’ survival until May 2015.

**Results:** This study analyzed 228 patients. Results showed that BNP and hANP had strong correlation in patients without chronic heart failure (EF>40%): R²=0.70 to those with atrial fibrillation (AI), R²=0.57 without AF. 69 deaths occurred in about 3 years; in univariate analysis, BNP and hANP were significant predicting factors (p=0.004 and p=0.013 for each) and in multivariate analysis, age and hANP were significant predicting factors in multivariate analysis (p=0.019 and 0.011).

**Conclusions:** BNP and hANP had strong correlation in hemodialysis patients without chronic heart failure. They also predicted life prognosis, and especially hANP had independent prediction ability. In hemodialysis patients, BNP and hANP are useful for assessment of life prognosis in spite of various known or unknown confounding factors.

**Funding:** Clinical Revenue Support

**TH-PO814**

**Intracranial Fluid Shifts During Hemodialysis Measured Using VIPS (Volumetric Integral Phase-Shift Spectroscopy) Is Influenced by Osmolarity, Sodium and Less So by Urea Nitrogen**

Chetham P. Venkatasubba rao,1 Sreedhar A. Mandayam,2 Eric Bershad,3 Euseba Calvillo,1 Jose Ignacio Suarez.1

1Neurology, Baylor College of Medicine, Houston, TX; 2Nephrology, Baylor College of Medicine, Houston, TX.

**Background:** End Stage Renal Disease (ESRD) patients undergoing hemodialysis(HD) experience a drop in serum osmolarity. This may result in cerebral edema. Cerebral edema has been measured by invasive monitors or imaging studies. We used Volumetric Integral Phase-Shift Spectroscopy(VIPS), a non-invasive technology that detects fluid-induced phase shifts in low-energy radio waves transmitted through the brain.

**Methods:** The protocol was approved by the IRB of Baylor College of Medicine. ESRD on HD subjects without Intracranial disorders were enrolled. VIPS monitoring was performed pre, intra and post HD. Measured and calculated serum osmolarity(osm) and mini state examination was performed pre and post HD.

**Results:** 19 patients (12 males) were enrolled. Median age was 50 years. 1 patient withdrew. Of the 31 HD runs, 21 complete data sets were analyzed. There was a mean increase of 10.6% in the total Intracranial fluid(ICF) value from baseline corresponding to an average of 7 mOsm reduction. The ICF change measured by VIPS correlated with osm changes (r=0.31), best with change in Sodium change [Post HD – pre HD] (r=0.51), less so with the BUN change (r=0.14) and least with glucose (r=0.01). Subjects with sodium < 135 at baseline had a tendency to develop lower ICF change (3% (n=5) as compared to euonaticern subjects (12%, n=16, p=0.22).

**Conclusions:** VIPS provides real-time non-invasive monitoring of intracranial fluid shifts. Subjects develop serum osmolar data sets were analyzed, which potentially be a model for studying cerebral edema. Sodium shifts had a higher correlation to ICF change in our study. Further research to confirm our findings are warranted.

**Funding:** Pharmaceutical Company Support - Cerebrotech Medical Systems, Inc.
Online Hemodiafiltration Using Citrata® Dialysis Solution – An Alternative to Systemic Anticoagulation? Pavlina Richtrova, Lukas Kielberger, Jan Mares, Tomas Reischig. 1st Medical Dept, Charles Univ Medical School and Teaching Hospital, Plzen, Czech Republic.

Background: Citrata® is a dialysis solution using citrate (contrary to more common acetate) as the acidifying buffer compound. According to recently published data, its application could decrease or even obviate the need for systemic anticoagulation in hemodialysis (HD) patients. Particularly so during online hemodiafiltration (HDF) as in this setting predialysis should provide yet higher in-dialyzer citrate concentrations resembling regional citrate anticoagulation (RCA).

Methods: In a prospective, randomized, cross-over study, 10 long-term HD patients were enrolled during 4h HDF procedure using Citrata® (0.8 mmol/l citrate) in a predialysis setting without additional systemic anticoagulation. Standard HDF procedure using acetate-buffered solution together with fractionated heparin was applied as a control. Along the session, blood and dialysate were sampled to enable analysis of thrombogenicity, acid base balance, calcium metabolism, and dialysis efficacy. Data are given as means±SD; statistical significance was calculated by ANOVA.

Results: No HDF session was terminated prematurely though the semiquantitative dialyzer clotting score showed increased clotting under citrate solution (p=0.001). At the same time, procedure efficacy assessed by spKt/V, as well as serum calcium, bicarbonate and pH did not differ significantly. While in controls the thrombin-antithrombin (TAT) levels remained unchanged, during citrate-buffered HDF a steady increase of TAT was observed: from 3.6±2.36 and 5.6±3.85 μg/l at 0h to 7.8±6.57 and 25.3±5.45 μg/l at 6h post HD and 15h post HD, respectively (p<0.001).

Conclusions: From a clinical standpoint, HDF using Citrata® excluding heparin may serve as a viable alternative to RCA where systemic anticoagulation is to be avoided. No issues were detected in terms of safety, tolerance, and dialyzer performance. Even then, increased laboratory markers of thrombogenicity suggest inferiority of such approach precluding its use for regular HD.

Funding: Government Support - Non-U.S.

TH-PO816

Hypertension in Hemodialysis Patients: Dialysis Techniques and Hormonal Regulation Guido Gatti, Chiara Lananzi, Marco Simonini, Simona Pozzoli, Stefano Tentori, Elena Brioni, Lorena Citterio, Elisabetta Messaggio, Simona Delli carpi, Nunzia Nascaismima, Teresa Aricadinio, Maria Teresa Sciarrone Alibrandi, Rita Quatragno, Marco Melandri, Giorgio Slaviero, Donatella Spotti, Paolo Munanta. Nephrology, Dialysis and Hypertension, IRCSS San Raffaele Scientific Inst, Milano, Italy.

Background: Hypertension in hemodialysis patients has a prevalence of 50-80% and is associated to increased cardiovascular mortality. Endogenous ouabain (EO), a digitalis-like cardiotonic steroid produced by adrenal glands, in hemodialysis patients is associated to left ventricular mass, volume and eccentric hypertrophy remodeling. N-terminal pro B-type natriuretic peptide (NT-proBNP) is associated with heart failure and fluid overload. Hemodiafiltration (HDF) improves cardiovascular survival than bicarbonate hemodialysis (HD). The aim is to explore the relationship between BP values, hormonal regulation (EO and NT-proBNP) and hemodialysis techniques.

Methods: We enrolled 93 chronic hemodialysis patients; we performed ABPM of 24 hours, blood and effluent dialysis fluid analysis. 42 patients were treated with HDF, 51 with HD.

Results: NT-proBNP is directly associated with SBP of 24h and indirectly with EF of left ventricle; it is removed by HD by convective clearance (decrease of 57%), as medium molecular weight compounds, and not by HDF (increase of 21%). EO is directly associated with interdialytic weight gain and interdialytic sepium; it decreases with dialysis session independently of dialysis technique (decrease of 20%). Patients with cardiopathy have higher EO plasma levels than patients without cardiopathy. Beta-2 microglobulin is directly associated with NT-proBNP and SBP of 24h.

Conclusions: These data show that NT-proBNP is an index of hypertension and heart failure, while EO is linked to fluid overload and left ventricular hypertrophy. NT-proBNP is removed by convection, while EO decreases independently of dialysis technique (ultrafiltration determine the decrease?). Convective clearance, expressed indirectly by beta-2 microglobulin, may influence BP control through the modulation of NT-proBNP.

TH-PO817

NT-proBNP Is a Useful Biomarker to Identify Cardiac Dysfunction in Japanese Hemodialysis Patients Minako Shimizu,1 Ayumu Nakashima,2 Shigehiro Doi,2 Takao Masaki. 1Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan; 2Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) is a well-established diagnostic biomarker of heart failure in populations without kidney dysfunction. However, the clinical significance of NT-proBNP in hemodialysis (HD) patients remains unclear.

Methods: We enrolled 1428 HD patients from 14 dialysis centers in Hiroshima, Japan and performed cross-sectional analysis. Blood samples for measurement of serum NT-proBNP were collected at pre- and post-HD sessions. Among all participants, ultrasonic evaluations of carotid intima-media thickness (CIG) was performed in 395 patients (27.7%). We evaluated whether serum NT-proBNP levels were associated with left ventricular hypertrophy (LVH) on the electrocardiogram (ECG), and LVH and ejection fraction (EF) on UCG. We also used multiple regression analysis to investigate the clinical factors that correlated with the reduction ratio of NT-proBNP.

Results: The mean pre- and post-HD NT-proBNP levels were 8789 ± 15311 and 5257 ± 8939 pg/ml, respectively. Multivariate regression analysis revealed that the post-HD NT-proBNP was significantly correlated with LVH on ECG as well as EF and LVH on UCG (p < 0.001). When both the mean of post-HD NT-proBNP were analyzed, patients with the same odds ratios (ORs) for LVH on ECG, and LVH and EF on UCG were lower at pre- than post-HD (ORs: 1.36, 2.16, 3.47 versus 1.19, 2.37, respectively). However, the sensitivity and specificity of pre- and post-HD NT-proBNP to predict LVH and EF were similar. In multiple linear regression analysis, the reduction ratio (%) of NT-proBNP due to HD was correlated with Kt/V (p < 0.001), membrane area (p < 0.001), membrane type (p < 0.001), % body weight gain (p < 0.001), treatment time (p < 0.001) and ultrafiltration rate (p = 0.003).

Conclusions: NT-proBNP is a useful biomarker to identify LVH and LV dysfunction in HD patients. Blood samples should be taken post-HD despite the NT-proBNP reduction due to HD.

Funding: Pharmaceutical Company Support - ROChe

TH-PO818

Similar Complement Activation by Heparin-Coated Dialyzer Compared with Heparin-Free Dialysis Using Predilution Susan J. Logtenberg,1,2 Casper F.M. Franssen,1 Marc Maj Seelen.1 1Nephrology, Univ Medical Center, Groningen, Netherlands; 2Internal Medicine, Diakonessenhuizen, Utrecht, Netherlands.

Background: Heparin-coated dialyzers have been shown to be an effective method for heparin-free hemodialysis and are increasingly used. Conflicting reports on complement activation by heparin have been published, however. Complement activation could therefore be potential harmful for patients that are scheduled for transplantation shortly after hemodialysis (HD). We investigated the difference in complement activation between heparin-coated dialyzers and heparin-free HD using conventional filters with predilution.

Methods: We measured C3 and C3d levels in 16 (5 F) consecutive patients that were treated with either a heparin coated filter (n=8 (Evodial®)) or a conventional filter (n=8 cellulose triclate, n=3 polyamide) with predilution 1-2h. C3 and C3d were measured before and at the end of a single HD treatment session. C3 to C3d ratios were calculated.

Results: Mean age was 58±16 years. The figure shows C3d/C3 ratios before and after HD for individual cases in the different filter groups. Mean C3/C3d ratios increased during HD with all types of dialyzers. Mean C3/C3d ratio in the heparin-coated dialyzer group increased from 9.7±7.6 before HD to 12.4±7.8 after HD (p<0.001). Mean C3/C3d ratio in the conventional filter group increased from 8.0±2.3 to 11.8±5.4 (p=0.03). C3d/C3 ratio increased during HD with both the polyamide (from 7.5±1.8 to 10.0±1.2; p<0.09) and the cellulose triclate dialyzer (from 8.3±2.4 to 12.9±6.9; p=0.02). There was no significant difference in the change of C3d/C3 ratio between the heparin coated filter group and the conventional filter group (2.7±1.4 v. 3.7±3.7, respectively (p=0.5).

Conclusions: Heparin-coated dialyzers induce similar complement activation during HD when compared to conventional dialyzers.

TH-PO819

A Heparin-Grafted Membrane plus Citrate Containing Dialysate versus Regional Citrate Anticoagulation: Results of the CITED Study Christoph Metalidis, Ruben Poesen, Annelore De winter, Dirk R. Kyupers, Pieter Evenepoel, Bjorn Meijers. Nephrology, Univ Hospitals Leuven, Belgium.

Background: Heparin is the mainstay anticoagulant during dialysis. Alternative anticoagulant strategies include regional citrate anticoagulation (RCA), heparin-grafted cardyzers or saline flushes. In the last case, RCA is the most efficacious, although technical complexity and labor intensiveness preclude widespread use. Heparin-grafted membranes are easy to use, but dialyzer patency is inferior to RCA. Whether combination of citrate-containing dialysate plus heparin-grafted membranes is non-inferior to RCA is unknown.

Methods: The CITrana plus EV odial in Dialysis (CiTED) study was an open, randomised crossover study comparing citrate-containing dialysate plus heparin-grafted membranes versus RCA. In the study arm, we scheduled 750 dialysis sessions using combination of a heparin-grafted AN69ST dialyzer (Evodial 180®, BAXTER) and 1 mmol/L citrate-containing dialysate (Selectroc Citrate®, BAXTER). In the control arm, the sessions of RCA were scheduled using Polysulfone 130 (BAXTER) dialyzers and calcium-containing dialysate. In all sessions, scheduled treatment duration was 4 hours.
No systemic heparin was used. Primary endpoint was non-inferiority for clotting events of the combination of a heparin-grafted membrane plus citrate-containing dialysate vs. RCA, with a prespecified non-inferiority margin of 10%.

Results: We included 25 patients, receiving 1285 study dialysis sessions in total, 636 in the study arm and 649 in the control arm. Both anticoagulation strategies were safe. Overall, clotting rates were low: 37/636 (5.82%) in the study arm and 42/649 (6.47%) in the control arm. The primary endpoint of non-inferiority was met (P < 0.0001). In secondary analysis, using Cox proportional hazard analysis, time to clotting did not differ between study arms (P 0.62).

Conclusions: Combination of a heparin-grafted dialyzer with citrate-containing dialysate is non-inferior to conventional RCA. The procedure is easy to perform without additional pumps or calcium measurements. Combination of a heparin-grafted dialyzer and citrate-containing dialysate is a valid alternative to RCA in patients requiring heparin-free dialysis.

Funding: Pharmaceutical Company Support - Gambro - Baxter

TH-P0820
Effect of L-Carnitine on Markers of Mineral Bone Disease in the CARNIDAL trial. Lucile Meyread,1 Michel Chonchol,2 Messaad Ouzirila,3 Christine Fumerton,1 Aude Servais,3 Sophie Tezenas du montcel.2


Background: Previous studies suggested that L-carnitine in hemodialysis patients decreases intact parathyroid hormone levels (iPTH). We studied the effects of L-carnitine on markers of mineral bone disease (MBD), including fibroblast growth factor (FGF23) in a randomized, double-blind trial.

Methods: We evaluated the effects of 1 g of intravenous L-carnitine after each dialysis session for 1 year when compared to placebo in a randomized, double-blind trial. C-terminal FGF23 (cFGF23) were measured at baseline, every 3 months and end of study in 23 patients. Serum calcium, phosphate and iPTH were available at similar time points. The effect of L-carnitine on serum calcium, phosphate, iPTH and plasma cFGF23 was studied by mixed linear models for repeated measurements in intent-to-treat. We also examined the relation of cFGF23 with intravenous (IV) iron and EPO dose.

Results: Serum calcium increased more in the L-carnitine than in the placebo group (calcium: β of L-carnitine x time 0.005 ± 0.002 mmol/L/month, p=0.03; phosphate: β of L-carnitine x time 0.02 ± 0.006 mmol/L/month, p=0.001). In both groups, serum iPTH was stable over time and plasma cFGF23 increased (β log FGF23 0.05 ± 0.01 Hu/mL/month, p=0.0001). In multivariable analyses on 166 measurements, cFGF23 was positively correlated with serum calcium (β 1.5 ± 0.6, p<0.01), serum phosphate (β 1.2 ± 0.2, p=0.0001) and negatively correlated with EPO dose (β 0.41 ± 0.17, p=0.02). No association was observed between cFGF23 and IV iron administration (p=0.13), serum ferritin (p=0.7).

Conclusions: L-carnitine treatment slightly increased serum calcium and phosphate without an effect on iPTH or cFGF23. FGF23 was inversely correlated with ESA dose but not with IV iron dose.

Funding: Government Support - Non-U.S.

TH-P0821
Clinicopathological Characteristics of Lanthanum Deposition in the Gastrointestinal Tract of Dialysis Patients Shigevi Han,1 Akira Fujimori,1 Shinichi Nishi,2 Dept of Diagnostic Pathology, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan; 2Div of Pathology, Ako City Hospital, Ako, Hyogo, Japan; 3Div of Nephrology, Konan Hospital, Kobe, Hyogo, Japan; 4Dept of Nephrology, Kobe Univ Graduate School of Medicine, Kobe, Hyogo, Japan.

Background: Lanthanum carbonate (LC) is a phosphate binder for dialysis patients with hyperphosphatemia. Recent studies have reported gastric lanthanum deposition in patients treated with LC (Haratake J et al. Am J Surg Pathol 2015; Makino M et al. Pathol Int 2015; Tokumoto H i d e k i  N .  H i r a k a t a , 2,5 Comparative Effectiveness of Oral and Injectable Vitamin D Receptor Activator on Infectious Mortality in Hemodialysis Patients: The Q Cohort Study Shigeru Tanaka,1 Toshisharu Ninomiya,2 Masatomo Taniguchi,2 Masanori Tokumoto,2 Hideki N, Hirakata,2 Hiroko Ooboshi,2 Kazuhiko Tsuryu,2,3 Takanaori Kitazono,2,3 1Div of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; 2Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Div of Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; 4Div of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 5Div of Research Management, Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Conclusions: A total of 3,278 subjects were divided into 3 groups by the administration type of VDRA: oral group (n=1,835), injectable group (n=459) and non-user (n=984). Impacts of VDRA on infectious mortality were examined using a Cox regression model adjusted with propensity score-based approaches.

Results: Among 3,324 patients during follow-up (median 3.9 years), 534 patients died and 115 patients developed infection death. The use of injectable VDRA was associated with a significant lower infectious mortality compared to non-user, while oral VDRA did not significantly reduce the risk of infection mortality compared to non-user (hazard ratio [HR] for injectable VDRA, 0.40; 95% confidence interval [CI], 0.13–0.91, and HR for oral VDRA, 0.78; 95% CI, 0.53–1.15, respectively). Direct comparison between oral and injectable VDRA revealed that the injectable group was also significantly associated with better survival than oral group (HR, 0.33; 95% CI, 0.13–0.83).

Conclusions: Treatment with injectable VDRA has a more favorable impact on the infectious mortality compared to oral VDRA in the real-world practice of hemodialysis patients.

Funding: Government Support - Non-U.S.

TH-P0823
Alcoholism Levels in Patients on Hemodialysis/Relationship with the Metabolic Syndrome María Jose Fernandez Reyes,1 Manuel M. Heras,1 María Gonzalez,2 Olaia Rodriguez fraga,3 Ramiro Callejas,1 Álvaro Molina,1 Vanessa Lopes-martin,1 María astrid Rodriguez gomez,1 Leonardo Calle.1 1Nephrology, Hospital General Segovia, Segovia, Spain; 2Biochemistry, Hospital Univ La Paz, Madrid, Spain.

Background: Recently it has been shown that serum aldosterone (SA) levels are correlated with several components of the metabolic syndrome (MSy). OBJECTIVE: to establish SA levels on hemodialysis patients and its possible association with insulin resistance (homeostasis model assessment of insulin resistance HOMA-IR), excess body fat and/or serum adipokine levels.

Methods: 44 stable patients on HD, not taking ACE inhibitors/angiotensin receptor blockers. Mean age: 72.5±12.5years; 52.3% men; 34.1% diabetics. Mean time on HD:43±24.9 months. 28 patients were anuric. All measurements were done prior to the midweek HD session.

Results: SA levels were above the normal range (1.17-23.6 ng/dl) in 63% of patients. Plasma Renin Activity (PRA) was above the normal range (0,23-3.32 ng/mL/hour) in 27.3% of patients. Median: 31.15 (p25: 5.56; p75: 411 ng/mL); PRA median: 1.14 (p25: 0.45; p75: 20.9 ng/mL/hora). There were not statistically significant difference (Student’s t) in SA levels between anuric and non-anuric; male and female; presence and absence of myocardialopathy or diabetes. There were no statistically significant correlations (Spearman) of SA levels or PRA with urine volume; residual renal function; dose or length of time on HD; age; or Charlson Comorbidity Index. SA levels were positively correlated (Spearman) with AP (r= 0.72; p < 0.0001); body fat mass in kg/m² (r=0.32; p<0.045); serum leptin levels (r=0.30; p= 0.05); HOMA-IR (r= 0.36; p=0.017) and negatively with serum adiponectin levels (r= -0.31; p<0.041). Multivariate logistic regression analysis showed that SA levels above its median level were independently associated to PRA and HOMA-IR.

Conclusions: SA levels are elevated in a high percentage of HD patients and such elevation is associated with PRA and several components of MSy (insulin resistance; body fat mass; and serum levels of adipokines).

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Higher iCa was also associated with higher HRV. The association of iCa with QTc interval and HRV remained significant in the repeated measures analysis. Associations with serum K, Mg, dCa, and dK were not significant at baseline or over follow-up. Serum-to-dialysate Ca gradient, but not K gradient was associated with higher HRV at baseline and over follow-up (β=0.3(0.0, 0.6) and 0.3(0.0, 0.6) respectively).

Conclusions: Serum iCa, but not K and Mg, is consistently inversely associated with QTc prolongation and the serum to dialysate gradient is also associated with HRV. This suggests that the absolute serum level as well as the lower dCa concentration increases arrhythmic risk.

TH-PO826
Phosphorus Kinetics During Hemodialysis: Further Validation of a Pseudo-One Compartment Model
J. Ken Luyckx1, 2, Baris U. Agar, 3 Alfred K. Cheung, 2 Angiello A. Bernardino, 2, 3 Medical Products (Renal), Baxter Healthcare Corporation, Deerfield, IL; 3 Medical Products (R&D), Baxter Healthcare Corporation, Round Lake, IL; 1 Nephrology, Univ of Utah, Salt Lake City, UT.

Background: A pseudo-one compartment model has been proposed to describe phosphorus kinetics during hemodialysis (HD) and postdialysis rebound. This model suggests that phosphorus mobilization from tissues is proportional to the difference between the predialysis serum (Cpre) and instantaneous serum concentration. The current study evaluated the ability of a pseudo-one compartment model to describe the kinetics of phosphorus during two short HD treatments on the same day separated by a 1-hr inter-treatment period without dialysis. The latter is the postdialysis rebound period for the first treatment.

Methods: Serum was collected frequently during both HD treatments and the inter-treatment period to assess phosphorus kinetics in 21 chronic HD patients. Phosphorus mobilization clearance (CMob) and predialysis central distribution volume (Vp) were estimated for each patient during the first HD treatment and the inter-treatment period. Assuming those kinetic parameters remained constant for each patient, phosphorus concentrations during the second HD treatment were used to estimate the driving force concentration (Cp) for phosphorus mobilization during that treatment.

Results: Treatment times (117±14 vs. 117±14 min), dialyzer phosphorus clearance (151±25 vs. 140±32 mL/min) and net fluid removal (1.44±0.74 vs. 1.47±0.76 L) were similar during both HD treatments. Phosphorus concentration at the start of the second HD treatment (3.3±0.9 mg/dL) was lower (P<0.001) than at the start of the first or Cpre (5.4±1.9 mg/dL). Kp and Vp were 98±44 mL/min and 11.0±4.2 L, respectively. Calculated Cm, was 4.9±2.0 mg/dL, not significantly different from Cpre (P=0.12). Cm and Cpre were correlated (R=0.72, P<0.001).

Conclusions: The results from this study demonstrate that the driving force concentration for phosphorus mobilization during HD is constant and equal to that predialysis, consistent with a fundamental assumption of the pseudo-one compartment model.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO827
Association of Sleep Apnea and Sleep Quality with Left Ventricular Mass in Hypertensive Hemodialysis Patients in the Blood Pressure in Dialysis–SLEEP study
Manisha Jambh, 1 Cynthia A. Kendrick, 2 Dana Miskulin, 3 Lavinia A. Negrea, 4 David W. Ploth, 5 Jennifer J. Gassman, 6 Mark L. Unruh, 4 Philip Zaget, 7, 3, 6, 7 Univ of Pittsburgh; 8Cleveland Clinic; 7Tafts; 3Case Western; 4MUSC; 7UNM; DCD.

Background: Sleep apnea (SA), short and fragmented sleep may contribute to cardiovascular disease in hemodialysis (HD) patients. However, the relationship of sleep quality with left ventricular mass (LVM) is not well described.

Methods: Chronic HD patients joined an ancillary study during the baseline period of the Blood Pressure in Dialysis (BID) trial. SA was monitored for 1 night with a portable home monitor (ApneaLink with oximetry) and measured as Apnea Hypopnea Index (AHI). Sleep wake behavior was assessed by actigraphy over a 5-day period. LVM was measured by MRI.

Results: We studied 42 patients. SA was present in 84% and was moderately severe (AHI>15) in 48%. 61% of patients slept <6 hrs/night and 89% had poor sleep efficiency. Patients with AHI>15 had longer dialysis vintage, lower hemoglobin, and lower Kt/V than those with AHI<15. BMI, systolic BP, diastolic BP, heart rate, number of antihypertensive medications, inter-dialytic weight gain, history of myocardial ischaemia, and MRI characteristics did not differ between the two groups. LVM index was inversely correlated with sleep duration and efficiency (Pearson’s r = -0.35, p ≤ 0.04 for both, AHI (r = -0.01) and hypoxic index (r = -0.04).

Funding: The National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Aging (NIA) (R01-AI068108 to J.C.)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: SA and poor sleep quality were common among hypertensive HD patients. Short sleep duration and poor sleep efficiency, but not the severity of SA, were associated with higher LVM indices.

Funding: NIDDK Support, Clinical Revenue Support

THI-PO828
Role of Nicotinic Acid as Phosphate Lowering Agent in End Stage Renal Disease Patients on Maintenance Hemodialysis
Khalid Tahir,1 Hafiz I. Ahmad,1 Syed Rizwan Bokhari,1 Syed A. Khalid,1 Arif Asif.2 1Dept of Nephrology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, Pakistan; 2Div of Nephrology and Hypertension, Albany Medical College, Albany, NY.

Background: Hyperphosphatemia is associated with higher risk of mortality and morbidity in End Stage Renal Disease (ESRD) patients. Use of Nicotinic Acid as phosphorus lowering agent has been studied in many countries but available data is sparse and limited. We conducted a small longitudinal pilot study to investigate the effects of HD initiation on brain MRI and cognitive function in 4 HD patients by obtaining pre- and post-HD body temperatures were measured with thermometers. The dialysate temperature was measured by the HD machine. The dialysate-to-patient temperature gradient was computed as dialysate temperature minus patient temperature. A two-tailed paired t-test was used to compare pre- and post- initiation results. Patients provided written informed consent to participate in the IRB-approved protocol.

Methods: We conducted a small longitudinal pilot study to investigate the effects of HD initiation on brain MRI and cognitive function in 4 HD patients by obtaining pre- and post- initiation brain MRIs and cognitive testing. The MRIs were obtained at 3-6 months before HD initiation, and at 6-12 months after HD initiation. The Modified Mini-Mental State Examination (3MSE) was performed within one month of the baseline and 12 month MRI examinations. MR diffusion tensor imaging (DTI) measured white matter (WM) fractional anisotropy (FA) (connectivity), and pseudo-continuos arterial spin labeling (PCASL) imaging was used to evaluate GM cerebral blood flow (CBF).

Results: Progressive and significant declines in frontal and temporal WM FA (Fig. 1), prefrontal CBF (Fig. 2), and cognitive function (Fig. 3, left) were found following HD initiation (Table 1 for p values). The decline in frontal WM FA on MRI was correlated with the 3MSE decline (R=0.42)(Fig. 3, right).

Table 1. P values from the comparisons between the baseline and follow-up sessions.

<table>
<thead>
<tr>
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<th>6 months</th>
<th>12 months</th>
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<tbody>
<tr>
<td>FA</td>
<td>0.031</td>
<td>0.025</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.049</td>
<td>0.044</td>
</tr>
<tr>
<td>CBF</td>
<td>0.038</td>
<td>0.038</td>
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<tr>
<td>Anterior Hippocampus</td>
<td>0.042</td>
<td>0.013</td>
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</table>

Conclusions: Our results suggest that HD may adversely alter cerebral vascular function and progressively induce cerebral structural abnormalities and associated cognitive decline.

Funding: NIDDK Support

THI-PO830
Patient and Dialysate Temperature Characteristics in Incident Hemodialysis Patients: Results from a Large U.S. Population
Xiaoling Ye,1,2 Len A. Usvyat,2 Yue Jiao,1 Peter Kotanko,1 Franklin W. Maddux.1 1Renal Research Inst, New York, NY; 2Fresenius Medical Care North America, Waltham, MA;1Icahn School of Medicine at Mount Sinai, New York, NY.

Background: In chronic hemodialysis (HD) patients the use of dialysate at a temperature below the patient’s core temperature (“cool” dialysate) has been associated with improved outcomes in observational and prospective randomized studies [Odudu et al., CJASN 2015; Eldehni et al., JASN 2015; Selby, Sem. Dial 2008]. Little is known about temperature profiles in large US populations.

Methods: We include a subset of incident HD patients who were treated in Fresenius Medical Care North America facilities from 1/2010 to 12/2014 and who survived the first year of HD. Pre- and post-HD body temperatures were measured with thermometers. The dialysate temperature was measured by the HD machine. The dialysate-to-patient temperature gradient was computed as dialysate temperature minus patient temperature.

Results: We studied 20,360 incident HD patients (age 62.5 (SD 14.5) years; 57.6 % males; 68.1% White, 29.2 Black, 2.7% others). The vast majority (83.8 %) had a dialysate temperature above body temperature at the start; and at the end (80.6%) of HD.

Conclusions: We studied 20,360 incident HD patients who were treated in Fresenius Medical Care North America facilities from 1/2010 to 12/2014 and who survived the first year of HD. Pre- and post-HD body temperatures were measured with thermometers. The dialysate-to-patient temperature gradient was computed as dialysate temperature minus patient temperature.

Funding: NIDDK Support
Effect of a Single Hemodialysis Session on Visual Evoked Potentials

Savas Sipahi, Ahmed Bilal Genc, Yalcin Solak, Nephrology, Sakarya Univ Research and Training Hospital, Sakarya, Turkey; Neurology, Sakarya Univ Research and Training Hospital, Sakarya, Turkey.

Background: Some studies have shown that visual evoked potentials (VEPs) may be a marker of dysfunction in visual pathways in uremic subjects. However, data are scarce regarding the effect of hemodialysis procedure on VEPs. We aimed to compare VEPs of hemodialysis patients with healthy volunteers and in particular to assess the impact of a single hemodialysis session on VEPs.

Methods: Thirty hemodialysis patients were included in the study. We also recruited 30 age and gender matched control subjects. Patients with diabetes mellitus, cataracts, glaucoma, and stroke were excluded.

Demographic characteristics, midweek predialysis and postdialysis laboratory values, amount of ultrafiltration at that dialysis session were recorded. Patients underwent VEP measurement through which P100 latency values were determined just before hemodialysis session and 24 hours after hemodialysis. We assessed the changes in P100 values with single hemodialysis session and 24 after hemodialysis session. We assessed the changes in P100 values with single hemodialysis session and 24 hours after hemodialysis. We assessed the changes in P100 values with single hemodialysis session and 24 hours after hemodialysis.

Results: There was no difference between the groups in terms of age and gender (mean age 49 ± 12 and 48 ± 11 years, respectively). Median duration of hemodialysis was 78 months (range 12-192). At baseline there was no difference with respect to P100 values between the groups (100.6 ± 8.8 vs 99 ± 5.8, p=0.4, for hemodialysis and controls respectively). Both right and left eye VEPs showed a significant decrease measured 24 hours after dialysis session compared with baseline values (right VEP, 100.6 ± 8.8 predialysis and 97 ± 8.7 postdialysis, p<0.001; left VEP, 101 ± 9.2 predialysis and 97.3 ± 8.1, p<0.001). There was no correlation between baseline predialysis P100 values and age, serum urea, hemoglobin, and dialysis vintage. Amount of ultrafiltration was not significantly correlated with postdialysis P100 latency values.

Conclusions: Our results did not show a significant difference in P100 latency values between hemodialysis patients and healthy controls. A single hemodialysis session significantly shortened P100 latency values compared with baseline values.

Blood Pressure in Hemodialysis Patients: Which Measurement Is More Reliable?

Jose Mora-Macia, Francesc J. Moreso, Jose Ignacio Merello, Rosa Ramos. Hemodialysis, Fresenius Medical Care, Spain.

Background: The reliability of blood pressure (BP) measurements during the hemodialysis (HD) is controversial. The aim of this study was to evaluate which interval of intradialytic BP has less Bias in comparison with home BP monitoring (HBPM).

Methods: A cross-sectional study was done with interdialytic HBPM as reference standard and interdialytic BP measurement as test. Index BP recordings tested were predialysis (pre-HD), postdialysis (post-HD) and intradialysis (intra-HD). Dialysis unit BP recordings were averaged over 1 week: 2 pre-HD, 2 post-HD and 7 intra-HD (every 30 min); and HBPM over 1 week (the same days): 3 morning and 3 evening readings. BP measurements during dialysis were measured by dialysis nurses using the validated oscillometric BP monitor OMRON M3 (HEM 7051 E, Omron Healthcare), and the same HBPM recordings were used for the patient at home. Patients were instructed to bring the device to the dialysis. Patients with symptomatic hypotension during dialysis were excluded. To measure Bias, average HBPM was subtracted from each of these three index BP/intradialytic recordings. Bias was defined as the mean difference in BP (pre-HD, intra-HD, post-HD) compared with HBPM.

Results: 192 patients, mean age 63.8±14.8 y.o. (70% male), of 11 HD clinics of Fresenius Medical Care of Spain were included, 33% diabetic. All patients were on thr three times weekly HD. The mean time on HD was 46±57 months.

<table>
<thead>
<tr>
<th>SBP</th>
<th>135±21.4 (80,194)</th>
<th>140±21.6 (92,225)*</th>
<th>130.7±20.9 (83,204)*</th>
<th>136.1±23.2 (84,207)*</th>
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<tbody>
<tr>
<td>DBP</td>
<td>69.3±11.2 (44,97)</td>
<td>71.1±11.1 (46,117)*</td>
<td>68.4±10.4 (49,105)**</td>
<td>70.2±10.4 (48,98)***</td>
</tr>
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</table>

Data are expressed as mean/SD (range). * p<0.001 vs HBPM. ** p=0.062 vs HBPM. *** p<0.001 ANOVA between HD

Conclusions: BP at the end of the HD, in not hypotensive symptomatic patients, not differ from HBPM and have less Bias that predialysis or intradialysis BP measurements. So, the post-dialysis BP measurements are the most reliable BP readings.
TH-PO834
End-Dialysis Overweight and Chronic Inflammation: A Dangerous Association – A 36-Month Prospective Observational Study Ezio Movilli, U.O. of Nephrology, Spedali Civili and Section of Nephrology Univ of Brescia, Brescia, Italy.

Background: Attaining dry body weight is paramount in dialysis practice, but this goal is not always reached. We hypothesized that the amount of end-dialysis overweight (edOW), could be associated to increased chronic inflammation and mortality. Aim of the study: to evaluate the effect of edOW on serum C-reactive protein (hsCRP) concentrations and on survival in a cohort of 182 prevalent HD patients (pts) followed for 36 months.

Methods: In 182 pts (117 men, age 65±12 years, vintage 48 months; range 6-336), edOW was present in 98/182 (54%) pts. Mean value was 0.4±0.2 Kg (range: 0.1-1.4). In the 98 pts with edOW (Group 1) and in the other 84 (Group 2) we evaluated: Ultrafiltration rate (UFR), hsCRP dry body weight (dBW), Kt/V, protein catabolic rate (PCRn), interdialytic weight gain (IDWG), mean arterial pressure (MAP). Unpaired Student’s t test was employed to compare groups, linear regression analysis to test correlations, log-rank test and Kaplan-Meier curves to evaluate survival.

Results: Mean UFR was 11.7±2.8 ml/Kg/hour, dBW 64±12 Kg, hsCRP 6.6 (0.2-36) mg/L, Kt/V 1.27±0.09, PCRn 1.06±0.10 g/Kg/day, IDWG 2.8±0.4 Kg, MAP 97±6.5 mmHg. edOW and hsCRP were directly and significantly correlated (r= 0.67; p<0.0001). Comparison between pts with (Group 1) and without (Group 2) edOW showed significant differences in: UFR (12.7±2.6 vs 10.9±2.6 ml/Kg/hour; p<0.001), hsCRP (13.0±5.3 vs 2.6±0.2 mg/L; p<0.001), and PCRn (1.03±0.09 vs 1.08±0.10 g/Kg/day; p<0.004). 98 pts (54%) died during follow-up for cardiovascular complications in 69% of cases. Survival curves showed significantly greater mortality in Group 1 vs Group 2 in relation to the amount of edOW, and hsCRP (p<0.0001).

Conclusions: edOW and chronic inflammation are directly correlated in HD pts, and both are associated to a greater long-term risk of mortality.

TH-PO835
Suicidal Erythrocyte Death in Hemodialysis Patients Anna Clementi, Grazia Maria Virzì, Alessandra Brocca, Massimo de Cal, Antonio Granata, Claudio Ronco. “Nephrology, Agrigento,” “Nephrology-IRRI, Vicenza.”

Background: Even though anaemia in ESRD results mainly from the lack of erythropoietin, compelling evidence points to the contribution of accelerated erythrocyte death/eryptosis, which is characterized by phosphatidylserine (PS) exposure at surface, cell shrinkage and cell membrane scrambling. Eryptosis may be stimulated both by uremic toxins and the mechanical stress induced by hemodialysis (HD). We investigated the possible difference in terms of eryptosis levels between healthy subjects and HD patients before and after HD session.

Methods: We enrolled 15 patients (4F, mean age 65±16yrs, 33% with diabetes) undergoing chronic HD and 15 healthy subjects (CTR). Blood samples were collected prior to and after 4h standard HD session. Measurements were made in isolated erythrocytes (RBCs). PS exposure was estimated from AnnexinV binding in flow cytometer.

Results: The percentage of AnnexinV reflecting the percentage of RBCs exposing PS to RBC surface was significantly higher (more than twice) in HD patients than CTR (2.2%; IQR 1.2-4.1 versus 0.8%; IQR 0.7-1.3; p<0.05). The average forward scatter reflecting cell volume was significantly higher in RBCs from HD patients than in CTR. There was no statistically significant relationship between area levels and eryptosis in HD patients. The percentage of AnnexinV and cell volume were measured prior to and after 4h of HD: no significant differences were observed between pre and postdialytic eryptosis.

Conclusions: Our data suggest that HD may lead to a significant increase in eryptosis, but no differences were observed before and after HD session. Although this procedure is known to be responsible for cytokines and inflammatory mediators release, because of the interaction between blood and circuit lines and filters, it does not seem to induce eryptosis. Further studies are needed to compare different types of HD treatments.

TH-PO836

Background: The aim of this study was to investigate the potential effect of a Dialysis Hospitalization Reduction Program (DHRP) on hospital admissions.

Methods: We deployed DHRP to 69 patients between 1/1/2014 and 5/5/2015 in a network of Fresenius Medical Care North America (FMCNA) dialysis clinics. These clinics were identified as being at high risk for hospitalization based on FMCNA’s data driven predictive modeling efforts and clinical assessments. The DHRP encompasses multiple interventions, targeting malnutrition, non-compliance, mental status issues, fluid overload, and others. Each patient is identified to have one or more “clinical tags”; 88 tags were identified for 69 patients. Interdisciplinary teams were deployed to design and implement interventions. Hospitalization rates were measured 90 days before and after the program.

Results: DHRP was associated with a reduction of all-cause hospitalization from 7.5 to 4.4 per patient year (ppy) (-42%) (Figure 1A). Interventions targeting patients with “malnutrition” tag were associated with a reduction of hospitalizations from 9.3 to 4.1 ppy (-56%) (Figure 1B).

Figure 1A. Overall intervention outcomes

<table>
<thead>
<tr>
<th>Number of clinical tags</th>
<th>Before</th>
<th>After</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions</td>
<td>85</td>
<td>85</td>
<td>0%</td>
</tr>
<tr>
<td>Hospital days</td>
<td>58</td>
<td>50</td>
<td>-14%</td>
</tr>
<tr>
<td>Missed treatments</td>
<td>7.9</td>
<td>7.4</td>
<td>-6%</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.52</td>
<td>3.51</td>
<td>-0%</td>
</tr>
<tr>
<td>Cachexia</td>
<td>31%</td>
<td>30%</td>
<td>-3%</td>
</tr>
<tr>
<td>Pre-dialysis SBP (mmHg)</td>
<td>146.5</td>
<td>147.1</td>
<td>0%</td>
</tr>
<tr>
<td>IDWG (kg)</td>
<td>2.49</td>
<td>2.47</td>
<td>-1%</td>
</tr>
</tbody>
</table>

Conclusions: DHRP was associated with reductions in hospital admissions and days. Reductions in overall hospital admissions were even higher in patients specifically identified to have malnutrition issues.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO837

Background: 3-day-a-week hemodialysis (HD) involves one long (72hr) and two short (48hr) inter-dialytic periods (IDP) with higher death risk after the long IDP. We investigated BP and CV biomarker patterns in clinically stable HD patients to determine whether BP control during the final 24 hrs of the long IDP is inferior to that of the short IDPs.

Methods: In an initial retrospective study, in-center BP readings over 1 month were analyzed for 81 adult HD patients with stable regimen and medical status for ≥ 3 mths. Next, 23 patients completed a prospective study in which ambulatory BP monitoring was performed for the final 24hrs of the long and one short IDP in the same week. Blood was collected for CRP, Tropomin T, BNP following each ABPM.

Results: In the retrospective study, mean pre-dialysis systolic and diastolic BP (SBP/ DBP) did not differ for the long and short IDPs despite greater weight gain during the long IDP. This observation was confirmed in the ABPM study and applied to both day- and night-time readings. Pre-dialysis CV biomarkers were not significantly higher following the long IDP. Inter-dialytic weight gain showed no correlation with BP indices.

Conclusions: Our data suggest that HD may lead to a significant increase in eryptosis,
Conclusions: In stable HD patients, BP control and CV biomarkers were similar during long compared to short IDP despite greater fluid gain. The adverse influence of excessive inter-dialytic fluid gain is unlikely to be mediated directly through a hypertensive effect.

TH-PO838

Notch Signaling in Bone Marrow-Derived FSP-1+ Cells Mediates a Phenotypic Change in Smooth Muscle Cells Leading to AVF Failure Ming Liang,1,2 Ten Li,1 Jie Zhang,1,2 William E. Mitch,1 Yichong Cheng,1 Medicine, Baylor College of Medicine, Houston, TX; 2Nephrology, Guangzhou Medical Univ, Guangzhou, Guangdong, China.

Background: Societal and economic costs of failed arteriovenous fistulas (AVF) are well known but mechanisms of AVF losses are controversial. We have shown that smooth muscle cells (SMCs) from anastomosed artery compose of ~50% of neointima in AVF. Arterial SMCs are also infiltrated by bone marrow (BM)-derived FSP-1+ cells, potentially linking FSP-1+ cells to SMC activation. However, whether Notch/RBP-JK signaling involves in BM-derived FSP-1+ cell activation has not been studied. We propose that Notch/RBP-JK activation in BM-derived FSP-1+ cells causes a phenotype-switch of SMCs, resulting in SMC translocation from the artery to the venous anastomosis, forming neointima.

Methods: We created CKD and AVFs in wild type and Notch knock out mice. The role of Notch signaling in activation and function of BM-derived FSP-1+ cells was explored. Activated SMCs were characterized by a loss of differentiation markers plus in gain in proliferation (PCNA+). Using BM transplantation, we examined if FSP-1+ cells lacking RBP-JK in CKD mice would suppress SMC phenotype switch and neointima formation in AVFs.

Results: BM-derived FSP-1+ inflammatory cells in AVFs from CKD mice were 45% greater vs. results in pair-fed, control mice. In the artery anastomosis, increased infiltration of FSP-1+ cells led to loss of SMC differentiation markers, SMMHC, SM-22 and SMA-a. Activation of Notch signaling (NICD+ and RBP-JK+) raised expression of cytokines (IL-1β, MCP-1) and growth factors (PIGF-BB, bFGF and TGF-β) in FSP-1+ cells. The cytokines and growth factors caused a SMC phenotype switch (characterized by loss of SMC markers), resulting in SMC migration and proliferation. RBP-JK KO in BM-derived FSP-1+ cells significantly decreased the production of cytokines and growth factors, suppressed SMC activation of and neointima formation in AVFs.

Conclusions: Thus, Notch signaling in BM-derived FSP-1+ cells can induce a phenotype switch in SMCs stimulating neointima growth. Targeting Notch signaling in FSP-1+ cells could improve AVF function.

Funding: NIDDK Support

TH-PO839


Background: Placement of an arteriovenous fistula (AVF) provides vascular access for lifesaving hemodialysis to patients with severe and chronic kidney disease. A significant percentage of AVF’s initially mature; serve as successful hemodialysis access points; but fail at some later time due to neointimal hyperplasia that occludes the vein. The causative underlying molecular, biochemical, and cellular factors that contribute to AVF failure are incompletely understood. CaMKII is a positive regulator of VSM cell proliferation and migration that results in occlusion of carotid arteries in both mice and rats. Currently, there is little known regarding the role of CaMKII in either physiological or pathophysiological venous function.

Methods: Cephalic veins from patients prior to AVF placement and after AVF failure were obtained. Immunohistochemical studies were performed on OCT embedded frozen sections. Molecular analyses were performed on RNA extracts from these venous segments and protein analyses were performed on protein extracts.

Results: Our results indicate that there is an increase in CaMKII and CaMKII expression in failed AVFs as compared to cephalic vein prior to AVF placement. CaMKII activity is regulated by both phosphorylation and oxidation. NADPH oxidases (Nosx) generate reactive oxygen species (ROS) that increases CaMKII activity. Analysis of failed AVFs shows an upregulation of Nosx and Nosx. Further studies show an increase in CaMKII activity. Interestingly, our data indicates that only a subset CaMKII isoforms are oxidized under these conditions.

Conclusions: These findings lead us to conclude that increases in [Ca2+] and [ROS] after AVF placement may result in increases of CaMKII and CaMKII expression and sustained activity that contribute to AVF failure. They also identify CaMKII as a rational target for therapeutic manipulation to prevent AVF failure.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund

TH-PO840

Identification of Ca2+/CaM-Dependent Protein Kinase (CaMKII) Isoforms and Their Selective Regulation by NADPH Oxidases in Failed Arteriovenous Fistula from Hemodialysis Patients Yongfeng Liu, Julia Steppich, Roman G. Ginnan, David J. Conti, Harold A. Singer,1 ‘Center for Cardiovascular Sciences, Albany Medical College, Albany, NY; 2Div of Nephrology and Hypertension, Albany Medical College, Albany, NY; 3UCM Surgery Group-Transplantation, Albany Medical College, Albany, NY.

Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction. In order to understand the cellular and molecular mechanisms involved in early AVF failure we evaluated the gene methylation profile (epigenetics) in conjunction with the gene expression profile (RNA Seq) from venous segment tissue samples obtained at the time of AVF creation. This approach allows us to identify genes that have altered expression (RNA Seq analysis) as a result of epigenetic changes (DNA methylation). The latter can be induced by different factors, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD).

Methods: Genomic DNA (gDNA) and RNA were isolated from venous segments collected at the time of AVFcreation. We divided the samples into 2 groups, THICK (n=5) and THIN (n = 5), based on a histological evaluation of the amount of neointimal hyperplasia. Deep sequencing technologies were then used to identify differentially regulated levels of gene expression between the THICK and THIN groups, that also had significant differences in RNA Seq analysis. Standard bioinformatic techniques were used to identify/interrogate these changes.

Results: We were able to identify a number of genes that were differentially regulated, either at the level of the transcriptome or at the level of DNA methylation (epigenetics) between the THICK and THIN groups. However, we were not able to identify individual genes that had changes in both the RNA Seq and DNA methylation analyses, at a high level of statistical significance.

Conclusions: While we were unable to identify differences in both gene expression and methylation of DNA methylation for individual genes, between our two groups (perhaps because of a small sample size), we do believe that these techniques and technologies could be used in larger studies, to dive deep into the mechanisms of AVF failure at a molecular and genetic level.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund

TH-PO841


Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction. In order to understand the cellular and molecular mechanisms involved in early AVF failure we evaluated the gene methylation profile (epigenetics) in conjunction with the gene expression profile (RNA Seq) from venous segment tissue samples obtained at the time of AVF creation. This approach allows us to identify genes that have altered expression (RNA Seq analysis) as a result of epigenetic changes (DNA methylation). The latter can be induced by different factors, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD).

Methods: Genomic DNA (gDNA) and RNA were isolated from venous segments collected at the time of AVFcreation. We divided the samples into 2 groups, THICK (n=5) and THIN (n = 5), based on a histological evaluation of the amount of neointimal hyperplasia. Deep sequencing technologies were then used to identify differentially regulated levels of gene expression between the THICK and THIN groups, that also had significant differences in RNA Seq analysis. Standard bioinformatic techniques were used to identify/interrogate these changes.

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Conclusions: While we were unable to identify differences in both gene expression and methylation of DNA methylation for individual genes, between our two groups (perhaps because of a small sample size), we do believe that these techniques and technologies could be used in larger studies, to dive deep into the mechanisms of AVF failure at a molecular and genetic level.

Funding: Pharmaceutical Company Support - DCI Paul Teschan Research Fund
TH-PO842
Computational Fluid Dynamic Analyses in a Uremic Mouse Model of AV Stenosis: Of Surgery, Techniques and Computation
Begoña Campos,1 Yang Wang,2 Yong He,2 John M. Pearce,1 Richard Scott Dunn,1 Keith Louis Saum,3 Janaka Wansapura,2 Charles L. Dumoulin,1 Scott A. Berceli,2 Prabir Roy-Chaudhury,1 Univ of Cincinnati,2 Univ of Florida,3 CCHMC.

Background: Although arteriovenous fistulae (AVF) are the preferred form of vascular access for hemodialysis patients, over 50% of AVFs fail to mature (inability to increase blood flow and diameter adequately to support dialysis). Work performed in our laboratory suggests that AVF maturation failure is due to an interaction between “upstream hemodynamics” and “downstream vascular biology”. In order to better elucidate the mechanisms involved in both these processes, we herein describe the techniques needed to develop a shear stress profile within a uremic mouse model.

Methods: In order to create a uremic mouse model, C57Bl/6 mice underwent an initial cauter of the left kidney followed 2 weeks later by a contralateral nephrectomy. Four weeks later AVFs were created in the neck. In order to generate different shear stress profiles, we created AVFs between the carotid artery and jugular vein in the following surgical configurations (a) end of carotid artery to end of jugular vein (b) end of jugular vein to end of carotid artery and (c) end of carotid artery to side of jugular vein. Mice were then perfused with a silicone rubber casting agent (Microfil). Fistulae were harvested, stored in 4% paraformaldehyde, and treated with Lugol solution as a micro-CT contrast agent. Each AVF was then scanned using micro-CT imaging to create a 3D reconstruction of AVF geometry. In order to obtain blood flow parameters we have developed an MRI technique to develop a shear stress profile within a uremic mouse model.

Results: We have described for the first time a hybrid surgery-fluid dynamics approach, which could allow us to identify the differential impacts of different surgical configurations, with or without the impact of uremia on AVF fistula functionality (with the promise of also being able to use genetically manipulated animals in the future).

Conclusions: We firmly believe that teasing out the relative roles of upstream hemodynamics and downstream uremic vascular biology will allow us to identify target(s) for future therapeutic interventions.

TH-PO843
Biodegradable Stents Improve Arteriovenous Fistula (AVF) Maturation
Begoña Campos, Yang Wang, Zhangzhang Yin, Keith Louis Saum, Diego Celdran-Bonafonte, Mark J. Schulz, Vesselin Shanov, Prabir Roy-Chaudhury, Univ of Cincinnati.

Background: Arteriovenous fistula (AVF) maturation failure is currently a huge clinical problem with no effective therapies. At a pathogenetic level the three main causes of AVF maturation failure are (a) small veins (b) abnormal non-laminar flow profiles and (c) abnormal local endothelial function. We therefore, hypothesize, that the placement of a malleable, biodegradable magnesium based maturation enhancing stent (bMES) within the venous segment, at the time of surgical AVF creation would displace small veins, optimize the anatomical configuration, and serve as a conduit for the future delivery of therapies to improve local vascular biology during the critical initial 4-8 week period with an absence of long term side effects (no stent after 4-8 weeks).

Methods: bMES were fabricated using pure Mg foil (125 mm) and Mg-Zn alloy wire. Bilateral AVFs were created between the femoral artery and vein of Yorkshire pigs. A bMES was inserted on one side and dilated to 8mm. A control AVF was created on the contralateral side. CT angiograms and ultrasounds were performed to document blood flow and diameter for the control and stented AVF.

Results: Preliminary data documents almost complete degradation of the bMES at 4-8 weeks with an increase in diameter of the stented AVFs on CT angiograms at 2 weeks (Figure). Histological examination performed on both the stented and control AVFs did not reveal any evidence of necrosis or inflammation.

Conclusions: These initial results clearly demonstrate technical feasibility and safety for the bMES, and also provide us with an efficacy signal based on our CT angiogram data (Figure). We believe that this technology could significantly reduce the huge morbidity and mortality associated with AVF maturation failure and also expand the patient population considered to be suitable for AVF placement in the future.
Conclusions: There is large international variability in site of AVF placement and AVF maturation. Differences in blood flow used (much higher in the US vs. Europe and Japan) may lead to different interpretation of the term “maturation” internationally, and may influence maturation rates.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd., BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGiN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

TH-PO847

Vascular Access in Acute Kidney Injury: Results from the ATN Study Kavitha Ganta, Yue-Harn Ng, Herbert T. Davis, Mark L. Unruh. Department of Internal Medicine, Univ of New Mexico, Albuquerque, NM.

Background: Acute kidney injury requiring renal replacement therapy (RRT) portends a poor prognosis. Currently, the decision regarding catheter placement is based solely on physician discretion. Limited data exist to guide catheter placement. The Acute Renal Failure Trial Network (ATN) study was a multicenter, prospective, randomized trial on the effects of dialysis dose on mortality in critically ill patients. Using data from this study, we assessed the complications rates and the adequacy of dialysis based on different catheter locations.

Methods: Baseline characteristics were gathered. The outcomes of interest include catheter related infections, cardiac arrhythmias, excessive bleeding, local thrombosis and dialysis adequacy. Categorical variables were analyzed using Chi-square test while continuous variables were analyzed using the Student T test. The SAS software was used for all analyses.

Results: There were 242 (11.7%) subclavian (SC), 951 (46.1%) internal jugular (IJ) and 861 (41.7%) femoral (FC) catheters inserted. The baseline characteristics based on catheter location is shown in Table 1.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Catheter Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>SC (%)</td>
</tr>
<tr>
<td>Age</td>
<td>61.3 ± 14.3</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>170 (70.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3 ± 6.0</td>
</tr>
<tr>
<td>Platelet (100/mm³)</td>
<td>141 ± 138</td>
</tr>
<tr>
<td>Diabetes</td>
<td>78 (32.2)</td>
</tr>
<tr>
<td>PVD</td>
<td>75 (31.0)</td>
</tr>
</tbody>
</table>

The rate of bacteremia was comparable between the 3 groups. (5.4% (SC) vs. 3.5% (IJ) vs. 3.5% (FC); p = 0.34). The IJ group experienced more cardiac arrhythmias (2%) compared to BM (0.8%) and FC (0.5%) group (p = 0.01) while the FC group had more venous thrombosis (0.7%) compared to none in the SC and IJ group (p = 0.02). Overall, complication rates were low. There was no clinically significant difference in the adequacy of dialysis between the 3 groups.

Conclusions: There was no significant differences in complication rates amongst the 3 catheter locations hence decision on catheter location should be based on operator experience and comfort level.

TH-PO848

Vascular Access at Dialysis Initiation in the United States Renal Data System (USRDS): Strong Agreement Between CMS 2728 Medical Evidence Form and CROWNWeb Purna Mukhopadhyay, Jeffrey Pearson, Kenneth J. Woodside, Sarah Bell, Ronald L. Pisoni, Douglas E. Schaubel, Kaitlyn Ratkowiak, Rajiv Saran. 1 Arbor Research Collaborative for Health, Ann Arbor, MI; 2 Univ of Michigan, Ann Arbor, MI.

Background: The USRDS has long reported vascular access (VA) at the start of hemodialysis (HD) initiation. This study compared VA used at the first HD session reported on the CMS-2728 and CROWNWeb. For pts incident during 2006-2013, data on VA at hemodialysis (HD) initiation (n=2,851) was categorized as catheter only (CVC), AV Fistula (AVF), AV Graft (AVG), CVC with maturing fistula, and CVC with maturing graft. Pts initiating HD between 6/1/2012-12/31/2012 (N=197), were tracked over 12 months. For prevalent pts, AVF & AVG groups include CVC/maturing fistula and CVC/maturing graft, respectively.

Results: From ’06-’12, incident pts began ESRD care using HD 39%, PD 36%, and transplant 25%. In 2013, in pts starting HD, 90% had a CVC, an increase from 84% in 2006. CVC was lower for the older pts (<4yrs: 99% vs. 14-17yrs: 83%, p<.05). VA trends over a year in a 7-month incident cohort showed the proportion of CVC decreased from 84% at 1 month to 31% at 1 year, while 16% were using or maturing an AVF. 1% were using or maturing an AVG. 13% of pts transitioned to PD and 35% received a TX by 1 year.

Conclusions: Our analysis confirms the large CVC burden among pediatric HD pts. Conversion to AVF were observed over the first year in an incident cohort where nearly 50% of pts transitioned to PD or TX. Further study will assess the impact of CVC dependence among pediatric ESRD pts with respect to future VA options and patient outcomes.

Funding: NIDDK Support

TH-PO850

In Search of an Optimal Screening Program for Containing Graft Thrombosis Nicola Tesseritore, Giuseppina Pessolato, Valeria Bedognà, Albino Poli, Antonio Lupò, Ennodialisi Borgo Roma, Verona, Italy; 2 Dept Public Health, Verona, Italy.

Background: KDOQI guidelines recommend regular screening for >50% stenosis (ST) in graft by surveillance (access blood flow (Qa) & venous static pressure ratio (vPVR) or Duplex Ultrasound to reduce the risk of thrombosis. Analysis of the literature suggests that the best predictor of thrombosis is sVPR>0.5, with an area under curve (AUC) of 0.81[95%CI:0.75-0.85] significantly higher than that of Qa:0.600 mmHg (0.72[95%CI:0.68-0.77]) & ST (0.49[95%CI:0.45-0.53]), but no study has compared vis-a-vis all of the tools.

Methods: To identify an optimal screening program, in 2013 we compared the diagnostic performance of the available tools for incipient thrombosis (within 3 mo) in the same population of 42 grafts (5 forearm loop & 37 straight upperarms), that underwent18 thrombotic episodes.

Results: Qa by Ultrasound Diffusion proved to be the best screening tool (AUC:0.81[0.69-0.93]) optimal thresholds between Qa:1000 mmH/min (63% sensitivity [SE], 18% false positives[FPR]) & Qa:1200 mmH/min (83% SE, 27% FPR). Its AUC was higher than that of ST (0.69[95%CI:0.54-0.84]) 78% SE, 39% FPR), monitoring (0.62[95%CI 0.45-0.79]) 33% SE, 9% FPR), & VAPR (0.58[95%CI:0.42-0.74]VAPR)0.87% SE, 58% FPR). At GLM analysis Qa was the only significant predictor of thrombosis, with 18%[95%CI 7-29] lower risk for each 100 mmH/min above a Qa 400 mmH/min. From January
The Impact of eGFR at Pre-HD Access Surgery on the Likelihood of Starting Hemodialysis with a Mature Vascular Access

**Background:** The optimal timing of pre-dialysis vascular access surgery is uncertain. Complications of CVCs may have economic consequences for dialysis providers and patients. The timing of surgery may influence the likelihood of starting HD within 2 years, and whether the permanent access was used on the first HD session.

**Methods:** We retrospectively queried a prospective computerized access database to identify patients with pre-HD access surgery (301 AVF and 64 AVG placed between 2006-12) with an eGFR recorded on the surgery date. Patients were stratified into 4 eGFR groups (<10, 10-14, 15-19, >20 ml/min).

**Results:** Overall, 208 (or 69%) of pts with pre-HD AVF surgery initiated HD within 2 years, but the proportion varied by eGFR at surgery (90, 81, 64, and 47% for eGFR <10, 10-14, 15-19, and >20 ml/min).

**Conclusions:** Our comparative study suggests that eGFR is the best predictor of graft patency & Qa surveillance using a Qa<1000 ml/min threshold allows for appropriate and timely stenosis repair & may contain the risk of thrombosis.

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**TH-PO853**

**Obesity Related Decrease In Intraoperative Blood Flow Is Associated with Maturation Failure of Radiocephalic Arteriovenous Fistula**

**Background:** Successful arteriovenous fistula (AVF) maturation is often challenging in obese patients. Optimal intraoperative blood flow (IOBF) is essential for adequate AVF maturation. This study was conducted to elucidate the effect of obesity on IOBF and radiocephalic AVF maturation.

**Methods:** Patients who newly created radiocephalic AVF were included (n=252). Obesity was defined as a baseline BMI ≥25 kg/m², and primary maturation failure was defined as the failure to use AVF successfully by 3 months after its creation. IOBF was measured immediately after construction of AVF using a VeriQTM system.

**Results:** The mean BMI was 24.1±3.9 kg/m², and the prevalence of obesity was 31.3%. Particularly, 8.3% (21 patients) were BMI ≥30 kg/m². Primary maturation failure occurred in 100 (39.7%) patients and an IOBF <190 mL/min was closely associated with the risk of maturation failure (relative risk, 3.05; 95% CI, 1.52–6.11). Compared to non-obese patients, obese subjects had a significantly higher prevalence of diabetes and elevated hs-CRP levels, whereas diameters of vessels were similar. When the patients were further divided into 3 groups at the BMI <25, 25-29.9, and ≥30 kg/m², patients in higher BMI groups had significantly lower IOBF and higher maturation failure rate. According to multivariate analysis, the statistically significant variables that determined maturation failure were obesity, previous vascular disease, increased hs-CRP levels, and IOBF <190 mL/min.

**Conclusions:** Obese patients had a significantly lower IOBF, and both obesity and low IOBF contributed to the primary maturation failure of AVF. Obesity-associated inflammation and atherosclerosis may play roles in this association.

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**TH-PO854**

**The Impact of Vascular Access on Hemodialysis Patient Survival and Risk Analysis**

**Background:** Maturation failure is the most common dialysis modality worldwide. However, the impact of different types of vascular access on hemodialysis patient survival has not been investigated in a large scale study. Therefore, we retrospectively reviewed the survival of hemodialysis patients in our center and analyzed the impact of vascular access on their survival. Other potential risk factors were also studied.

**Methods:** From 2001 to 2010, patients, who aged more than 40 years old and received regular hemodialysis in our center for at least 3 months, were included into this study. A total 916 patients were enrolled. The mean followed up interval was 4.4±2.5 years. Among these patients, 51.1% were male, while 48.9% were female. These patients were divided into three groups according to their vascular access. Group A: patients used either native arteriovenous fistula or arteriovenous graft at the all time and dialysis catheter had never been used during the whole study period. Group B: patients used either native arteriovenous fistula or arteriovenous graft before they used dialysis catheter at least once during study period. Group C: patients used dialysis catheter as their vascular access and arteriovenous shunt had never been established during the study period. Other survival associated factors were analyzed by using univariate and multivariate factor analysis.

**Results:** The results showed that group C patients had significantly worst survival rate (P<0.0001). The group B patients also had significantly worse survival rate when compared with group A patients.
with group A patients (P=0.0001). The hazard ratio was 1.71 (1.31-2.24) for group B and 3.56 (2.08-6.08) for group C when compared to group A patients. Multivariate analysis showed that the associated risk factors for patient survival were male sex, diabetes mellitus, low albumin, high hsCRP, and abnormal AST level.

Conclusions: The use of dialysis catheter imposed high risk for patient mortality on top of other associated risk factors. Early establishment of vascular access can eliminate this risk factor and improve patient outcome.

TH-PO855

Early Experience with a Novel Device for Ultrasound-Guided Management and Cannulation of Hemodialysis Vascular Access

William D. Paulson, 1 Deborah J. Brouwer-Maier, 2 Lillian A. Pryor, 3 John Jason White, 1 Laura L. Mullloy, 1 Lu Y. Huber, 1 Matthew J. Diamond. 1 1 Charlie Norwood VAMC & Georgia Regents Univ, Augusta, GA; 2 Fresenius Medical Care, Waltham, MA.

Background: The vascular access continues to be the Achilles heel of dialysis. Methods that facilitate easier management and cannulation of accesses are needed. We describe early experience with a novel ultrasound device.

Methods: The Sonic Window (Analogic Corp, Peabody, MA, USA) is designed to assist management of vessels in a variety of contexts. It differs from conventional ultrasound in that it provides a coronal view of vessels that yields determination of characteristics such as depth and luminal diameter, and assists in cannulation for dialysis. We have initiated a program in 4 FMC dialysis units which is designed to identify its role and limitations.

Results: Two experts in the use of the Sonic Window have trained dialysis staff in the 4 FMC units. Staff have successfully cannulated 33 AV fistulas and synthetic grafts. Set up and use of the device generally adds an extra 1-3 minutes to cannulation time. Staff are able to easily visualize advancement of dialysis needles into the vessel lumen (figure).

We plan to evaluate the following potential uses of the device: 1. Assessing fistula maturation by measuring increase in luminal diameter over time; 2. Evaluating accesses that are difficult to cannulate; 3. Evaluating accesses with low blood flow, or high negative arterial or positive venous dialysis pressure; 4. Identifying alternative access sites for cannulation. Possible disadvantages to be addressed: potential staff & patient reluctance to accept new technology and additional cannulation time, to be assessed in surveys.

Conclusions: Our early experience supports the concept that Sonic Window is a significant advance in managing and cannulating accesses in both routine and difficult situations.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

TH-PO856

Modifiable Risk Factors Affecting the Outcome Hemodialysis Graft

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Background: Arterio-venous graft (AVG) for hemodialysis has poorer outcome than arterio-venous fistula (AVF) with its frequent stenosis and thrombosis. We investigated modifiable risk factors affecting the outcome of AVG.

Methods: A single-center cohort of 254 patients (pts) receiving AVG for hemodialysis access from Sep 2010 to Oct 2014 were included. Demographics, laboratory data, comorbidities, and medications were collected from the medical records. Surgical factors related to AVG operation including the type and diameter of connected vessels, graft site, and type of operation (elective or emergent) were also recorded. End points was the interval from initial access formation to any intervention intended to restore patency (primary patency, days) and the total access survival duration (secondary patency, days).

Results: Data of 225 pts were analyzed. During the follow-up period, 139 (62%) pts received intervention and 45 (20%) pts underwent permanent failure. Survival analyses using Kaplan-Meier method was shown in the figure. In multivariate analysis, primary patency duration was associated with RAS inhibitor (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.13-2.46), and upper arm graft (HR 0.62, 95% CI 0.40-0.94). Secondary patency duration was associated with serum albumin level (HR 0.28, 95% CI 0.13-0.61), diastolic blood pressure (BP) (HR 0.93, 95% CI 0.89-0.98) and warfarin (HR 5.80, 95% CI 2.04-16.46).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Conclusions: A DBP ≥ 77 mmHg prior to surgery may be considered as a key prognostic indicator of the Bresciano-Cimiru procedure.

Funding: Government Support - Non-U.S.

TH-PO858

Vascular Access Outcomes following Peritoneal Dialysis to Hemodialysis Transition

Timmy C. Lee,1 Mae Thamer,1 Qian Zhang,2 Yi Zhang,2 Michael Allon.1 1 Univ of Alabama at Birmingham; 2 Medical Technology and Practice Patterns Inst.

Background: Few studies have evaluated vascular access (VA) use following transition from PD to HD. Our goal was to examine short-term VA utilization following PD to HD transition.

Methods: Using USRDS and Medicare claims data from July 2010-December 2012, we identified 3,565 incident Medicare-insured PD patients who were ≥85yrs and initiated dialysis between July 2010-June 2011. Patients had at least one dialysis claim within 90 days of dialysis initiation and were followed for 1 year until one of the following events: switched to HD, kidney transplant, death, or end of follow-up. We used Cox-regression models to examine the association of risk factors and switching to HD, with death and transplantation used as competing events.

Results: 991 (27.8%) patients switched from PD to HD during the 1 year follow-up. Of these, 46% switched to HD within 90 days of dialysis initiation and 66% by 6 months. The median switch time was 114 days (IQR: 32-226). Patients with cardiovascular disease (Adjusted Hazard Ratio (HR) 1.25, 95% CI 1.10-1.43), COPD (HR 1.29, 95% CI 1.01-1.66), and without pre-dialysis nephropathy care (HR 1.46; 95% CI 1.21-1.76 versus those with >12 months nephropathologist care) were more likely to switch from PD to HD. After switching from PD to HD, 89% used a catheter, 6.6% AVF, and 1.9% AVG. 90 and 180 days after switching to HD, 71% and 50% of patients, respectively, who remained on HD still used a catheter as their VA.

Conclusions: The majority of patients transitioning from PD to HD initiate HD with a catheter. 50% dialyze with a catheter at 6 months. This highlights the need for VA planning in patients with failed PD to ensure timely transition to permanent VA.

Funding: Private Foundation Support

TH-PO859

Temporal Trends in Pre-Hemodialysis Vascular Access Creation in Elderly Patients with CKD

Timmy C. Lee,1 Mae Thamer,1 Qian Zhang,2 Yi Zhang,2 Michael Allon.1 1 Univ of Alabama at Birmingham; 2 Medical Technology and Practice Patterns Inst.

Background: Optimal timing of pre-dialysis vascular access (VA) creation remains unclear. Elderly CKD patients with high comorbidity are more likely to die before starting HD, so deferring VA creation may be reasonable. We assessed whether nephrologists have started selecting healthier elderly patients for pre-HD VA surgery.

Methods: Using Medicare claims data we identified 3418 elderly patients (aged ≥70 years) with CKD undergoing pre-HD VA creation in 2004 to 2009, and divided them into 3 time cohorts (2004-05, 2006-07 and 2008-09). For each temporal cohort, we assessed the likelihood of initiating dialysis during 2 years of follow-up after VA surgery. We collected data on cardiovascular co-morbidities and cardiovascular events prior to VA surgery and after dialysis initiation to determine if there were significant changes in these variables during the 3 time cohorts.

Results: Of these, 46% switched to HD within 90 days of dialysis initiation and 66% by 6 months. The median switch time was 114 days (IQR: 32-226). Patients with cardiovascular disease (Adjusted Hazard Ratio (HR) 1.25, 95% CI 1.10-1.43), COPD (HR 1.29, 95% CI 1.01-1.66), and without pre-dialysis nephropathy care (HR 1.46; 95% CI 1.21-1.76 versus those with >12 months nephropathologist care) were more likely to switch from PD to HD. After switching from PD to HD, 89% used a catheter, 6.6% AVF, and 1.9% AVG. 90 and 180 days after switching to HD, 71% and 50% of patients, respectively, who remained on HD still used a catheter as their VA.

Conclusions: The majority of patients transitioning from PD to HD initiate HD with a catheter. 50% dialyze with a catheter at 6 months. This highlights the need for VA planning in patients with failed PD to ensure timely transition to permanent VA.

Funding: Private Foundation Support

TH-PO860

Hemodynamic Changes in Arteriovenous Fistula During Dialysis

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Background: Optimal blood flow velocity (BFV) in arteriovenous fistulas (AVF) to prevent neointimal hyperplasia is yet to be determined. We have hypothesized that changes in BFV and diameter in a brachiocephalic fistula (BCF) are affected by fistula maturation and blood flow induced during hemodialysis.

Methods: Eight subjects with primary BCF participated. Doppler BFV was measured pre-dialysis and during dialysis at 250, 350 and 450 mL/min blood flow for up to 14 months. BFV was measured in the straight portion of the cephalic vein 10 cm proximal to the cephalic arch. The relationship between BFV and diameter was examined using a linear mixed effects model. Computational modeling using venography was performed at 3 and 12 months.

Results: The change in measured diameter and BFV showed an inverse relationship with a significant association at baseline (p=0.0074) and 350 mL/min dialysis blood flow (p=0.0092). The computational model of the cephalic arch in one subject showed a 4 fold increase in Reynolds number with a dramatic recirculation region shown by a swirling eddy at the upper elbow of the arch.

Conclusions: From 2004-2009, there has been a progressive decrease in cardiovascular co-morbidities in elderly CKD patients undergoing pre-HD VA surgery, and this has been associated with a decrease in patients dying before HD and in patients with cardiovascular events after starting HD. Clinicians are becoming more selective in pre-HD placement of VA in this patient population.

Funding: Private Foundation Support

TH-PO861

Arteriovenous Fistula (AVF) Maturation Among Hemodialysis (HD) Patients: Results from the USRDS

Rajiv Saran,1 Sarah Bell,1 Brett W. Platter,1 Douglas E. Schaubel,1 Sudipta Dasmunshi,1 Purna Mukhopadhyay,2 Jeffrey Pearson,1 Ronald L. Pisoni,1 Kenneth J. Woodside.1 1 Univ of Michigan; 2 Arbor Research Collaborative for Health.

Background: AVF are considered the gold standard for HD vascular access, but require time to mature and may not adequately develop, resulting in prolonged central venous catheter (CVC) use. We describe AVF survival from placement until time to first use for prevalent HD patients in the US.

Methods: We examined HD patients with new AVF placements during 2013 using Medicare claims. Failure of maturation was identified by non-use following placement using CROWNWeb (CW) where patient access use is reported monthly by the facility. Patients were followed until end 2014. We assessed the relationship between patient characteristics and time-to-first-use of AVF with a Cox model.

Results: In 2013, 51,561 AVF were placed among 42,160 HD patients followed through 2014. No subsequent evidence of use occurred in 44.3% of the placements. Of successfully used AVF, median time to first use was 113 days. Older age groups were incrementally associated with lower probability of using AVF. Pts in the 0-21 and 22-44yr groups (HR=1.23 [95% CI=1.06-1.44], and 1.06 [1.03-1.11], respectively), were more likely to use AVF’s compared to the 45-64yr group (ref). Sex (Female; Fig. 1a), race (e.g., Black; Fig. 1b), comorbidity (cardiovascular disease, peripheral artery disease, diabetes, needing assistance or institutionalized status), vintage ≤1year, CVC and/or AV graft use at incidence, were also associated with lower probability of AVF use.

This region, present at baseline and 3 months is much deeper at 12 months and with increased dialysis blood flow rate of 450 mL/min.

Conclusions: In patients with BCF, as the AVF matures and with increased dialysis blood flow, an increase in diameter of the cephalic vein with subsequent decrease in BFV is observed. Increased blood flow during hemodialysis evokes recirculation eddy’s which may result in endothermal damage and subsequent intimal hyperplasia unless the arterialized vein is able to adapt and remodel to the pressures and flows that are generated during hemodialysis.

Funding: NIDDK Support

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

Underline represents presenting author.

289A
Conclusions: We have characterized AVF maturation in a national US sample and identified important associations with multiple patient-level factors. Research is urgently required into the importance of patient, region and practice factors that could improve AVF placement and maturation, decrease CVC use, to improve patient outcomes and experience.

Figure 1. Probability of first use of fistula placed in 2015 by race (a) and by sex (b).

Funding: NIDDK Support

TH-PO862

Elderly Age Does Not Affect Long-Term Survival of Non-Transposed and Transposed Upper Extremity Arteriovenous Fistulae

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Background: The Fistula First initiative has successfully increased the placement of arteriovenous fistulae (AVF) for vascular access. Some authors have suggested that there is a higher failure rate of AVF in elderly patients. The purpose of this study was to determine if elderly age influences the overall survival of transposed brachial-basilic fistulae (TBBF) and non-transposed AVFs (NT) placed in the upper extremity (UE).

Methods: Our prospective, computerized clinical database was queried retrospectively to identify the survival outcomes of all upper extremity (UE) fistulae placed in CKD and ESRD patients over a 6-year period at our VA hospital. All fistulae were placed by a single surgeon, hence eliminating inter-operator variability. Patient demographics and comorbid conditions were noted from the electronic record. The primary end point was permanent failure of the access. Kaplan Meier survival analysis was performed using SPSS.

Results: 230 UE fistulae were placed, which were categorized into two groups by patient age at the time of AVF placement: < 75 years and 75 years and older. The table shows the distribution by access type and age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Type of AVF</th>
<th>TOTAL NUMBER OF AVFs</th>
<th>TOTAL NUMBER OF FAILED AVFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 75 years</td>
<td>NT</td>
<td>124</td>
<td>40</td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>TBBF</td>
<td>72</td>
<td>19</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>NT</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>TBBF</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

The figure shows that there was no difference in the Kaplan-Meier survival curves for the two age groups when NT and TBBF were analyzed collectively (P=0.833). Furthermore, there was no statistical difference between the survival curves when each group above was analyzed separately (P=0.996).

Conclusions: In conclusion, overall survival was similar for TBBF and NT AVF in our study and was not influenced by elderly age. This finding is contrary to popular opinion and some other reports.

TH-PO863

Peripherally Inserted Central Catheter (PICC) Placement in Hemodialysis Patients with Central Venous Catheters (CVC)

Rita L. McGill, Robin Ruthazer, Klemens B. Meyer, Dana Miskulin, Daniel E. Weiner. Tufts Medical Center, Boston, MA.

Background: PICC insertion threatens opportunities for AVF creation and may reduce achievement of AVF. Accordingly, we evaluated the incidence of PICC placement in ESRD patients after starting dialysis and in the 2 years prior to starting dialysis, and recognizing that AVF rates are lower in women, whether PICC rates differed by sex.

Methods: After restricting to patients with pre-dialysis Medicare claims, we used CPT codes to ascertain all PICCs placed during the 2 years before HD initiation and up to 12/31/2012 in the subset of adult HD patients entering USRDS in 2010 or 2011 with CVC as sole vascular access. Accounting for censoring due to death and ESRD modality treatment change, and using Poisson regression to adjust for age, race, BMI, diabetes and peripheral vascular disease, we calculated sex-based incidence ratios (IRR) using PICC per 100,000 patient months.

Results: PICC were placed in 2437 (14.6%) of women and 2250 (12.2%) of men.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16686</td>
<td>18494</td>
</tr>
<tr>
<td># PICC placed during the 2 years prior to HD</td>
<td>1983</td>
<td>1469</td>
</tr>
<tr>
<td># PICC placed during first year of HD</td>
<td>1438</td>
<td>1330</td>
</tr>
<tr>
<td># PICC placed after first year of HD</td>
<td>567</td>
<td>532</td>
</tr>
<tr>
<td>PICC TOTAL</td>
<td>3988</td>
<td>3331</td>
</tr>
</tbody>
</table>

Compared to men, crude and adjusted IRR of PICC for female sex were 1.35 [1.28-1.41] and 1.34 [1.27-1.41]. Multiple PICC (range=2 to 14) were placed in 648/2260 (29%) men and 803/2437 (33%) women who had any PICC.

Conclusions: Despite persuasive indications for PICC avoidance, people dialyzing via CVC frequently receive one or more PICC before and even after starting dialysis. The PICC rate was 35% higher in women, a difference not attenuated by adjustment for demographic and clinical factors. More frequent PICC placement may explain some of the lower fistula rate in women. Eliminating frequent PICC placements in patients with CVC may improve achievement of AVF.

Funding: Other NIH Support - NIH/NIDDK T32 DK007777 "Epidemiology, Clinical Trials and Outcomes Research In Nephrology"

Tufts CTSI Grant [UL1 TR001064]

TH-PO864

Arteriovenous Fistula Outcomes in an Elderly UK Population

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Background: The merit of placing arteriovenous fistulas (AVFs) in the elderly is debated in the literature. We sought to investigate AVF outcomes in the population aged ≥ 65 years in our region.

Methods: The Northern Ireland Vascular Access Database incorporates vascular access data on patients with chronic kidney disease stage 4 and 5. The database includes information on all patients ≥ 65 years who had an AVF created during January 2009-December 2014 and had a functional outcome by the 1st March 2015. Functional AVF patency was defined as sustained 2-needle use on haemodialysis for at least 6 sessions. Failure to mature (FTM) was defined by either clinical examination or failure to sustain 6 sessions of 2-needle dialysis.

Results: During the study period 344 patients ≥ 65 years had an AVF created. One AVF failed immediately, three AVFs were ligated due to steal, 56 patients had not started dialysis by the study end-point and records were incomplete for 50 patients. A total of 254 patients (98% White) remained included for functional AVF patency analysis. Table 1: Clinical Characteristics of Patients ≥ 65 years with AVF Patency Outcomes (n=254)

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, median, range)</td>
<td>74, 74, 65-92</td>
</tr>
<tr>
<td>Male gender</td>
<td>170 (67)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>102 (40)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>102 (40)</td>
</tr>
<tr>
<td>Lower arm AVF</td>
<td>134 (53)</td>
</tr>
</tbody>
</table>

A total of 150 AVFs (59%) achieved functional patency and 105 (41%) FTM. Binary logistic regression revealed that a lower arm AVF in this elderly population was associated with FTM (p < 0.001, OR 0.23, CI 0.13-0.40).

Conclusions: Given their shorter life-expectancy, the goal of vascular access creation in the elderly should be to create one functional AVF using the best vessels identified. The greater risk of FTM with lower arm AVFs may mean preferential creation of an upper arm AVF if these vessels are better on clinical and ultrasound assessment.

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

Underline represents presenting author.

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Type of Vascular Access and Mortality in Japan: Comparison of Arteriovenous Fistula and Arteriovenous Graft on Patient Survival and Access Patency in Non-Elderly versus Elderly Population

**Background:** The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) guidelines have recommended the use of AVFs at dialysis initiation of dialysis. However, it has been reported that the dialysis environment has been significantly different between Japan and the United States, and there are few people who continue hemodialysis with CVCs in Japan. The aim of this study is to examine the association between type of vascular access at dialysis initiation and mortality in Japan.

**Methods:** This study is retrospective, multicenter, cohort study which data was collected by "Aichi Cohort study of Prognosis in Patients" (AICOPP) newly initiated into dialysis. 18 tertiary care centers in Japan participating in the "AICOPP". This study enrolled 1,525 patients who started maintenance dialysis between October 1, 2011 and March 31, 2014. After exclusion of 129 patients who started peritoneal dialysis or without data, 1396 (87.1%) patients were enrolled. Cox regression was used to determine the effect of access type on total mortality. Type of vascular access was divided into four categories: AVFs, AVGs, CVCs changed to AVF during the course (CAVF), CVCs changed to AVG during the course (CAVG).

**Results:** This research showed prevalence of type of blood access in Japan.

Under multivariate analysis, CAVGs had a higher risk of mortality compared with AVFs group [hazard ratio (HR): 2.408; p value: 0.003]. No significant differences were observed compared AVFs with AVGs [hazard ratio (HR): 1.466; p value: 0.219] and CAVFs [hazard ratio (HR): 1.223; p value: 0.389].

**Conclusions:** As it is known, high AVF use was seen in Japan. Compared with AVFs, using CVCs changed to AVG during the course is associated with higher risks of mortality.

comparison of arteriovenous fistula and arteriovenous graft on patient survival and access patency in non-elderly versus elderly population

**Background:** Arteriovenous fistula (AVF) is generally known to be the ideal option as a vascular access. However, this consensus can be challenging in elderly population.

**Methods:** From August in 2008 to April in 2014, 1452 adult incident hemodialysis patients were included from Clinical Research Center registry for ESRD prospective cohort, from 31 centers in the South Korea.

**Results:** In the whole population, AVF vs. AVG use was associated with the better patient survival only in male (p < 0.001) and DM (p = 0.004) patients. Multivariate Cox regression analysis showed AVG (vs. AVF; odds ratio [OR] 2.308, 95% confidence interval [CI]: 1.031–4.829; p = 0.026), catheter vs. AVG (OR: 0.658, 95% CI: 5.379–21.19; p < 0.001) and age (OR 1.035, 95% CI: 1.012–1.058; p = 0.003) were significantly associated with poor patient survival. In the elderly patients (≥ 65 years old), the survival benefit by AVF use also existed in only male (p < 0.001) and DM (p = 0.009) patients, but AVG compared with AVG showed better access patency only in female (p < 0.001) and DM (p = 0.001) patients. Multivariate Cox regression analysis in the elderly population showed AVG (vs. AVF; OR 3.158, 95% CI: 1.080–9.238; p = 0.036), male (vs. female; OR 3.941, 95% CI: 1.031–15.066; p = 0.045) and the presence of peripheral vascular disease (OR 4.659, 95% CI: 1.389–15.626; p = 0.013) were significantly associated with poor patient survival. AVF showed the survival benefit compared with AVG in the even septuagenarian patients (≥ 70 years old), which is contrast to the previous reports about western population (p = 0.01). However, the superior access patency of AVF in comparison with AVG began to decrease in post-septuagenarian population.

**Conclusions:** In the Korean septuagenarian patients, AVF placement can be considered because of its survival benefit. However, it seems appropriate that AVG is preferably placed in the septuagenarian patients with multiple comorbidities.

**Type of Vascular Access and Mortality in Japan:** Toshikazu Ozeki,1 Shin Minatoguchi,1 Yukako Ohyama,1 Hideaki Shimizu,1 Yoshiro Fujita,1 Daisuke Inaguma.1 1Nephrology, Chubu Rosai Hospital, Nagoya, Japan; 2Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Japan.

**Background:** The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) guidelines have recommended the use of AVFs at dialysis initiation of dialysis. However, it has been reported that the dialysis environment has been significantly different between Japan and the United States, and there are few people who continue hemodialysis with CVCs in Japan. The aim of this study is to examine the association between type of vascular access at dialysis initiation and mortality in Japan.

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**Conclusions:** As it is known, high AVF use was seen in Japan. Compared with AVFs, using CVCs changed to AVG during the course is associated with higher risks of mortality.

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

Underline represents presenting author.
Dilator-Assisted Banding and Beyond: Proposing an Algorithm for Managing Dialysis Access-Associated Steal Syndrome

Showen Wang, AKDHC Access Centers, Arizona Kidney Disease and Hypertension Center; Phoenix, AZ.

Background: Dialysis Access-associated Steal Syndrome (DASS) is a major complication of arteriovenous dialysis accesses and its proper management is of critical clinical importance. However, the reported approaches are diverse and general consensus is lacking. Unilateral, guided banding approaches have gained popularity, as they are minimally invasive. This report analyzes the clinical outcome of Dilator-assisted Banding (DAB), a simple technique initially described by the author for managing DASS.

Methods: This series included 30 patients that underwent DAB for DASS due to excessive dialysis access flow. Results: Of the 30 patients: 29 had upper arm fistulas or grafts and 1 had a forearm fistula; 23 had arteriogram - 3 of which required angioplasty ± stent for feeding artery stenosis. The DAB procedures included: intraluminal DAB (12/30), extraluminal DAB (14/30) and open fistula reduction plus DAB (4/30). After DAB, the average severity scores of ischemic symptoms was reduced from 2.8 ± 0.4 to 0.2 ± 0.4 for the fistula group (n=24, p<0.001) and from 3.0 ± 0.0 to 1.2 ± 1.2 for the graft group (n=6, p=0.041). Of the 24 patients with fistula, 19 had resolution of ischemic symptoms and 5 had minimal residual symptoms while 3 had finger necrosis that healed after DAB. Of the 6 patients with graft, 2 had resolution, 2 had minimal residual and 2 had no change of ischemic symptoms. These two DAB-ineffective patients underwent proximalization of arterial inflow (PAI) revisions that resulted in resolution of ischemic symptoms. During follow-up of 18.7 ± 14.5 months (range 1-50), all dialysis accesses remained functional. At 24-month post-DAB, the primary patency, primary-assisted patency and secondary patency rates of the fistula group were 72%, 91% and 100%, respectively. Conclusions: DAB is a simple, effective and versatile approach for managing DASS due to excessiveflow, especially in patients with fistula. In patients with failed banding, PAI can be effectively used for rescue. Based on the data in this series and the literature, an algorithm is proposed for managing DASS.

Outcomes of Vascular Access Creation in Incident Hemodialysis Patients in Singapore

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Background: Hemodialysis is the main modality of renal replacement therapy for end-stage renal disease (ESRD) patients in Singapore. Vascular access is critical for effective therapy. This study evaluated the impact of pre-operative vein mapping on vascular access creation in patients newly initiated on hemodialysis in Singapore General Hospital.

Methods: Data of ESRD patients initiated on hemodialysis from January 2010 to December 2012 were retrospectively collected from electronic medical records. 708 patients (mean 62.8 ± 12 years, 61% male, 71.3% Chinese) who underwent surgical creation of their first vascular access were followed up for a mean of 2.3 ± 1.2 years. Results: 694 (98%) arteriovenous fistulae (AVF) and 14 (2%) arteriovenous grafts (AVG) were created. Successful AVF cannulation was established in 543 patients (78.2%). After 1 year, 511 (73.6%) remained patent with 43.5% (302/694) primary and 30.1% (210/694) secondary patency. 23 had arteriogram - 3 of which required angioplasty (AV) and 30 (4.3%) secondary patency. Upper arm AVFs had significantly higher patency rates (85.0% ± 76.4% vs. 80.0% ± 66.5% in the lower arm, p = 0.011). Pre-operative vein mapping was performed in 42.5% (295/694) patients. The mean vein diameter was 2.44 ± 0.21mm. Maturation rates with and without vein mapping were 72.2% and 62.2% respectively (p = 0.001). Between vein diameters of <2 and ≥2mm, there was no statistical difference in maturation rates (p = 0.001). Of the 24 patients with fistula, 19 had resolution of ischemic symptoms and 5 had minimal residual symptoms while 3 had finger necrosis that healed after DAB. Of the 6 patients with graft, 2 had resolution, 2 had minimal residual and 2 had no change of ischemic symptoms. These two DAB-ineffective patients underwent proximalization of arterial inflow (PAI) revisions that resulted in resolution of ischemic symptoms. During follow-up of 18.7 ± 14.5 months (range 1-50), all dialysis accesses remained functional. At 24-month post-DAB, the primary patency, primary-assisted patency and secondary patency rates of the fistula group were 72%, 91% and 100%, respectively. Conclusions: DAB is a simple, effective and versatile approach for managing DASS due to excessiveflow, especially in patients with fistula. In patients with failed banding, PAI can be effectively used for rescue. Based on the data in this series and the literature, an algorithm is proposed for managing DASS.

Chlorhexidine-Impregnated Transparent Dressing for Prevention of Catheter-Related Bacteremia in Hemodialysis Patients: A Quality Improvement Study

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Background: CRBSI are a major cause of morbidity in HD patients dialyzing with a CVC. A major route of catheter contamination is introduction of organisms from the skin to the catheter. Tegaderm-CHG is a transparent catheter dressing with an integrated gel containing chlorhexidine, designed to combine the benefits of transparent dressings; and the antecedial and bacteriostatic benefits of chlorhexidine. We conducted a QI project to assess the rates of catheter-related bloodstream infection (CRBSI) in three dialysis units following the introduction of chlorhexidine-impregnated transparent catheter dressings.

Methods: Our study was conducted in two phases. In the first phase (9/12 through 10/13), we introduced the intervention, Tegaderm-CHG, to EDC, one of the three Emory hemodialysis units. EDGB and EDNS were the control sites where standard gauze catheter dressings were maintained. The rates of CRBSI at each dialysis units during the 12-month intervention were compared against the rates of CRBSI for the 12 month pre-intervention period. CRBSI rates were also compared between the dialysis units. The second phase of the study started in 11/2013, with the extension of Tegaderm-CHG dressing to EDGB and EDNS (the control sites in Phase 1). Tegaderm-CHG was maintained at EDC.

Results: The three dialysis units were comparable in terms of age, sex, and race of patients. In phase 1, the catheter infection rate (per 1,000 catheter days) in EDC decreased by 51% (pre: 1.69, post: 0.82). At EDGB, the infection rate increased by 12% (pre: 1.80; post: 2.02) while the infection rate increased by 35% (pre: 0.91; post: 1.23) at EDN. However, none of these increases in infection rates were significant (i.e., p > 0.05). The infection rates at EDGB and EDN decreased significantly in phase 2 by 86% (pre: 1.86; post: 0.26), and 53% (pre: 1.89; post: 0.88), respectively. At EDC, the catheter infection rate did not change significantly in phase 2.

Conclusions: The use of Tegaderm CHG dressing was associated with decreased rates of CRBSI in Emory outpatient dialysis units. Funding: Other NIH Support - Partially supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
TH-PO873
In-Patient Permanent Access Is Associated with Reduced Catheter Time for Emergent Start Hemodialysis Patients Catherine A. Moore,1 Richard E. Wing,2 Scott E. Lieberman.1 1Medicine- Nephrology Div, Univ of Rochester; Rochester, NY; 2Aurora Medical Group, Marinette Menominee Clinic, Marinette, WI.

Background: Hemodialysis initiation with a tunneled catheter carries increased risk of morbidity and mortality. Conversion from a hemodialysis catheter to permanent access at any time is associated with improved outcomes. This study investigates whether a strategy of placing permanent dialysis access in incident HD patients without permanent access while still hospitalized is associated with reduced exposure to hemodialysis catheters.

Methods: We conducted a retrospective cohort study of ESRD patients initiating Hemodialysis with a catheter while hospitalized at a single University Hospital Medical Center from October 2010 through June 2013. Patients were divided into two groups: those with permanent access placed during the hospitalization (N = 22) vs. those discharged without permanent access (N = 67). Our primary endpoint was removal of the hemodialysis catheter.

Results: Subjects who underwent permanent access placement while still hospitalized had a median catheter exposure time of 114 days compared with 241 days for those who did not. The median time with HD catheter in place was shorter by 127 days in the Inpatient Access group. There was no significant difference in length of hospital stay or early access loss.

Conclusions: The practice of placing permanent access while the patient is still admitted to the hospital is associated with greater likelihood of hemodialysis catheter removal.

TH-PO874
Factors Affecting Haemodialysis Arterio-Venous Fistula Maturation Hannah R. Wilson, Salman Ahmed, Joseph Russell, Nicola Ding, Maggi Steele, Ayeshia Iritza-Ali, David Makanjuola, Nihil Chitalia. Renal Unit, St. Helier Hospital, Surrey, United Kingdom.

Background: Arterio-venous fistulae (AVF) are the preferred access for haemodialysis (HD). Many AVFs however, fail to mature. We investigated the factors affecting maturation of AVFs in order to identify any characteristics which were predictive of AVF maturation.

Methods: All AVFs created between 2006 and 2014 were reviewed. Data analysis was performed using GraphPad. AVFs were deemed to have failed to mature if by 90 days post-creation, it was not possible to use them for HD. The patients were divided into 2 groups – those who had the AVF created pre-emptively (group 1) and those already on HD at the time of AVF creation (group 2). Characteristics reviewed were age, gender, ethnicity, co-morbidity scores, diabetes status and ethnicity had no impact on AVF maturation rates.

Conclusions: The timing of AVF creation is important; those formed pre-emptively are more likely to mature than those created when the patient is on dialysis. It is possible that the presence of a dialysis line might delay maturation, especially if it is ipsilateral to the AVF. It highlights the importance of prompt referral to nephrology services so that AVFs can be created in a timely manner.

Hand Held Ultrasound Device Solves Vascular Access (VA) Cannulation Problems Beth Adams, Vivek Soi, Jerry Yee, Lalathaksha Murthy Kumar. Henry Ford Hospital, Detroit, MI.

Background: The Fistula First Catheter Last workgroup coalition identifies VA cannulation as a fundamental “failure” point in optimizing arteriovenous fistula (AVF) usage. Infiltration from cannulation difficulties result in significant morbidity including loss of VA and cost. Cannulation success is reliant on cannulators’ skill and VA characteristics. Surface marking of VA to aid cannulation is frequently used but lacks real time information. Traditional ultrasound devices are expensive and need skilled operators rendering inapt for routine use in hemodialysis units. Sonic Window© (Analogic Ultrasound) is a coronal mode ultrasound device (CMUD) approved for VA cannulation. We present our early experience using this novel hand held CMUD for real time guidance of VA cannulation.

Methods: Three patients with cannulation failure defined as inability to achieve 3 needle cannulations leading to tunnel cuffed catheter (TCC) removal were identified. AVF was evaluated initially for 1-2 dialysis sessions with CMUD for course, depth from skin, optimal site for cannulation, needle length and size. Infiltration rates, subsequent procedures and hospitalizations were noted before and after CMUD use and cannulation failure days (days from initial VA clearance for use to TCC removal).

Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mature AVF</th>
<th>Non-mature AVF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-emptive</td>
<td>415 (55.7%)</td>
<td>241 (28.9%)</td>
<td>*</td>
</tr>
<tr>
<td>Non pre-emptive</td>
<td>330 (44.3%)</td>
<td>592 (71.1%)</td>
<td>*</td>
</tr>
<tr>
<td>Age in years [mean(SD)]</td>
<td>63 ±15.6</td>
<td>64 ±15.6</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies co-morbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>56%</td>
<td>55%</td>
<td>ns</td>
</tr>
<tr>
<td>Asian</td>
<td>12%</td>
<td>13%</td>
<td>ns</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>8%</td>
<td>9%</td>
<td>ns</td>
</tr>
<tr>
<td>Not stated</td>
<td>24%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Upper arm AVF</td>
<td>54%</td>
<td>52%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetic</td>
<td>35%</td>
<td>37%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetic</td>
<td>18%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetic</td>
<td>68%</td>
<td>68%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetic</td>
<td>14%</td>
<td>17%</td>
<td>ns</td>
</tr>
<tr>
<td>Davies co-morbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (no co-morbidities)</td>
<td>18%</td>
<td>15%</td>
<td>ns</td>
</tr>
<tr>
<td>1 (1-2 co-morbidities)</td>
<td>68%</td>
<td>68%</td>
<td>ns</td>
</tr>
<tr>
<td>2 (3 or more co-morbidities)</td>
<td>14%</td>
<td>17%</td>
<td>ns</td>
</tr>
</tbody>
</table>

*p<0.0001 for percentage of mature AVFs in pre-emptive vs non-pre-emptive groups.

Conclusions: Our data show that the timing of AVF creation is important; those formed pre-emptively are more likely to mature than those created when the patient is on dialysis. It is possible that the presence of a dialysis line might delay maturation, especially if it is ipsilateral to the AVF. It highlights the importance of prompt referral to nephrology services so that AVFs can be created in a timely manner.
TH-PO876

Reaching First Dialysis Quickly and Unassisted with Sirolimus Treated Fistulae – Serial Ultrasound Results and Clinical Outcomes
Maria V. DeVita,1 Eric S. Chemla,2 Konstantine B. Kipiani,3 Nutsa K. Beridze,3 Srram Iyer,1 *Nephrology, Lenox Hill Hospital, New York, NY; 1Vascular Surgery, St. George’s NHS Foundation Trust, London, United Kingdom; 2Vascular Surgery, Georgian Center of Angiology and Surgery, Tbilisi, Georgia; 3Vascular Therapies Inc, Cresskill, NJ.

Background: Neointimal hyperplasia (NH) resulting in a flow limiting stenosis within the juxta-anastomotic segment (JAS) of an AV Fistula (AVF), impairs increase in upstream vein diameter (VD), often requires supplementary procedures and prolongs time to 1st cannulation for dialysis (D). Sirolimus delivered locally to the vessel wall can suppress NH and preserve lumen patency (“sirolimus effect”).

Methods: 30 pts (29 on D) undergoing AVF surgery [22 Radiocephalic (RCF), 8 Brachiocephalic fistulae (BCF)] received a Sirolimus eluting collagen implant at and around the JAS. 1st cannulation was based on clinical evaluation.

Results: 18 males, mean age 50.8y, 20% diabetic. Analysis excludes 4/22 RCF that thrombosed ≤2 weeks; 18/22 RCF (88%) and all 8 BCF maintained Primary Patency (PP) prior to 1st cannulation (mean 49 days); 13 AVF were cannulated ≤6wks, 74% AVF maintained suitability for D with PP at 12mns. Table shows serial Ultrasound results.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre op</th>
<th>6-8 hours Post op</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCF (n=18)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VD Mean (±SD)</td>
<td>2.7 (0.5)</td>
<td>4.4 (0.5)</td>
<td>5.1 (0.8)</td>
<td>5.8 (0.7)</td>
<td>6.1 (0.4)</td>
<td>6.4 (0.4)</td>
</tr>
<tr>
<td>VD change from prior time point</td>
<td>-</td>
<td>63%</td>
<td>16%</td>
<td>5%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td><strong>RCF (n=18)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VD Mean (±SD)</td>
<td>1.9 (0.6)</td>
<td>5.4 (0.8)</td>
<td>6.8 (0.8)</td>
<td>7.5 (0.9)</td>
<td>7.9 (1.7)</td>
<td>8.4 (1.38)</td>
</tr>
<tr>
<td>VD change from prior time point</td>
<td>-</td>
<td>38%</td>
<td>26%</td>
<td>9%</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Conclusions: Maximum % increase in VD occurred within 8hrs of surgery with gradual continued increments thereafter. At 4, 6 and 8wks, VD of 6mm was attained by 62%, 81% and 100% of the AVF respectively. 3. 26/30 AVF(87%) maintained PP before 1st cannulation, time to 1st dialysis for 13 AVF(50%) was ≤6wks and at 12mos 75% were functional with PP. 4.Results signal a “sirolimus effect” and will be tested in an upcoming randomized trial.

Funding: Pharmaceutical Company Support - CorMedix Inc

TH-PO877

Economic Burden to Medicare of Central Venous Catheter (CVC)-Related Blood Stream Infections (BSI) and Occlusions Among Incident Hemodialysis (HD) Patients
Scott Sibbel,1 Steven M. Brunelli,1 Abigail Hunt,2 Wendy Turemne,1 Antony E. Paffie,2 *DaVita Clinical Research, Minneapolis, MN; 1CorMedix Inc, Bedminster, NJ.

Background: Episodes of CVC-related BSI and occlusion in HD patients result in hospitalizations and vascular access-related procedures, with attendant increases in costs. We sought to quantify this burden to the payor among Medicare-enrolled patients at a large dialysis organization.

Methods: Patients received HD via CVC during 2011 and were enrolled in Medicare Parts A and B. In parallel analyses, patients who developed BSI (N=1413) or occlusion (N=793) were matched with controls who did not, on the basis of entry month and incident/prevalent dialysis status. Outcomes were assessed from date of BSI/occlusion (or corresponding date for controls) for 6 months or until censoring for modality change, transfer of care, loss of Medicare benefits or death. Comparisons were made using linear mixed models including fixed effects for exposure status and month, adjusted for covariates that were imbalanced at baseline.

Results: CVC-related BSI was associated with greater rate of hospitalization (incidence rate difference [IRD], 1.07 events/patient [pt]-year) and vascular-related procedures (IRD, 2.87 events/pt-year). Mean per patient per month (PPPM) costs were $2850 higher for BSI patients versus controls, driven primarily by increased inpatient costs. CVC occlusion was associated with modestly greater rate of hospitalization (IRD, 0.29 events/pt-year), but substantively greater rate of ambulatory procedures (IRD, 4.00 events/pt-year). Mean PPPM costs were $2354 greater for occlusion patients versus controls, driven by higher ancillary service and procedure costs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
There was no difference in AVF survival between the groups (DPP4-I: 45.5 ± 7.2 pg/ml, p = 0.03). Among other drugs, no correlation was indicated between AVF dysfunction with insulin, RAS blocker, other antihypertensive drugs nor antplatelet agents. 

Conclusions: DPP4-I did not show any advantage in AVF outcome despite anti-inflammatory effect of lowering serum IL-6 level.

TH-PO881 

Background: The purpose of this article is to report our experience with drug-eluting balloon(DEB) for the treatment of failing Arteriovenous Fistula(AVF). Mean life expectancy of the vascular access after the procedure, influence on adequate dialysis parameters postintervention and percentage of complications.

Methods: DEB procedures made in our hospital were evaluated. Main objective was to analyze: a)Reason of consulting and vascular lesion found. b)Haemodialytic arteriovenous shunt type. c)Kt/V, Qb, PV d)Survival of the vascular access at the end of the study e)Complications related to the procedure.

Results: 9 angioplasty were made by DEB. Mean age:74,6 years, 50% male. 5 left native radiocephalic fistula and 1 humero-axillary prosthetic.Most of the patients had at least 4 previous interventions. Principal reason of consultation was low flow,being the most frequent arterial stenosis. No complications were found related to any procedure. Every vascular access is permeable at the actual time, mean life since the intervention: 24 months, being necessary only one reintervention in the target lesion. Blood flow, venous pressure and Kt/V improvement regarding to the basal was observed, after the procedure and at the end of the study.

Conclusions: There is limited experience with the use of drug-eluting balloon in haemodialysis arteriovenous fistula, an increase in average life expectancy of the vascular access with bad prognosis ( led to a new vascular access) was found, an improvement on adequate dialysis parameters was observed, preserving vascular system of the patient, decreasing costs and with no complications. More studies would be needed.

TH-PO882 
Alteplase Infusion as Rescue Therapy for Central Venous Haemodialysis Catheter Dysfunction Sanjana Gupta, Stephen B. Walsh, Karlene Thomas,1 Ravindra Rajakariar.1 1Barts Health NHS Trust; 2UCL Centre for Nephrology.

Background: Central venous haemodialysis catheters (CVHC) can become occluded or have poor blood flow (Qb). CVHC complication estimates are 35% and result in hospitalisation and interventional procedures. This study aimed to review alteplase infusion success and patency rates.

Methods: We undertook a retrospective review of all patients that had an alteplase infusion at the Royal London Renal Unit over a 15-month period. Patients who had failed an alteplase lock and 4mg alteplase was used in both lumens. Data was collected using the renal database.

Results: Baseline characteristics were identical between 2 groups in age, sex, blood pressure, body mass index, history of congestive heart failure and coronary artery disease. There was no difference in AVF survival between the groups (DPP4-I: 45.5 ± 7.2 pg/ml, p = 0.03). Among other drugs, no correlation was indicated between AVF dysfunction with insulin, RAS blocker, other antihypertensive drugs nor antplatelet agents. 

Conclusions: DPP4-I did not show any advantage in AVF outcome despite anti-inflammatory effect of lowering serum IL-6 level.
Results: There are 1002 haemodialysis patients; 412 diastole via a CVHC.

- Total uses / total patients (n) 94 / 74
- Repeat Alteplase, same CVHC n (%) 20 (21)
- Median age of CVHC (IQR) 147 days (77 - 300)
- Indication (occlusion / Poor Qb) n 31 / 63

CVHC age was statistically different depending on the indication; occluded CVHC age was 124 ± 22 vs 244 ± 27 days for low Qb (P=0.01). Rescued CVHC age was significantly lower than those in whom the alteplase was unsuccessful (147 ± 18.4 vs 269 ± 35.8; P=0.004). In 48% of patients with an occluded CVHC, flow was restored; the remaining 52% required further intervention. Low Qb CVHC success rate was 60% compared to 38% requiring further intervention, 2% were removed (arteriovenous fistula or transplant). There was no significant difference between success rates depending on the indication (P=0.34).

Alteplase infusion significantly increased litres processed in subsequent dialysis sessions, in whom the indication was low Qb (6.2 ± 1.16 litres; P < 0.0001). All of infusions undertaken; 1 month patency was 56%, 3 months 45% and 6% removed. No patient had an adverse bleeding event as a result of the alteplase infusion.

Conclusions: Alteplase infusion use is common; approximately once a week in our centre. Interestingly, complete occlusion of CVHC occurs early, possibly suggesting rapid growth of fibrin following insertion. Total litres processed improves after an alteplase infusion in over half of patients. This study demonstrates the safety and success rates of an alteplase infusion, providing evidence for its role prior to replacing the CVHC and importance in saving resources.

TH-PO883

Temporal Evolution of Parameters Before and After Initiation of Hemodialysis

Jochen G. Raimann, John W. Larkin, Carly Van Zandt, Len A. Usyniak, Jeroen Koornman, Frank van der Sande, Barbara Cannon, Chad Sowers, Mark Stuart, Terry Ketchersid, Dugan Maddux, Peter Kotanko, Franklin W. Maddux.

1 Renal Research Inst; 2 Fresenius Medical Care North America; 3Maastricht Univ Medical Center; 4Ichim School of Medicine at Mount Sinai.

Background: Little is known about the dynamics of clinical and laboratory parameters during the transition before pre-dialysis chronic kidney disease and end stage kidney disease (ESKD). The goal of our research was to explore the temporal evolution of albumin (Alb), systolic blood pressure (SBP) and serum sodium (SnA) by analyzing monthly data before and after hemodialysis (HD) initiation.

Methods: We analyzed all available data from the de-identified Fresenius Medical Care CKD Data Registry to understand progression of clinical and laboratory markers before and after HD initiation. Average values of Alb, SBP and SnA were compared for 12 months prior and after HD initiation using t-test. To estimate the trends of the average values, we fitted a linear regression function through monthly averages.

Results: We studied 136846 patients (64/14 years, 56% male) over 48 months. Average SBP increased prior to HD initiation (1.2 mmHg/year), immediately decreased following HD initiation, and remained lower for the following 12 months (142.4±22.8 vs 136.1±23.2 mmHg; P<0.05). Before starting HD, Alb was found to be relatively unchanged, however an increase was observed after HD initiation (average Alb increased by 0.14 g/dL per year, levels were slightly higher 12 months after HD initiation [3.7±0.5 vs 3.8±0.4 g/dL; P<0.05]). Average SnA pre-ESKD had a declining trend (-0.5 mEq/L per year) and was lower compared to slightly higher 12 months after HD initiation [3.7±0.5 vs 3.8±0.4 mEq/L; P<0.05].

Conclusion: This study demonstrates a trend toward improvement in SBP and Alb following HD initiation. The etiology of the SnA decrease after HD initiation requires further investigation.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO884

Accelerated Arterial Stiffening in Vitamin-K-Antagonist Treated Hemodialysis Patients

Christian D. Peters, Krista D Kjaergaard, J. Dam Jensen, Bente Jespersen. Dept. of Renal Medicine, Aarhus Univ Hospital, Aarhus, Denmark.

Background: Many hemodialysis (HD) patients are treated with vitamin-K-antagonists (VKA) in order to prevent thromboembolic events. A potential side effect to VKA treatment is an increase in soft tissue calcification due to the inhibitory effect of VKAs on the central (liver) and peripheral (e.g. vascular) carboxylation cycle synthesis of several vitamin K-dependant calcification-inhibiting factors. The aim of the present study was to investigate the impact of VKA-treatment on arterial stiffness in a longitudinal, prospective comparative study.

Methods: Seventy-five HD patients from the SAFIR study with urine output >300 mL/day and HD-vintage <1 year were divided into controls (n=67) and VKA-treated (n=8) and followed for one year. The groups were well matched according to age, sex, comorbidity, and intervention (placebo/irbesartan). Arterial stiffness was assessed with carotid-femoral pulse wave velocity (PWV) and pulse wave analysis using the SphygmoCor device.

Results: Blood pressure (BP), PWV, and glomerular filtration rate (GFR) were similar at baseline (controls/VKA-treated) systolic BP: 148±20/145±17 mmHg; PWV: 11.6±3.2/11.0±3.9 m/s; GFR: 53±5.3 vs 51±1.7 m/min. Dialysis treatment and BP-medication were also similar. During follow up, GFR decreased similarly in both groups (P<0.02). There was no significant difference in BP between the two groups over time although BP tended to decrease more in the controls. PWV decreased in the controls -0.9(-1.4; -0.3) m/s; P<0.004 and increased in the VKA-treated 1.6(0.0; 3.2) m/s; P<0.005. Mean difference among 12 months between the groups (DPPWV) was: 2.5(0.7; 4.2) m/s; P<0.006. DPPWV was gained significant after adjustment for ∆GFR, ∆MAP, age at baseline, and ∆BP-medication: 2.2(0.4; 4.0) m/s; P<0.02. Mean differences among 12 months between the groups in heart rate adjusted augmentation index and time to pulse wave reflection were: 7(-2; 15) %; P=0.11, (14±27; 21±2) ms; P<0.03 (TR).

Conclusions: Our findings indicate that VKA-treatment increases arterial stiffening significantly. We speculate that vitamin K-dependant calcification-inhibiting factors in HD patients may be inadvertently affected by VKA treatment.

Funding: Private Foundation Support, Government Support - Non-U.S.
Different Impact of Malnutrition-Inflammation and Metabolic Syndrome on Long-Term Mortality and Cardiovascular Events in Hemodialysis Patients

Naoki Nakaawag. Renal Div, Dept of Internal Medicine, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan.

Background: Malnutrition syndrome confers an increased risk of cardiovascular disease (CVD) in the general population. The relationship between adipocytokines, and clinical outcomes in hemodialysis patients remains controversial. We investigated whether adipocytokines, biomarkers of inflammation, nutrition status and clinical features predict the mortality of hemodialysis patients for 6 years.

Methods: We measured baseline plasma total and high-molecular-weight (HMW) adipocytokines, tumor necrosis factor (TNF-α) serum high sensitivity C-reactive protein (hsCRP), and clinical characteristics including visceral fat area (VFA) and the Geriatric Nutritional Risk Index (GNRI) in 133 hemodialysis patients.

Results: During the 6-year follow-up period, 41 (30.9%) patients died (heart failure, n = 13; acute myocardial infarction, n = 11; stroke, n = 2; infection, n = 10; and malignant cancer, n = 5). The deceased patients were significantly older, had more prior CVD and diabetes, higher TNF-α and hsCRP levels but lower GNRI, VFA, and total and HMW adipocytokin did not significantly differ between the two groups. TNF-α and hsCRP levels and GNRI score were significant for predicting all-cause and cardiovascular mortality in receiver operating curve analyses. The present ROC curve analysis for all-cause 6-year mortality found the predictive value of GNRI for mortality was 96. When stratified by a GNRI score of 96, Cox proportional hazards analyses identified TNF-α as a significant predictor of all-cause mortality (hazard ratio [HR] 1.23, P = 0.038) and hsCRP as a significant predictor of all-cause and cardiovascular mortality (HR, 2.32, P = 0.003; HR, 2.30, P = 0.012, respectively) after adjusting for age, sex, diabetes mellitus, and prior CVD, only in malnourished patients.

Conclusions: These results demonstrate that malnutrition and the inflammatory markers TNF-α and hsCRP, but not metabolic markers, including VFA and adiponectins have a significant impact on 6-year all-cause and cardiovascular mortality in hemodialysis patients.

Funding: Government Support - Non-U.S.

Non-Traditional Risk Factors Predict Atherosclerotic Events in Haemodialysis Patients – Post-Hoc Analyses of the AURORA Trial

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Background: Patients on haemodialysis are at high risk for cardiovascular events, but heart failure and sudden death dominate and atherosclerotic events are less common. The AURORA trial was designed to assess the effect of rosuvastatin on myocardial infarction and death from any cardiac cause in haemodialysis patients. We studied predictors of the atherosclerotic, and not all cardiovascular, events in AURORA.

Methods: We re adjudicated all deaths and presumed myocardial infarctions according to stricter criteria to separate atherosclerotic from non-atherosclerotic cardiovascular events. The re adjudicated atherosclerotic endpoint included non-fatal myocardial infarction, fatal coronary heart disease, non-fatal and fatal non-haemorrhagic stroke, revascularisation procedures and death from ischaemic limb disease. Baseline predictors were assessed for the 2776 participants of the AURORA trial, and step-wise Cox regression analysis was applied.

Results: During a mean follow-up of 3.2 years, 716 patients experienced a re adjudicated atherosclerotic event. Baseline phosphate (HR 1.33; 95% CI 1.16-1.53 per 1 mmol/L increase), albumin (HR 0.93; 95% CI 0.91-0.96 per 1 g/L increase) and high sensitive CRP (HR 1.07; 95% CI 1.00-1.14 per mg/L increase) were significant predictors in addition to female sex, age, prevalent diabetes and cardiovascular disease. LDL cholesterol was not a significant risk factor.

Conclusions: Even with the use of strict criteria for endpoint definition, non-traditional risk factors, but not lipid disturbances, predicted atherosclerotic events in haemodialysis patients.

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Proteomic Studies of Blood Plasma Using 2DE and Mass Spectrometry for Deeper View into the Mechanisms Involved in Atherosclerosis in Chronic Kidney Disease

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Background: The exact participation and association of particular risk factors and specific mechanisms that promote cardiovascular complications (CVD) in patients with chronic kidney disease (CKD) remain unclear. The close relationship between CVD and CKD is most likely due to the co-existence of both traditional and novel risk factors. To gain insight into better recognition of the mechanisms of CKD-related accelerated atherosclerosis, a comparative proteomic analyses have been performed.

Methods: Blood samples were taken from 90 patients (CKD1-2, CKD3-4, CKD5), 30 patients with CVD, but without CKD and 30 healthy volunteers. Plasma samples were depleted using affinity chromatography and divided into three fractions: high-abundance protein, low-abundance protein and low molecular weight protein. The first two fractions were analyzed by two dimensional gel electrophoresis and mass spectrometry, the last one has been subjected to direct MS/MS analysis. Differential accumulated proteins were confirmed by selected reaction monitoring analysis.

Results: 49 proteins (13 high and 36 low molecular mass) showed differences in accumulation levels. The proteomic profiles in CKD5 and CVD patients differed in the accumulation of four LAPs the relative accumulations of alfa -2-macroglobulin, second isoform of alfa 1 microglobulin and higher in CKD5 compared with CVD; fold changes 1.77, 4.14, 2.68 and 1.79, respectively. Moreover, the relative abundances of these proteins were up-regulated in CKD3-4 compared with CVD. CKD1-2 and CVD group differed in the accumulation of apolipoprotein A-4 and apolipoprotein A-1.

Conclusions: Our results definitely indicated similar proteomic profiles in CKD1-2 and CVD patients, in contrast to CVD and CKD5 patients, suggesting that mechanisms of CVD acceleration may be different in initial and advanced stages of CKD. It seems that it is related to chronic inflammation and immune disturbances, typical for CKD.

Hemodialysis-Induced Release of Microparticles

Liina Vassal,1 Inga Soeveri,1 Fairzbot Mobarrez,2 Tora Almqvist,3 Bengt C. Fellstrom,3 Dept of Medical Sciences, Uppsala Univ, Uppsala, Sweden; Dept of Medicine, Karolinska Inst, Stockholm, Sweden; Dept of Clinical Sciences, Danderyd Hospital, Karolinska Inst, Stockholm, Sweden.

Background: Microparticles (MPs) are 0.1 - 1.0 μm vesicles that are released from cells upon activation or during apoptosis. MPs are believed to be involved in the pathophysiology of atherosclerosis and thrombosis. Patients with cardiovascular risk factors have significant MP elevation. Measurements of MPs may uncover new insight into mechanisms behind the severe increased cardiovascular disease (CVD) risk in hemodialysis (HD) patients.

The aim was to study whether a hemodialysis session affects MP formation and release.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

297A
**Methods:** Plasma samples from 20 HD patients were drawn before and 1 h after the start of HD session. MPs derived from platelets (CD41+), monocytes (CD14+), endothelial cells (CD31+), and their expression of phosphatidlyserine (PS) and tissue factor (CD142) were measured by flow cytometry. P-selectin (CD62P) and CD40 ligand (CD154) were measured on platelet-MPs. In addition, Klotho and the receptor for advanced glycation end products (RAGE) were measured on MPs. Paired t-test was used.

**Results:** Mean age was 73.6 years (range 54-91), 5 patients were female, 14 had central dialysis catheter, 8 patients had diabetes and 14 had CVD.

<table>
<thead>
<tr>
<th>Marker (x10^3/L)</th>
<th>Before HD</th>
<th>1h after start of HD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactadherin (PS-MPs)</td>
<td>3645(1690-9784)</td>
<td>4388(1966-12672)</td>
<td>0.08</td>
</tr>
<tr>
<td>Lactadherin + CD41</td>
<td>464(153-2321)</td>
<td>774(169-3000)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lactadherin+CD41+CD62P</td>
<td>186(50-1098)</td>
<td>550(70-1369)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactadherin+CD41+CD154</td>
<td>205(13-992)</td>
<td>56(32-1236)</td>
<td>0.05</td>
</tr>
<tr>
<td>Lactadherin+CD14</td>
<td>216(75-443)</td>
<td>337(205-584)</td>
<td>0.00</td>
</tr>
<tr>
<td>Lactadherin+CD62P a</td>
<td>713(233)</td>
<td>845(348)</td>
<td>0.03</td>
</tr>
<tr>
<td>CD41+CD142 a</td>
<td>467(262)</td>
<td>541(337)</td>
<td>0.30</td>
</tr>
<tr>
<td>CD62E+CD142</td>
<td>135(15-392)</td>
<td>171(26-900)</td>
<td>0.06</td>
</tr>
<tr>
<td>CD14+CD142</td>
<td>31(11-121)</td>
<td>58(17-193)</td>
<td>0.00</td>
</tr>
<tr>
<td>Klotho a</td>
<td>2260(276)</td>
<td>2612(414)</td>
<td>0.00</td>
</tr>
<tr>
<td>RAGE</td>
<td>154(122-1536)</td>
<td>252(178-1941)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Mean ± (SD) or (Median) range

**Conclusions:** The majority of MP levels increase significantly after the start of a HD session. Whether this is driven by patient or dialysis specific factors remains unclear. The clinical significance of MP release during HD needs to be evaluated. *Funding:* Government Support - Non-U.S.

**TH-PO891**

The Monocyte Subset of CD14+CD16+ Cells Plays a Key Role in Promoting Atherosclerosis in Hemodialysis Patients

**Methods:** Subjects included 62 HD patients and 30 healthy controls. Peripherial monocytes were isolated using magnetically labeled Whole Blood CD14+ microbeads. Transcriptional levels of CD14 and CD16 in circulating monocytes play a key role in promoting foam cell formation by binding and internalizing oxidized low-density lipoprotein. In addition, heterogeneity of monocytes and macrophage- colony stimulating factor (M-CSF) may facilitate the atherosclerotic process by SR over-expression.

**Results:** The CD14+CD16+ monocytes were expressed higher in HD patients than in those from controls (2.35 vs 1.29, p=0.0006). Moreover, it was higher in HD patients with CVD than in those without (2.79 vs 1.64, p=0.0023). Plasma concentration of M-CSF was measured with M-CSF ELISA kit. Additionally, CD16 protein expression was analyzed by a flow cytometry.

**Conclusions:** The CD14+CD16+ monocytes play a key role in promoting atherosclerosis in hemodialysis patients.

**TH-PO892**

Active Ghrelin Enhances the Association Between BMI and Clinical Outcome in Hemodialysis Patients Irrespective of Appetite Ilia Beberenvishev, Inna Sinutin, Ada Azar, Leonid Feldman, Shai Efrati. 1Nephrology, Assaf Harofeh Medical Center, Israel; 2Nutrition, Assaf Harofeh Medical Center, Zerifin, Israel; 3Nutrition, Assaf Harofeh Medical Center, Zerifin, Israel.

**Background:** Ghrelin, a gastric orexigenic peptide, and BMI are known as inversely associated with left ventricular hypertrophy and dysfunction, and may predict cardiovascular mortality in end-stage renal disease (ESRD) patients. This study was to evaluate the association of predialysis serum ghrelin levels with echocardiographic markers in ESRD patients.

**Methods:** Serum ghrelin, albumin, CRP, iPTH levels were obtained from predialysis blood samples at 123 incident HD patients. Echocardiographic parameters and left ventricular mass index (LVMI) and ejection fraction, ratio of peak early transmural flow velocity to peak early diastolic annular flow velocity (E/E’ ratio), ratio of peak early transmitral flow velocity to peak late transmitral flow velocity (E/A ratio), and mitral valve-deceleration time (DT).

**Results:** A direct correlation was found between PICP and Left ventricular mass index (r=0.308, P=0.002), between PICP and E/E’ ratio (r=0.236, P=0.009), between PICP and ratio of peak early transmural flow velocity to peak late transmural flow velocity (E/A) (r=0.285, P=0.002). A negative correlation was found between PICP and Left ventricular ejection fraction (r=−0.289, P=0.001), between PICP and mitral valve-deceleration time (r=−0.203, P=0.026). In the multivariate linear regression analysis, the PICP was independently positively associated with LVMI and E’ and negatively associated with Left ventricular ejection fraction. In the multivariate Cox regression analysis, previous CV event (HR 15.224, CI 3.26-71.04), and High PICP group (vs low PICP group) (HR 9.478, CI 1.10-81.82) were the significant prognostic factors cardiovascular event.

**Conclusions:** Serum predialysis ghrelin concentration is associated with left ventricular hypertrophy and dysfunction, and may predict cardiovascular event in incidential dialysis patient.

**TH-PO894**

Associations of Soluble Receptor for Advanced Glycation End Products with Cardiovascular Biomarkers and S100A12 (EN-RAGE) with Mortality in Long-Term Hemodialysis Patients Jun Yung Jung, Eul Sik Jung, Byoungcho Choi, Yun Jung Oh, Chungsik Lee, Ae Jin Kim, Han Ro, Jae Hyun Chang, Hyun Hee Lee, Wookyung Chung. 1Dept of Nephrology, Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea; 2Dept of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea.

**Background:** Hemodialysis (HD) patients have been associated with vascular calcification and ultimately with high mortality rates. Formerly, we reported association of soluble receptor for advanced glycation end products (s-RAGE) and S100A12 (EN-RAGE) with mortality in end-stage renal disease (ESRD) patients. This study was to examine whether those biomarkers could be proposed for predicting cardiovascular morbidity and mortality in these subjects.

**Methods:** This is a prospective observational cohort study in 199 HD patients from extended analyses of our previous study. Serum S-RAGE, S100A12, comorbiddity, and other traditional risk factors were also investigated. The cumulative incidences for death using Cox proportional-hazards regression were evaluated in multivariable analyses. A mean observation period was 29 months.

**Results:** The patients were 57±14.3 years of age, 54.3% were male, 49.2% were diabetic, and 36.2% had a history of cardiovascular disease. During the observation period, 27 patients (13.6%) were died. Univariate analysis demonstrated that S100A12 was correlated with diabetes (P=0.04) and hs-CRP (P=0.01). In multivariable analyses, serum s-RAGE (HR [hazard ratio], 1.16; 95% CI [confidence interval], 0.61-2.19; P=0.65) and S100A12 (HR 1.05; 95% CI, 0.62-1.77; P=0.87) were not associated with mortality in hemodialysis patients, though traditional predictors for mortality including age, history of cardiovascular diseases, serum albumin and serum high-sensitivity C reactive protein (hs-CRP) were related to mortality. Powerful predictors for mortality were age, previous cardiovascular disease and serum albumin level.

**Conclusions:** Serum S-RAGE and S100A12 may be weak surrogate markers to predict all-cause mortality in patients receiving hemodialysis, even though S100A12 was partly related with diabetes and inflammation.
Impact of Sodium-Dependent Phosphate Co-Transport, Pit-1, in Peripheral Blood Mononuclear Cells on Cardiac Calcification in Maintenance Hemodialysis Patients: Minwen Ding, Mengjing Wang, Minmin Zhang, Jing Chen, Huashan Hospital, Fudan Univ.

Background: Vascular calcification (VC) is an important risk factor for cardiovascular disease in MHD patients, however, the mechanisms of which are still under investigation. The aims of this study were to explore the risk factors of VC in MHD patients, and to identify the expression of sodium-dependent phosphate co-transporter (Npt) in peripheral blood mononuclear cells (PBMCs) and assess its association with cardiac calcification and its possible impact factors.

Methods: This was a cross-sectional analysis of adult MHD patients who received at least 6-month regular MHD in our dialysis center. The coronary artery calcification (CAC) was measured by cardiac MSCT. The gene expression of Npt in PBMCs was measured by Real-time PCR and we tested serum TNF-α and IL-6 by ELISA. Multivariate logistic analysis was used to determine the risk factors of CAC. Correlation between the gene expression of Npt and other parameters was examined by Pearson's correlation analysis.

Results: 1,681 eligible patients were enrolled. 2. Three kinds of Npts were detected in PBMCs of MHD patients. They were type I Npt, Npt2b, type III Npt, Pit-1 and Pit-2, among which Pit-1 mRNA expression was significantly associated with extent of CAC. 3. The results of the logistic regression analysis were listed in Table 1. 4. Pearson's correlation analysis showed Pit-1 mRNA expression of PBMCs was significantly correlated with serum phosphorus (r=0.43, P<0.002), CAC score (r=0.63, P<0.001) and Pit-2 mRNA expression of PBMCs (r=0.53, P<0.001).

Table 1. Multiple logistic regression analysis of factors associated with CAC score tertile in MHD patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.36</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.63</td>
<td>0.062</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic vintage (y)</td>
<td>1.02</td>
<td>0.007</td>
<td>1.03 (1.01-1.05)</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.28</td>
<td>0.074</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.56</td>
<td>0.004</td>
<td>7.14 (0.03-0.75)</td>
<td>0.021</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/l)</td>
<td>0.91</td>
<td>0.080</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF (pg/ml)</td>
<td>1.20</td>
<td>0.019</td>
<td>1.29 (1.01-1.66)</td>
<td>0.044</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.06</td>
<td>0.030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.48</td>
<td>0.038</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBMC Pit-1 mRNA (mqm)</td>
<td>1.79</td>
<td>0.055</td>
<td>2.52 (1.05-5.83)</td>
<td>0.02</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>0.35</td>
<td>0.075</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>0.41</td>
<td>0.099</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Our result showed that longer dialysis vintage, diabetes, higher concentration of serum TNF-α and Pit-1 mRNA expression of PBMCs are the risk factors of CAC in MHD patients. Pit-1 mRNA expression of PBMCs was significantly correlated with serum phosphorus, CAC score and Pit-2 mRNA expression of PBMCs.

Funding: Government Support - Non-U.S.

TH-PO898

HDL Subfractions in End-Stage Renal Disease (ESRD) Patients: Anna Gliba-Brozeka, Beata Franzczyk-Skora, Jacke Ryta, Dept of Nephrology, Hypertension and Family Medicine, Medical Univ of Lodz, Poland.

Background: Chronic kidney disease is a common disease associated with high cardiovascular risk. Recent studies have suggested that HDL not LDL may play the more important role in the progression of atherosclerosis in CKD patients. HDL from CKD patients was shown to become dysfunctional, lose its vasoprotective properties and begin to promote endothelial dysfunction and inflammation.

Methods: The aim of this study was to investigate the subfractions of HDL in ESRD patients, which is the first study investigating this phenomenon in dialysis patients. To our knowledge, this study included 50 ESRD patients (16 women, 34 men) on dialysis (WAM University Hospital, Lodz, Poland) and 20 healthy volunteers (14 women, 6 men). Blood samples were collected from all subjects and HDL subfractions were analyzed with the use of Lipoprint system. Moreover, all patients had IMT measured.

Results: This study revealed statistically significant differences in HDL subfractions between control and study group: HDL1 [5.6 (2.0-7.1) vs. 13.0 (8.2-15.8), P<0.0001], HDL2 [13.1 (3.5-14.9) vs. 15.2 (2.1-40.0), P=0.006], HDL3 [5.5 (0.8-8.6) vs. 9.4 (7.8-11.3), P<0.0001], HDL4 [8.5 (0.10-4.0) vs. 10.6 (9.5-12.0), P=0.003], HDL5 [9.2 (3.3-10.5) vs. 11.4 (9.9-12.1), P=0.01], HDL7 [7.6 (7.2-8.4) vs. 5.3 (4.2-7.2), P<0.0001], HDL8 [8.7 (8.0-9.5) vs. 4.8 (3.5-5.8), P<0.0001], HDL9 [7.0 (5.9-8.2) vs. 3.8 (3.0-4.8), P<0.0001], HDL10 [7.0 (6.2-8.7) vs. 4.3 (2.6-7.1), P=0.001] and large HDL [26.5 (17.5-29.2) vs. 40.3 (33.0-47.0), P<0.0001] and HDL Small [30.8 (22.3-43.2) vs. 12.8 (9.4-17.9), P<0.0001]. Significant differences were also observed in HDL7 [9.3 (6.6-12.9) vs. 13.4 (8.7-16.9), P=0.014], HDL6 [20.2 (18.0-23.2) vs. 17.6 (15.2-20.1), P=0.020], HDL Large [35.0 (23.7-56.8) vs. 41.4 (33.6-48.0), P=0.007] and HDL Medium [35.0 (22.2-51.7) vs. 45.8 (40.9-49.1), P=0.017] between HD patients with INT > 0.9 mm and < 0.9 mm.

Conclusions: This study revealed that ESRD influences HDL subfractions. Subfractions of large HDL are more abundant in patients with ESRD while small HDL fraction is more frequent in healthy persons. It is possible that the shift in HDL subfractions may be responsible for the increased risk of atherosclerosis in CKD patients.

TH-PO897

High Non-HDL Cholesterol as an Independent Risk Factor for Coronary Restenosis in Hemodialysis Patients Undergoing Percutaneous Coronary Interventions: Shoko Hasegawa, Toshiaki Nakano, Yasushi Mukai, Yuta Matsukuma, Ryusuke Yotsueda, Akiohiro Fujimoto, Kichiro Fujisaki, Kazuhiko Tsuruya, Takamaki Kitanazato, Department of Medicine and Clinical Science, Kyushu Univ Graduate School of Medical Sciences, Fukuoka, Japan; Dept of Cardiovascular Medicine, Kyushu Univ Graduate School of Medical Sciences, Fukuoka, Japan; Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ Graduate School of Medical Sciences, Fukuoka, Japan.

Background: It has been reported that patients with end-stage kidney disease (ESKD) have a higher risk of restenosis after percutaneous coronary intervention (PCI). The aim of this study was to investigate the risk factors of restenosis after PCI in hemodialysis (HD) patients.

Methods: From January 2007 to December 2014, we enrolled 54 consecutive ESKD patients undergoing HD (mean age: 66.5 +/- 10.1 years; 15 women, 39 men; mean HD duration: 3.7 years), who received PCI and follow-up coronary angiography (CAG) after about 6 months. The coronary restenosis was defined by the patient having target lesion revascularization on follow-up CAG.

Results: Of 54 patients who had received PCI, restenosis occurred in 22 patients (40.7%) within 5-12 months after PCI. In the univariable logistic analysis, serum levels of low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, serum levels of non-high-density lipoprotein cholesterol (non-HDL-C), and history of major adverse cardiovascular events (MACE) were significantly associated with the occurrence of coronary restenosis; odds ratio (OR) [95% confidence interval (CI)] was 1.89 [1.02-3.50], 8.7 [4.8-16.9], and 5.0 [2.9-8.7], respectively. In the multivariable logistic analysis, non-HDL-C and the history of MACE were significantly associated with the coronary restenosis; OR [95% CI] was 1.35 [1.08-1.69]/per 10 mg/dl increase in non-HDL-C) and 8.55 [1.38-8.85], respectively.

Conclusions: Non-HDL-C was an independent risk factor for the occurrence of coronary restenosis in HD patients undergoing PCI. This result suggests the significance and necessity of strict management of lipid metabolism after PCI in even HD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Galectin-3 Does Not Correlate within Markers of Cardiac Structure and Function on Cardiac MRI: A Study in Haemodialysis Patients


Estrella.

Galectin-3 does not have a role in risk stratification of this patient group. Our results suggest that LVMI (r=-0.22 p=0.24), LVEF (r=0.08 p=0.65) or LVEDV (r=0.012 p=0.94). The previously diastolic volume 143.4ml was only associated with unintentional weight loss (OR=0.93; 95%CI: 0.88-0.98). FGF23 was only associated with self-reported exhaustion (OR=0.54, 95%CI: 0.30-0.95) while higher sKlotho was associated with lower odds of frailty (Table).

Methods: We conducted a cross-sectional study of incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Events (PACE) Study. Multivariable logistic regression models were used to estimate the association of S-Klotho and FGF23 with odds of frailty and frailty subcomponents.

Results: Of 336 individuals, 71% were black; 59% were male. Mean age was 55y. All had hypertension and 56% had diabetes, 38% CAD, and 37% obesity. Median sKlotho level was 364.4 pg/ml (IQR 272.5-494.6); mean FGF23 level was 656.2 U/ml (SD: 498). 40% of participants were frail. Adjusting for demographic factors, obesity, Charlson Comorbidity Index, hsCRP, serum albumin and Kt/V, higher sKlotho was associated with lower odds of frailty (Table). FGF23 did not predict arterial stiffness in dialysis-dependent CKD patients.

Conclusions: In this prospective cohort study, FGF23 did not predict arterial stiffness beyond known risk factors of age, mean arterial pressure, heart rate and the presence of diabetes. Our findings suggest that the excess cardiovascular mortality observed with elevated FGF23 in CKD is not primarily driven by effects on arterial stiffening.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

Funding: NIDDK Support

TH-PO999

FGF23 Is Not Associated with Arterial Stiffness in Patients with CKDSD

Kenneth J. Lim, Stephen M. Ting, Daniel Zehnder, Thomas F. Hiemstra, Stephen M.S. Ting, Tessa Kimberly Novick, Lucy A. Mecon, Stephen M. Sozio, Bernard G. Jaar, Larisa Tereschenko, Rulan S. Parekh, Michelle M. Estrella, Albert Einstein College of Medicine; Univ of Toronto; Johns Hopkins Univ; Univ of Oregon.

Background: Arterial stiffening is thought to be a key determinant of excess cardiovascular mortality in CKD patients. In CKD, the bone-derived phosphatonin fibroblast growth factor (FGF) 23 is elevated and has been implicated in the development of Cardiovascular disease. In this study, we sought to determine whether FGF23 is a predictor of arterial stiffness in dialysis-dependent CKD patients.

Methods: In this cross-sectional study, we enrolled 352 patients with advanced CKD and 150 healthy controls. Pulse wave velocity (PWV) was recorded by application tonometry, and blood pressure and biochemical parameters including plasma intact-FGF23 concentrations determined.

Results: Patients with CKD were significantly younger than controls (46±14 versus 49±11 years, p=0.02), had a higher blood pressure (MAP 97±14 vs 94±10 mmHg, p=0.003), and were more likely to be male (61% versus 49%, p=0.008). CKD patients had significantly higher FGF23 (605 pg/ml, IQR 112-1772 vs 40 pg/ml, IQR 33-49, p<0.001) and parathyroid hormone (25 pmol/L, IQR 13-56 versus 3.8 pmol/L, IQR 3.5-5.0 pmol/L, p<0.001). PWV was elevated in patients with CKD (8 ms/msec, IQR 6.9-9.6 vs 7.3 msec/m, IQR 6.6-8.4, p<0.0002). In a regression model adjusted for known predictors of PWV, FGF23 did not predict PWV (p=0.15, p=0.063), but was positively associated with the presence of CKD (p=0.009), age (p=0.001), mean arterial pressure (p=0.001) and heart rate (p=0.001).

Conclusions: In this prospective cohort study, FGF23 did not predict arterial stiffening beyond known risk factors of age, mean arterial pressure, heart rate and the presence of diabetes. Our findings suggest that the excess cardiovascular mortality observed with elevated FGF23 in CKD is not primarily driven by effects on arterial stiffening.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

Funding: NIDDK Support

TH-PO900

Association of Klotho and FGF23 with Frailty in Patients Initiating Hemodialysis

Sahar T. Aghoghodaro, Lucy A. Mecon, Rulan S. Parekh, Michelle M. Estrella, Johns Hopkins; Univ of Toronto; Univ of Oregon.

Background: Frailty at dialysis initiation is associated with higher mortality. Both FGF23 and its co-receptor, klotho, have been implicated in the development of frailty. We aimed to evaluate the independent association of FGF23 and soluble klotho (sKlotho) with frailty in hemodialysis (HD) patients.

Methods: We conducted a cross-sectional study of incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Events in ESRD (PACE) Study. Frailty was defined by 3 of the following: unintentional weight loss >10 lbs in prior year, self-reported exhaustion, weakness (by hand grip strength), slowness (by walking distance) and self-reported low physical activity. Logistic regression was used to examine the associations of sKlotho and FGF23 with odds of frailty and frailty subcomponents.

Results: Of 336 participants, 71% were black; 59% were male. Mean age was 55y. All had hypertension and 56% had diabetes, 38% CAD, and 37% obesity. Median sKlotho level was 364.4 pg/ml (IQR 272.5-494.6); mean FGF23 level was 656.2 U/ml (SD: 498). 40% of participants were frail. Adjusting for demographic factors, obesity, Charlson Comorbidity Index, hsCRP, serum albumin and Kt/V, higher sKlotho was associated with lower odds of frailty (Table). Of S-Klotho and FGF23 with odds of frailty.

Table: Association of FGF23 and sKlotho with LVH

<table>
<thead>
<tr>
<th>Model</th>
<th>sKlotho, per 1 log pg/mL higher</th>
<th>FGF23, per 100 rU/mL higher</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF23, per 100 rU/mL higher*</td>
<td>1.03</td>
<td>0.98 – 1.10</td>
<td>0.20</td>
<td></td>
<td></td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sKlotho, per 1 log pg/mL higher*</td>
<td>0.51</td>
<td>0.27 – 0.95</td>
<td>0.03</td>
<td></td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, race, BMI, systolic BP, serum albumin and Kt/V.

Conclusions: sKlotho, not FGF23, is associated with a lower odds of LVH among incident hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

Funding: NIDDK Support

TH-PO902

Differential Association of Fibroblast Growth Factor-23 and Soluble Klotho with Left Ventricular Hypertrophy

Tanya S. Johns, Esther D. Kim, Tessa Kimberly Novick, Lucy A. Mecon, Stephen M. Sozio, Bernard G. Jaar, Larisa Tereschenko, Rulan S. Parekh, Michelle M. Estrella, Albert Einstein College of Medicine; Univ of Toronto; Johns Hopkins Univ; Univ of Oregon.

Background: Fibroblast growth factor-23 (FGF23), a phosphaturic hormone, has been implicated in the pathogenesis of left ventricular hypertrophy (LVH) among patients with chronic kidney disease. Whether FGF23’s co-receptor, klotho, is independently associated with LVH is unclear.

Methods: To determine whether soluble klotho (sKlotho) is independently associated with LVH among incident hemodialysis patients, we conducted a cross-sectional study among participants who underwent baseline 2D echocardiograms in the Predictors of Arrhythmia and Cardiovascular Events (PACE) Study. Multivariable logistic regression models with FGF23, sKlotho, and both as primary predictors were constructed to estimate the odds of LVH (defined as LV mass index >116 g/m² in men and >104 g/m² in women).

Results: Of 391 participants who underwent echocardiogram, 371 and 387 had sKlotho and FGF23 levels available, respectively; 72% had LVH. Mean age was 54 years and 72% were black. All participants had hypertension with mean systolic BP 154 mm Hg. Median volume removed per HD session was 2.6L. (IQR: 1.6 – 3.7). FGF23 was not associated with LVH after adjusting for age, race, gender, BMI, systolic BP, serum albumin level, and ultrafiltration volume. In contrast, higher sKlotho was independently associated with lower odds of LVH (OR=0.51 per 1 log higher; 95% CI=0.28-0.96); this association remained robust with additional adjustment for FGF23 and Charlson Co-Morbidity Index.

Conclusions: sKlotho, not FGF23, is associated with a lower odds of LVH among incident hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

Funding: NIDDK Support
TH-PO903
Predictors of Arterial Stiffness in Incident Hemodialysis Patients
Stephanie M. Toth-Manikowski,1 Esther D. Kim,2 Lucy A. Meoni,3 Bernard G. Jaar,4 Tariq Shafi,1 Michelle M. Estrella,1 Rulan S. Parekh,4,7 Stephen M. Sozio,5 1Johns Hopkins Univ; 2Univ of Toronto.

Background: Premature vascular aging and arterial stiffening characterize CKD progression to ESRD and are associated with increased cardiovascular (CVD) morbidity and mortality. We identified predictors of arterial stiffness over time in HD patients.

Methods: In 339 incident HD patients in the Predictors of Arthrythmic and Cardiovascular Risk in ESRD (PACE) study, we examined the associations of baseline age, sex, race, comorbidities, CVD medications, and dialysis characteristics with longitudinal vascular stiffness measured by carotid-femoral pulse wave velocity (PWV) using generalized estimating equations. Annual change in PWV for up to 3 years was analyzed using linear regression.

Results: Mean age was 54, 58% male, 74% African-American, mean (SD) baseline PWV 10.7 (3.4) m/s, and annual PWV change 0.2 (2.6) m/s. Several factors were associated with higher PWV in univariate and multivariate longitudinal models. None were associated with PWV change.

| Table: TH-PO903 Predictors of Arterial Stiffness in Incident Hemodialysis Patients |
|--------------------------|--------------------------|
| Demographics             |                          |
| Age (10y)                 | 1.03 (0.81-1.24)         |
| Female                   | -0.35 (-1.03-0.32)       |
| African-American         | -0.62 (-1.39-0.14)       |
| Comorbidities            |                          |
| Diabetes                 | 2.62 (2.00-3.24)         |
| Coronary Disease         | 0.87 (0.71-1.56)         |
| Congestive Heart Failure  | 0.93 (0.26-1.60)         |
| LV Mass Index            | -0.03 (-1.03-0.04)       |
| Tobacco Use              | -0.51 (-1.18-0.17)       |
| Medications              |                          |
| Renin-Angiotensin Inhibitor | -0.01 (-0.70-0.67)     |
| Beta Blocker             | 0.83 (0.16-1.51)         |
| Clinical Characteristics  |                          |
| Pulse Pressure (10mmHg)  | 1.12 (0.88-1.37)         |
| Phosphorus (mg/dL)       | -0.24 (-0.57-0.10)       |
| iPTh (mg/dL)             | -0.01 (-0.02-0.00)       |
| Albumin (mg/dL)          | -0.38 (-1.11-0.34)       |

P-values: <0.001, <0.01, <0.05, <0.1, ns = not significant

Conclusions: Although PWV did not change significantly over time in incident HD patients, age, male sex, diabetes, and pulse pressure were independently associated with higher PWV. It may be difficult to modify PWV after HD initiation and clinical factors should be optimized prior to starting HD.

TH-PO904
Differences in Risk Factors for Coronary Artery Calcification Between Non-diabetic and Diabetic Hemodialysis Patients
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Background: The differences in risk factors for coronary artery calcification between nondiabetic and diabetic hemodialysis (HD) patients have not been fully explored.

Methods: We examined Agatston coronary artery calcium score (CACS) using MDCT, age, sex, presence of diabetes, dialysis vintage, smoking history, administration of phosphorus binders, geriatric nutritional risk index (GNRI), HbA1c, serum calcium, phosphate, iPTh, CRP, B2MG, LDL-cholesterol and triglyceride (TG) in 355 HD patients: 242 nondiabetics and 113 diabetics. Factors related to CACS were assessed by multivariate regression analysis using all of the above independent variables. Differences in the above parameters according to quartile (Q) of CACS were also assessed.

Results: Mean age (years), dialysis vintage (months), CACS (H) and serum phosphate (mg/dL) were 63.14 vs. 66.1 ± 12 (ns), 125.1 ± 100 vs. 133.5 ± 50 months (P<0.01), 1651 ± 2177 vs. 2177 ± 2533 (P<0.05), and 5.3 ± 1.3 vs. 5.0 ± 1.4 mg/dL in nondiabetics and diabetics, respectively. Patients with CACS Q4 showed higher prevalence of diabetes (40 vs. 19%), age (68.12 vs. 58.14 years), and CRP (0.7 ± 1.3 vs. 0.2 ± 0.4 mg/dl), but lower iPTh (1461 ± 133 vs. 193 ± 131 mg/dL) levels than patients with CACS Q1 (P<0.05), and other parameters were not significantly different except HbA1c. Significant associations were observed between CACS and age (P<0.001, β: 0.21), female (P<0.001, β: -0.21), dialysis vintage (P<0.001, β: 0.31), CRP (P<0.05, β: 0.16), TG (P<0.05, β: 0.13) in nondiabetics. However, CACS was significantly associated only with age (P<0.05, β: 0.30) and HbA1c (P<0.05, β: 0.26) in diabetics.

Conclusions: Risk factors for coronary artery calcification differ between nondiabetic and diabetic HD patients, and poor glycemic control is the major factor in the latter.

TH-PO905
Hemodialysis and Hemodilatation Improve Serum Calcium Propensity
Marijke J.E. Dekker,1 Andreas Pasch,2 Frank van der Sande,1 Constantijn Konings,2 Matthias Bachtl,1 Mauro Dionisi,3 Jeroen Kooman,1 Bernard J. Cauana,4 1Maastricht Univ Medical Center; 2Catharina Hospital Eindhoven; 3Univ Hospital Bern; 4Calcisco AG; 5Fresenius Medical Care.

Background: Calciprotein particles (CPPs) may play an important role in the calcification process. The calcification propensity of serum (Tc) is highly predictive of all-cause mortality in chronic kidney disease patients. Whether Tc is therapeutically improvable, by hemodialysis (HD) or even further by hemodilatation (HD), has not been studied yet.

Methods: We designed a cross-sectional single center study, and included prevalent patients on HD or HDF. Patients were divided into two groups based on dialysis modality. We included patients on a thrice-weekly schedule, with a dialysis vintage of >3 months and vascular access providing a blood flow rate of >300 ml/min. Calcium propensitity of serum was measured by the time of transformation from primary to secondary CPP (Tc, min), by time-resolved nephelometry.

Results: In total 64 patients were included and, Tc was measured in 376 pre- and post-dialysis samples of all-in-center dialysis sessions during one week. Tc levels improved in both the HD and HDF group with pre- and post-dialysis (mean (SD)) of 244±6(301±57) and 253±55(304±61) min respectively (P=0.43). The mean improvement of Tc was 26.29% in the HD group and 21.97% in the HDF group (P=0.61). The delta values (A) of calcium, phosphate (P) and albumin were equal in both groups. The DTA was mostly influenced by DP (P=0.280; P=0.01 HD and r=0.259; P=0.02 HDF).

Conclusions: HD and HDF patients present with same baseline vascular calcification risk values pre-dialysis. Calcification propensity is significantly improved during both HD and HDF. Tc should be a useful guide to optimize renal replacement strategy to improve the individual calcification risk in dialysis patients.

Funding: Pharmaceutical Company Support - Unrestricted Grand from Fresenius Medical Care

TH-PO906
Association of Circulating Biomarkers with Vascular Stiffness and Coronary Artery Calcium in Incident Hemodialysis
Esther D. Kim,1 Stephen M. Sozio,2 Bernard G. Jaar,3 Lucy A. Meoni,2 Michelle M. Estrella,1 Rulan S. Parekh.1 1Univ of Toronto, Canada; 2Johns Hopkins Univ.

Background: Vascular calcification and stiffness are associated with higher mortality in hemodialysis. Studies examining the role of circulating biomarkers – specifically, FGF23, desphospho-uncarboxylated matrix GlA protein (dpuGMPI, Fetuin A, osteoprotegerin (OPG), and C-reactive protein (CRP) – in vascular calcification have reported contradictory findings, and the independent association of the biomarkers remains inconclusive.

Methods: In 392 incident hemodialysis patients in the Predictors of Arrhythmic and Cardiovascular Risk End Stage Renal Disease (PACE) study, we examined the associations of baseline FGF23, dpupGMPI, Fetuin A, OPG, and CRP with total coronary calcium score (Agatston) at baseline and vascular stiffness (pulse wave velocity [PWV]) at baseline and over 4 study visits. Baseline associations were determined using linear regression and repeated measures over visits were examined using mixed-effects models.

Results: At baseline, higher OPG was associated with increased odds of having a high coronary calcium score (>257), independent of other biomarkers (OR=1.11, 95%CI: 1.06,
1.6). The remaining biomarkers were not associated with high coronary calcium. Higher OPG was associated with higher PWV, and higher FGF23 was associated with lower PWV after adjusting for demographic factors, body mass index, comorbidity index, calcium phosphorus product, systolic blood pressure, and albumin.

<table>
<thead>
<tr>
<th>Adjusted association with PWV</th>
<th>β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG (1 pmol/l)</td>
<td>0.10 (0.02, 0.19)∗</td>
</tr>
<tr>
<td>FGF23 (100 RU/ml)</td>
<td>-0.10 (-0.18, -0.02)†</td>
</tr>
<tr>
<td>dpmuMGP (1-log pm)</td>
<td>0.07 (-0.38, 0.53)</td>
</tr>
<tr>
<td>Fetuin A (1 g/l)</td>
<td>-0.79 (-2.77, 1.19)</td>
</tr>
<tr>
<td>CRP (1-log μg/ml)</td>
<td>0.02 (-0.27, 0.30)</td>
</tr>
</tbody>
</table>

∗P<0.05 †Adjusted for all biomarkers

OPG and FGF23 remained associated with PWV over follow-up and after additionally adjusting for all biomarkers (β=0.08, 95% CI: 0.01, 0.15 and β=−0.07, 95% CI: -0.13, -0.01).

Conclusions: Several vascular and phosphate biomarkers are associated with vascular calcification at baseline and/or stiffness longitudinally in incident dialysis patients. Further studies assessing interventions on these biomarkers are warranted.

Funding: NIDDK Support

TH-P0097

Association of Arterial Stiffness with Cognitive Impairment in Incident Hemodialysis Patients

Methods: This study included 390 incident hemodialysis patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study. Arterial stiffness was measured using aortic pulse wave velocity (PWV) and augmentation index (Aix). Cognitive function was measured using time to complete Trail Making tests A and B (TMT A and TMT B) and the modified mini-mental state exam (3MS) score. Log-linear, Tobit, and logistic regression models were used to examine the baseline association of PWV with TMT A, TMT B, and 3MS, respectively. Changes in the scores over visits and mixed-effect models were used to examine association over time at 1 year follow-up.

Results: A baseline, higher PWV was associated with longer time to complete TMT A after adjusting for demographic factors, reading comprehension score, comorbidity index, systolic blood pressure, and atrial fibrillation (%TMT A=−3.12, 95% CI: 0.37−5.87). In the repeated measures analysis, higher PWV was still associated with longer TMT A time (%TMT A=2.05, 95% CI: 0.00−4.11), and higher Aix was associated with longer TMT B time (β=0.80, 95% CI: 0.01−1.58).

Conclusions: Vascular stiffness was not associated with 3MS.

Funding: NIDDK Support

TH-P0098

Close Relationship Between Vascular Endothelial Function and Serum Uric Acid Level in Hemodialysis Patients

Methods: We enrolled 48 patients undergoing maintenance HD at Ueda Kidney Clinic in Japan. No patient had a history of CVD. Reactive hyperemia index (RHI) as evaluated by Endo-PAT (Tamar Medical, Ltd., Caesarea, Israel) was used to assess VEF, whereby a higher RHI was indicative of better function. We also assessed for correlations between the natural logarithm of RHI (LnRHI) and clinical parameters.

Results: The median age of our patients was 67 years, the male-to-female ratio was approximately 2:1, and median LnRHI was low at 0.36. Analysis of Spearman’s rank correlation coefficient revealed a significant positive correlation between serum uric acid level (sUA) and LnRHI (r=0.372, p=0.009). As sUA is influenced by diet and dietary intake, we also performed multivariable linear regression analysis adjusted by age, body mass index, diagnosis by KiV, and normalized protein catabolic rate, and observed that sUA was significantly related to LnRHI (β=0.042, 95% CI: 0.007−0.078, p=0.006, r²=0.221).

Conclusions: The current study suggests that VEF is closely associated with sUA in HD patients. Although the precise mechanism is unknown, a marked decrease in sUA might be correlated with VEF impairment and should be avoided in individuals undergoing HD.

TH-P0099

Ambulatory Arterial Stiffness Index: An Early Marker of Cardiovascular Disease in Young Hemodialysis Patients

Methods: Retrospective review of 24-hour ambulatory blood pressure monitoring (ABPM) was performed in 11 pediatric patients on chronic HD (16±3.6yrs) and dialysis vintage of 32±18 months. AASI was calculated as 1-regression slope of the diastolic over systolic BP. Echocardiogram and bilateral carotid artery ultrasounds were performed to assess left ventricular mass index(LVMi) and carotid intimal medial thickness (cIMT). Carotid artery stiffness indices included distensibility coefficient(DC), stiffness index-β (SI-β) and PP. These were compared with reference values for healthy pediatric controls.

Results: AASI was significantly increased in HD patients compared to controls (2.02±0.1 versus 20±0.2; p<0.01). When matched to controls with similar BP’s and PP’s, the AASI detected increased vascular stiffness independent of PP. cIMT,LVMi, and DC were also significantly increased in HD patients (p<0.01).

Conclusions: Young HD patients demonstrate early surrogate markers of CVD including increased LVMi, cIMT and decreased vascular compliance. Increased AASI detected vascular stiffness that was independent of BP’s and PP’s. AASI may be an early non-invasive marker of vascular disease in young HD patients that merits further investigation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Endovascular Renal Denervation Ameliorates Pathological Left Ventricular Dilatation in Dialysis Patients

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Background: Endovascular renal denervation (RDN) ameliorates left ventricular hypertrophy and improves contractile function in resistant hypertension. Its cardiac effects on a dialysis population are unknown. We hypothesised that RDN would improve blood pressure (BP) control and sympathetic overload, resulting in improved ventricular function.

Methods: Nine dialysis patients with uncontrolled office BP (>140/90mmHg despite two or more agents at maximal tolerated doses) were recruited into this feasibility study. Office and ambulatory BP monitoring (ABPM) were performed before baseline, one and three months post RDN, along with supine muscle sympathetic nerve activity (MSNA). Echocardiography was performed at baseline and three months. Bilateral RDN was undertaken with an EnLightH™ catheter.

Results:

Baseline 1 Month 3 Months P-value
Office Systolic BP (mmHg) 179±28 156±24 152±25 <0.05
Office Diastolic BP (mmHg) 90±17 76±13 82±12 0.137
Mean Systolic ABPM (mmHg) 173±19 173±23 166±24 0.544
Mean Diastolic ABPM (mmHg) 92±11 89±13 88±11 0.906
MSNA Burst Frequency (bursts/ min) 59±12 59±15 59±13 0.872
LVIDd (mm) 54±6 50±7 <0.05
LV EDV (ml) 168±43 150±42 0.391
LV ESV (ml) 102±41 80±29 0.397
LV EF (%) 41±14 47±11 0.801
LVD mass/BSA (g/m2) 97±16 91±19 0.490
Diastolic Dysfunction Grade 2.0±0.7 1.1±0.4 0.003

Similar to previous, office systolic BP reduced and the effect on ABPM was attenuated. MSNA did not change, a novel finding. Despite lack of change in MSNA, LVIDd reduced, with an improving trend in diastolic dysfunction, another novel finding. There was no correlation between change in office systolic BP and ventricular dilatation (R=0.255) or dysfunction (R=-0.034), suggesting BP-independent effects.

Conclusions: RDN in dialysis patients improves office systolic BP and leads to a BP-independent improvement in ventricular dilatation and probably dysfunction. Further controlled studies are warranted in this population.

Temporal Loss of Bone Mineral Density Is Associated with Cardiovascular Diseases in Japanese Patients Starting Renal Replacement Therapy

Sawako Kato, 1 Shoichi Manayama, 1 Bengt Lindholm, 2 Yukio Yuzawa, 2 Yoshinari Tsuruta, 1 Seiichi Matsuo. 1 Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 2 Baxter Novum & Renal Medicine Karolinska Inst, Stockholm, Sweden; 3 Nephrology, Fujita Health Univ School of Medicine, Toyoake, Japan; 4 Miyoi Clinic, Toyohashi, Japan.

Background: Atherosclerosis, vascular calcification and alterations of bone metabolism are common aging disorders, which may be biologically linked via bone-vascular interactions. However, clinical studies on associations of temporal bone loss with cardiovascular disease (CVD) in dialysis patients are limited.

Methods: Seventy-six incident Japanese dialysis patients (46 males, age 60 ± 10 years) were enrolled and followed for a median of 3.8 years (range 1-5.8 years). Bone mineral density (BMD) of the lumbar spine was measured by dual X-ray absorptiometry at baseline and after 1 year.

Results: Baseline BMD, median value 1.05 (0.67-1.56) g/cm², negatively correlated to albumin (r=−0.28, P=0.015) and iPTH (r=−0.14, P=0.0002). When dividing patients into two groups according to delta BMD (defined as baseline - 1 year), those with high delta BMD had an increased mortality risk (Log rank 6.36, P=0.012) and time from dialysis initiation to the first CVD event appeared, although not significant, shorter in patients with high delta BMD (Log rank 2.81, P=0.094). Patients with high delta BMD had a significantly increased relative risk (RR; Cox hazard model) of mortality (10.9, 95% CI; 1.34-250.6) even after adjustments for age, gender, diabetes and smoking, compared with those with low delta BMD. RR of the first CVD event was 5.52 (95% CI; 1.15-73.8) with adjustments for age and gender.

Conclusions: Progressive loss of BMD associated with an increasing risk of CVD and mortality. Whereas in end-stage renal disease patients, BMD may have limited value as a predictor of a fracture risk, temporal changes of BMD, potentially reflecting bone-vascular interactions, may be useful as a marker of a CVD risk.

Funding: Government Support - Non-U.S.

First in Man: Reduction of Inflammation with Medium Cut-Off (MCO) Membranes

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Background: High mortality in dialysis patients may be related to reduced clearance of cytokines with conventional dialysis membranes. Attempts to provide a better clearance with high cut-off membranes also leads to albumin loss. A new Medium-Cutoff membrane with better permeability for molecules up to 45 kDa but with limited permeability for albumin was tested clinically for the first time.

Methods: 50 patients were dialyzed with MCO and conventional high-flux (HF) membranes for four weeks following a randomized cross-over design. After the second phase, another 12-week-period was conducted to test for long-term effects. Serum samples were tested for inflammatory effects and cytokine concentrations. Support was granted by the German Federal Ministry of Education and Research (FKZ 13N11796-99).

Results: The primary end point mRNA content of TNF-α in leukocytes was reduced to a higher degree and significantly better after 4 weeks on MCO compared to HF (r=0.01). Interleukin-6 mRNA was markedly reduced with MCO (p<0.001). After a significant drop after four weeks of MCO dialysis, albumin concentrations stabilized after 12 weeks.

Funding: Pharmaceutical Company Support - Gambro, Government Support - Non-U.S.
Vitamin D and Cardiac Autonomic Tone in End-Stage Kidney Disease: A Blinded, Randomized Controlled Trial
Sofiga B. Ahmed,1 Michelle C. Mann,1 Brenda Hemmelgarn,1 David A. Hanley,1 Tanvir Chowdhury Turin,1 Jennifer M. MacRae,2 David C. Wheeler,3 Sharanya Ramesh,3 Darlene Y. Sola,3 Derek Exner,1 1Univ of Calgary, Canada; 2Univ College London, United Kingdom.

Background: Importance: End-stage kidney disease (ESKD) patients are at high cardiovascular (CV) risk. Vitamin D deficiency is associated with depressed heart rate variability (HRV), a risk factor for CV death. Both vitamin D deficiency and depressed HRV are highly prevalent in ESKD.

Methods: Objective: To determine the effects of activated vitamin D (conventional) compared to activated and nutritional vitamin D (intensive) on HRV (low to high frequency spectrum; LF:HF) in patients with ESKD on hemodialysis (HD). Design: 2x2 crossover, blinded, randomized controlled trial in outpatient HD units. Fifty-six patients were randomized 1:1 to begin either conventional (0.25mg alfacalcidol and placebo 3 times/week) or intensive vitamin D therapy (0.25mg alfacalcidol 3 times/week and 5000U1 Erythropoietin weekly for 6 weeks). Main Outcomes: HRV is a surrogate index of cardiac autonomic nerve function and independently predicts CV mortality. The primary outcome was the change in LF:HF from the 1st to 6th week HD session. Secondary endpoints included individual changes in LF and HF, parameters of mineral metabolism and renin angiotensin system (RAS) activity.

Results: There was no difference in LF:HF from baseline to 6 weeks for either vitamin D treatment (conventional p=0.9; intensive p=0.07). There were no significant changes in any other measure of HRV, mineral metabolism or RAS activity. On exploratory subgroup analysis, participants who remained vitamin D deficient (25-hydroxyvitamin D<50nmol/L) after treatment had a significant increase in LF:HF (conventional: n=13, p<0.001 vs. insufficient and sufficient groups; intensive: n=8, p=0.001 vs. sufficient group).

Conclusions: Six weeks of treatment with conventional or intensive vitamin D did not alter LF:HF in ESKD patients. However, improved LF:HF was observed in the vitamin D-deficient subgroup. This finding may translate into decreased CV risk and should be considered hypothesis-generating and deserving of further study. Trial Registration: ClinicalTrials.gov NCT01774812. Funding: Private Foundation Support

The Validity of Left Ventricular Mass as a Surrogate Endpoint for Mortality Outcomes in Chronic Kidney Disease
Sunil V. Badve,1,2 Suetoona Palmer,1 Giovanni F.M. Strippoli,1,2 Matthew A. Roberts,1 Neil Borkon,1 Ali Ansari,1 Alan Cass,2 Carmel M. Hawley,2 Swapnil Hiremath,1 Elaine M. Pascoe,1 Vlad Perkovic,1 Gillian A. Whalley,1 Jonathan C. Craig,1 David W. Johnson,1 1Univ of Queensland; 2Princess Alexander Hospital; 3Univ of Otago; 4Univ of Bari; 5Monash Univ; 6Univ of Western Australia; 7Menzies School of Health Research; 8Univ of Ottawa; 9The George Inst for Global Health; 10Univ Inst of Technology; 11Univ of Sydney.

Background: Left ventricular mass (LVM) is increasingly used as a surrogate endpoint in trials involving chronic kidney disease (CKD) patients, as intervention-induced reductions in LVM are associated with improved outcomes. However, the prognostic value of LVM change and relative risk of mortality were estimated using random-effects models. Correlations between LVM change and mortality endpoints were summarized across all trials involving a bivariate random-effects Bayesian model together with 95% credible intervals (CrI).

Methods: The aim of this systematic review was to determine the validity of LVM as a surrogate endpoint for all-cause and cardiovascular (CV) mortality in trials involving chronic kidney disease (CKD) patients, as intervention-induced reductions to early mitral annulus velocity (E) called E/e’ is a less volume dependent, non-invasive index to estimate left ventricular (LV) filling pressure. However, the prognostic value of E/e’ has not been evaluated sufficiently in patients with end-stage renal disease (ESRD).

Results: The patients who newly started maintenance dialysis therapy between 2009 and 2012, had survived for at least 3 months after dialysis initiation, and had E/e’ data, were analyzed. E/e’ was calculated by pulse and tissue Doppler echocardiography. Cardiovascular (CV) composite endpoint comprised hospitalization for heart failure (HF), acute coronary disease (ACD) requiring intervention, ventricular arrhythmia, cerebral infarction or hemorrhage, and CV death. The patients were followed up until 2013.

E/e’ Calculated by Tissue Doppler Echocardiography and Cardiovascular Outcome in Incident Dialysis Patients
Jongha Park,1 Jongmin Lee,1 Kyung sun Park,2 Sang Hyeon Son,3 Shin-Jae Kim,4 Jong soo Lee,1 Hyun Chul Chung,4 1Ulsan Univ Hospital, Ulsan, Republic of Korea; 2Dongkang Medical Center, Ulsan, Republic of Korea; 3BHS Han-Sea Hospital, Busan, Republic of Korea.

Background: The ratio of early diastolic peak mitral flow velocity (E) to early mitral annulus velocity (e’), called E/e’ is a less volume dependent, non-invasive index to estimate left ventricular (LV) filling pressure. However, the prognostic value of E/e’ has not been evaluated sufficiently in patients with end-stage renal disease (ESRD).

Methods: The patients who newly started maintenance dialysis therapy between 2009 and 2012, had survived for at least 3 months after dialysis initiation, and had E/e’ data, were analyzed. E/e’ was calculated by pulse and tissue Doppler echocardiography. Cardiovascular (CV) composite endpoint comprised hospitalization for heart failure (HF), acute coronary disease (ACD) requiring intervention, ventricular arrhythmia, cerebral infarction or hemorrhage, and CV death. The patients were followed up until 2013.

Results: A total of 206 patients were analyzed (mean age 55.0±13.7 years old, female 51.5%). Median follow-up duration was 29.2 months (range 3.1-61.3). Forty-two CV events occurred during follow-up (15 HF, 17 ACD, 1 cerebral infarction, and 9 CV deaths). Mean E/e’ was 13.6±5.4 (range 5.3-29). After adjusting age, sex, diabetes, mean arterial pressure, LV ejection fraction, hemoglobin, serum albumin, C-reactive protein and volume status, one unit increase in E/e’ ratio was associated with 7% increase in the risk of CV composite endpoint (hazard ratio 1.07, 95% confidence interval 1.02-1.13, p=0.09). Adjusted hazard ratio linearly increased above 15 of E/e’ in Cox regression with cubic splines.

Non-Invasive Left Ventricular End-Diastolic Pressure (LVEDP) Measurement in Hemodialysis Patients: A Pilot Study

Background: Optimal volume status in dialysis patients is difﬁcult to assess. The Valuaversal maneuver is recognized as an bedside marker of central volume overload. A novel handheld device that combines ﬁnger photoplethysmography with Valuaversal maneuver can reliably estimate LVEDP (normal: <12mmHg). (Stieler H. PMID: 22893989). The goal of our pilot study is to determine the role of this non-invasive LVEDP measurement in managing volume in hemodialysis patients.

Methods: The LVEDP-Guided Volume Management Study is being conducted at 2 dialysis units in Baltimore. Baseline data collected includes demographics, medical history, KDQOL-36, NYHA dyspnea scale, intra/post dialysis symptoms, predialysis metrics [LVEDP, bioimpedance, blood pressure (BP) and echocardiogram]. We assessed the cross-sectional association of predialysis LVEDP with dyspnea symptoms and intradialytic hypotension (IDH, deﬁned as ≥20mmHg drop in systolic BP × nursing interventions).

Results: In the first 28 participants (mean age 56 years, 71% male, 82% black, median (25%, 75% percentiles) for predialysis LVEDP was 14 mmHg (12, 19), interdialytic weight gain (IDWG) was 1.7 kg (0.9, 2.9) and systolic BP was 150 mmHg (133, 164). LVEDP was signiﬁcantly higher in patients with dyspnea vs. those without. (Mean, 19 y vs. 14.6; p<0.03). IDH occurred in 5 (18%) patients and all had LVEDP £14 mmHg (Table). The unadjusted odds ratio for IDH per SD decrease in LVEDP was 4.37 (p=0.08). There was no signiﬁcant association between IDH and predialysis systolic BP or IDWG.

Conclusions: Non-invasive LVEDP measurements can identify hemodialysis patients with volume overload associated with symptoms (high LVEDP) and patients at risk for IDH (low LVEDP). Our ongoing study may help conﬁrm these initial ﬁndings and deﬁne the role of this measurement for volume management in dialysis patients.

Table: Associations of IDH

<table>
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<th>No (n=23)</th>
<th>Yes (n=5)</th>
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<td>Pre Dialysis Factors</td>
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<td>Mean (SD)</td>
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<td>11.8 (2.8)</td>
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<tr>
<td>Systolic BP</td>
<td>153.8 (22.3)</td>
<td>135 (15.5)</td>
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<tr>
<td>Interdialytic weight gain</td>
<td>1.97 (1.5)</td>
<td>1.92 (0.8)</td>
</tr>
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</table>

Non-Invasive Left Ventricular End-Diastolic Pressure (LVEDP) Measurement in Hemodialysis Patients: A Pilot Study
TH-PO914

TH-PO915

TH-PO916

Conclusions: A higher E/e’ ratio, reflecting high LV ﬁlling pressure which is the main physiological ﬁnding of diastolic HF, may be associated with a higher CV risk in patients with ESRD.
TH-PO918

Background: Tallium-201 (201TI) washout rate of single photon emission computed tomography (SPECT) has been reported to correlate with coronary flow reserve which is an index of myocardial microcirculation and be useful to detect coronary artery disease and evaluate the severity. However, the evidence for its use in chronic kidney disease (CKD) has been lacking, and the association between 201TI washout rate and mortality is unknown. Therefore, a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of 201TI washout rate for mortality in CKD patients undergoing hemodialysis.

Methods: A total of 156 patients who had been started on maintenance hemodialysis undergoing pharmacologic stress thallium-201 SPECT within 1 year, 107 men and 49 women, with a median age of 67 years, were studied. The endpoint was defined as all-cause death. The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Results: During the mean follow-up period of 3.2 ± 2.4 years, 30 (19.2%) deaths occurred. The median (interquartile range) of 201TI washout rate was 45.1 (37.4 - 50.8)%. Cumulative survival rates at 5 years after starting dialysis, with 201TI washout rate levels above and below the median, were 76.7% and 63.8% (p = 0.992, log-rank test), respectively. Overall, the multivariate Cox regression analysis revealed that 201TI washout rate remained an independent predictor of death after adjusting by confounding variables (HR 0.95, 95% CI 0.90 to 0.99).

Conclusions: Among CKD patients undergoing hemodialysis, 201TI washout rate seems to be useful for predicting death.

TH-PO919
Research Cardiovascular Magnetic Resonance Imaging in Chronic Kidney Disease – Incidence, Significance and Implications of Unexpected Incidental Findings  Elaine Rutherford,1 Jonathan Weir,1 Rutherford Inst of Card Sci, Edinburgh, UK; 1Div of Cardiovascular & Diabetes Medicine, Univ of Dundee; 2Inst of Cardiovascular & Medical Sciences, Univ of Glasgow.

Background: Left ventricular (LV) mass on cardiac magnetic resonance imaging (CMR) is a common end point of clinical trials in nephrology. Incidental findings (IF) on research images have ethical & clinical implications. We retrospectively investigated the incidence of IF in research CMR & reviewed their impact on patient care.

Methods: 161 CKD patients underwent CMR for a 2002-2006 research study into transplant assessment. Images were used to assess LV mass & function. In our study a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of 201TI washout rate for mortality in CKD patients undergoing hemodialysis.

Results: During the mean follow-up period of 3.2 ± 2.4 years, 30 (19.2%) deaths occurred. The median (interquartile range) of 201TI washout rate was 45.1 (37.4 - 50.8)%. Cumulative survival rates at 5 years after starting dialysis, with 201TI washout rate levels above and below the median, were 76.7% and 63.8% (p = 0.992, log-rank test), respectively. Overall, the multivariate Cox regression analysis revealed that 201TI washout rate remained an independent predictor of death after adjusting by confounding variables (HR 0.95, 95% CI 0.90 to 0.99).

Conclusions: Among CKD patients undergoing hemodialysis, 201TI washout rate seems to be useful for predicting death.

TH-PO920
A Significance of Cardiothoracic Ratio for Mortality in Hemodialysis Patients: The Q-Cohort Study  Ryusuke Yotsuwa,1 Masahiro Erguchi,1 Shigeru Tanaka,2 Masatomo Taniguchi,1 Hideki N. Hirakata,1 Kazuhiko Tsuruya,1,2 Takanari Kitazono,1,2 Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 2Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; 3Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan.

Background: Cardiothoracic ratio (CTR) of chest X-ray is commonly used to determine the volume status in hemodialysis (HD) patients. Thus, the present study was conducted to evaluate the significance of CTR in terms of longitudinal prognosis of HD patients.

Methods: A total of 3,347 Japanese HD patients aged 18 years were followed for 4 years. Patients were divided into four groups according to quartiles of CTR levels by sex. Risk estimates were calculated by a Cox proportional hazards model, adjusting for potential confounders. We investigated stratified analysis by sex, age, etiology of end-stage kidney disease, history of major adverse cardiac events (MACE) and blood pressure for subanalysis.

Results: The median values (interquartile range) of CTR were 0.49 (0.46–0.53) in male and 0.52 (0.48–0.56) in female. During the follow-up period, 564 patients (16%) died from any causes and the 4 years survival rate decreased significantly with higher CTR levels (p for trend <0.001). Compared with the lowest CTR quartile, the multivariable–adjusted hazard ratios (HRs) for all-cause mortality were 0.89 (95% confidence intervals, 0.66–1.21), 1.41 (1.07–1.86), and 1.52 (1.17–2.00) in subjects with low–intermediate, high–intermediate and highest quartile, respectively. Furthermore, the combination of higher CTR levels and history of MACE or lower blood pressure before HD (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) synergistically increased the risk of all-cause mortality.

Conclusions: A higher CTR level is closely related to increased mortality in HD patients. This association is more remarkable in patients with history of MACE or lower blood pressure before HD.

TH-PO921
High Convection Volumes in Postdilution Online Hemodiafiltration (HDF) Are Feasible in the Vast Majority of ESKD Patients  Camiel LM de Roij van Zuijdewijn,1 Isabelle Chapdelaine,1 Men Jan Nub,1 Peter J. Blankenstijn,1 Constantijn Konings,2 Tonnis K. Kremer Hovinga,2 Neelke C. Van Der Weerd,3 Pieter M. Ter Wee,1 Muriel P. Grooteiman,1 1Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; 2Internal Medicine, Catharina Hospital, Eindhoven, Netherlands; 3Internal Medicine, Martini Hospital, Groningen, Netherlands; 4Nephrology, Academic Medical Center, Amsterdam, Netherlands.

Background: Available evidence suggests a survival benefit for patients treated with high volume postdilution HDF (hvHDF) when compared to HD. Since these studies are limited by an observational design, we investigated whether hvHDF (>2L/session) is feasible in the majority of patients (>75%).
Methods: A prospective, multicenter study was performed (NCT01877499). HD (F) patients (n = 178) were eligible if treated 3 times/week for 36 weeks. Non-participating eligible patients formed a reference group to examine the representativeness of the study group. Treatment-related determinants of the convection volume were optimized in a stepwise fashion (treatment time [TT] up to 4 hours, blood flow rate [BFR] up to 400 mL/min and filtration fraction [FF] up to 33%). At the end of this protocol (T0) and 4 (T4) and 8 (T8) weeks thereafter, the convection volume was determined.

Results: Baseline characteristics were comparable in participants (n = 86) and references (n = 58). At T0 and at T4, 79/86 (92%) and 68/79 (86%) patients achieved hvHDF (mean 26.3 ± 3.56 and 26.3 ± 3.36L/session, resp). Hereafter, 2 patients died and 1 was transplanted. 83 patients remained; 66 (80%) reached hvHDF (mean 25.9 ± 3.53L/session, fig 1). Study discontinuation (n = 9), TT <4h (n = 4) or BFR £300 mL/min (n = 4) caused a convection volume <22L/session.

Conclusions: hvHDF is feasible in the vast majority of ESKD patients. As TT remained virtually unaltered, these findings were mainly due to a higher BFR and FF.

Funding: Pharmaceutical Company Support- Fresenius Medical Care

TH-PO922

Physical Activity Among Patients with End-Stage Renal Disease: Use of the Exercise Vital Sign

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Background: Exercise has been shown to improve physical functioning among ESRD patients. However, ESRD patients report exceedingly low levels of physical activity (PA) with only 13-34% engaging in recommended levels of PA. Although ESRD is characterized by substantial barriers to PA, low PA puts patients at risk for serious complications and higher mortality. Within Kaiser Permanente (KP), patients are administered the Exercise Vital Sign (EVS) just prior to dialysis treatment. The purpose of this study was to describe PA levels in ESRD patients using the EVS and to examine patient and caregiver priorities for outcomes in hemodialysis (HD).

Methods: ESRD patients (³18y) were eligible if treated 3x/week for ≥6 weeks. Non-participating eligible patients formed a reference group to examine the representativeness of the study group. Treatment-related determinants of the convection volume were optimized in a stepwise fashion (treatment time [TT] up to 4 hours, blood flow rate [BFR] up to 400 mL/min and filtration fraction [FF] up to 33%). At the end of this protocol (T0) and 4 (T4) and 8 (T8) weeks thereafter, the convection volume was determined.

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Conclusions: hvHDF is feasible in the vast majority of ESKD patients. As TT remained virtually unaltered, these findings were mainly due to a higher BFR and FF.

Funding: Pharmaceutical Company Support- Fresenius Medical Care
Dialysis: Epidemiology, Outcomes, and Clinical Trials: Noncardiovascular - I

TH-PO925

Medicare Advantage (MA) Is Associated with Lower Rates of Mortality versus Medicare Fee-For-Service (MFFS) Among Incident End-Stage Renal Disease (ESRD) Patients

Steven M. Brunelli,1,2 Carey Colson,1 Scott Sibbel,1 Abigail Hunt,1 Allen R. Nissenson,2 Mahesh Krishnan.2

1DaVita Clinical Research, Minneapolis, MN; 2DaVita HealthCare Partners Inc, Denver, CO.

Background: Patients with ESRD have a high burden of comorbid illness and are complex to manage and may therefore benefit from programs like MA that facilitate care coordination. Currently, ESRD patients are barred from enrolling in MA after onset of ESRD; however, those already enrolled at the time of ESRD onset may remain enrolled.

Methods: Adult patients initiating hemodialysis (HD) or peritoneal dialysis (PD) between 01 Jan 2009 and 30 Jun 2011 who were enrolled with MA or MFFS as of ESRD onset were considered. MA patients were matched 1:1 to MFFS controls based on initial modality, access type, and propensity score (based on 26 demographic and clinical characteristics). Patients were followed from dialysis initiation until death, transplant, loss to follow up, change in benefits status, or end of study (31 Dec 2011). Mortality rates were compared using negative binomial models. Sensitivity analyses considering early and latent effects were performed using piecewise methods.

Results: Compared to MFFS, MA was associated with lower rates of mortality (64.3 vs 70.7 deaths/100 patient-years; incidence rate ratio, 0.91). Mortality effects were limited to MA patients and were attenuated after the first 24 months of dialysis.

Conclusions: Enrollment in MA was associated with substantially lower rates of mortality during 2009-2011.

TH-PO926

Characteristics of Patients Receiving Dialysis at a Comprehensive Cancer Center and Outcomes

Ala Abudayyah,1 Jai prakash babu Thippai Jadegondanahalli,2 Rima N. Pai,1 Maria del Pilar Fernandez,2 Alvin H. Moss.3

1Section of Nephrology, UT MD Anderson Cancer Center; 2Nephrology and Hypertension, UT at Houston Medical School; 3Section of Nephrology, West Virginia Univ School of Medicine.

Background: With the increasing therapeutic options from the traditional cytotoxic therapies, small molecules for targeted therapies and more recently immunotherapies, cancer patients have been given a massive arsenal to tackle their cancer. With the associated renal toxicities from the chemotherapies, sepsis, infections, antibiotics, and obstruction we are often faced with decisions about the utility of dialysis. This is often the situation in the patients with advanced solid tumors that have failed multiple lines of treatment and are admitted with renal failure necessitating hemodialysis. Our hypothesis for this study is offering dialysis to advanced solid tumor patients will not improve overall survival and is not cost effective.

Methods: All patients diagnosed with Acute Kidney Injury in their last hospital admission with solid tumor and nephrology consult between 01/01/2005 through 12/31/2014 were identified using billing data. Patient demographic data for those records was extracted: date of birth, gender, race, financial class, vital status and last contact date. Our final study cohort is a total of 2,268 unique patient records.

Results: Out of 2,268 patients, 392 patients (17.28%) received dialysis and 1876 patients (82.72%) did not. A total of 1470 patients (64.81%) were discharged alive and 798 patients (35.19%) resulted in a hospital death. The hospital deaths included 269 patients (33.71%) that received dialysis and 529 patients (66.29%) that did not receive dialysis in the hospital.

Conclusions: Our preliminary data indicates that patients who survived their last hospitalization were less likely to have undergone dialysis (8.36%) when compared to patients that died during their last hospitalization (33.71%) dialyzed. Therefore, reaffirming that dialysis in advanced cancer patients would not likely add further benefit to their mortality.

TH-PO927

Emergency Room Utilization by Dialysis Patients: A Population Based Study

Claudio Rigatto,1,2 James M. Zacharias,1,2 Bing Hu,1 Brett M. Hiebert,1 Navdeep Tangri,1,2 Paul Komenda.1,2 1Internal Medicine, Univ of Manitoba, Winnipeg, MB, Canada; 2Renal Health/Dialysis, Seven Oaks General Hospital, Winnipeg, MB, Canada; 2Renal Health/Dialysis, Winnipeg Health Sciences Centre, Winnipeg, MB, Canada; 3Manitoba Renal Program, Winnipeg Regional Health Authority, Winnipeg, MB, Canada.

Background: Patients with kidney failure are frail and have high rates of cardiovascular and infectious comorbidities. As a result, they are heavy users of non-dialysis acute health services such as the emergency department (ED). Despite this, accurate population based data on rates and patterns of ED visits by dialysis patients are lacking. The objective of the current study was to determine rates and patterns of ED utilization by adult dialysis patients vs. the adult general population.

Methods: We linked two large regional databases in Winnipeg, Manitoba, Canada (population 1.3 million), the Manitoba Renal Program Patient Registry and the Winnipeg Regional Emergency Program Admission Discharge Triage database. Data were analyzed for the years 2000-2010. Poisson Regression was used to compare rates.

Results: Over the study period, the linked dataset comprised >2.0 million visits in 1.2 million non-dialysis patients, and 17,738 visits in 3260 dialysis patients. Our key findings were 1) Age and Sex adjusted rates of ER visits were 8.5X higher among dialysis patients (153 vs 18 visits per 100 patient-years, p<0.001), with negligible variation year to year over the study period; 2) Rate of ER visits were 25% higher on Mondays and Tuesdays overall; this “post-weekend” risk phenomenon was more pronounced in dialysis patients vs. the general population (p<0.001 for interaction); 3) among dialysis patients, ER visits were 8X higher during the two weeks before and after initiation of dialysis, reflecting a period of heightened vulnerability for patients with kidney disease.

Conclusions: Our population based rates of ED utilization will help health administrators predict the “collateral” impact of a typical dialysis unit on the health system. Strategies to mitigate the high risk of ED utilization “post weekend” and around the time of transition to dialysis are urgently needed and should be a focus of future health systems research.

Funding: Private Foundation Support

TH-PO928

Development of a Clinical Risk Prediction Tool for Six-Month Mortality After Dialysis Initiation Among Older Adults

James Wick, Tanvir Choudhury Turin, Peter D. Faris, Jennifer M. MacRae, Robert G. Weaver, Brenda Hemmelgarn. Univ of Calgary, Calgary, AB, Canada.

Background: Early mortality after dialysis initiation is common among older adults. We sought to develop a tool to predict mortality within 6 months of dialysis initiation in an older adult population.

Methods: We linked administrative and dialysis registry data to define a cohort of older adults (age 65+) in Alberta, Canada who initiated chronic dialysis between May 2003 and March 2012. The outcome was all-cause mortality within 6 months of dialysis initiation. Potential predictors included demographics, comorbidities, health-system use, funding and care processes. The Cox model and adjusted risk ratios were computed. A risk score that predicts 6-month mortality was developed.

Conclusions: An intervention to improve discharge planning and case management for dialysis patients is needed to reduce early dialysis mortality.

Funding: Alberta Heritage Foundation for Medical Research, the Canadian Institutes of Health Research, the Canadian Health Services Research Foundation.

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

Underline represents presenting author.
laboratory measurements and dialysis-related information. We used logistic regression and 10-fold cross validation to identify and validate a model of significant predictors. The Model discrimination and calibration were measured by c-statistic and Hosmer-Lemeshow goodness-of-fit respectively. A point system was created based on regression coefficients of predictors in the final model.

**Results:** 2,211 dialysis patients, of whom 386 (17.4%) died within 6 months. Significant predictors of 6-month mortality were: age > 69 years, vascular access with central venous catheter, baseline eGFR < 10.14-9 or > 31 ML/min/1.73m², normal proteinuria, atrial fibrillation, lymphoma and congestive heart failure (CHF). Model discrimination (C-Statistic: 0.73) and calibration (Hosmer-Lemeshow c²: 6.09, p=0.64) were good. A 40-point scale for 6-month mortality was created based on model coefficients with points assigned based on strength of each predictor as specified in Table 1.

<table>
<thead>
<tr>
<th>Category</th>
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<td>Age</td>
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<tr>
<td>65-79.9</td>
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<td>CHF</td>
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Conclusions: We derived and internally validated a clinical risk prediction tool for 6-month mortality for older adults initiating dialysis, using age, vascular access, eGFR, proteinuria, atrial fibrillation lymphoma and CHF as predictors. The results require external validation prior to use in clinical practice. A tool such as this can guide decision making for older adults with kidney failure.

**TH-PO929**

**Coping Strategies and Outcomes Among Hemodialysis (HD) Patients in the DOPPS**

**Elodie Speyer,1** Malomenstern,2 Peter G. Kerr,3 Antonio Alberto Lopes,4 Hugh C. Rayner,5 Bruce M. Robinson,6 Ronald L. Pisoni.7

1Arbor Research, USA; 2Univ of Michigan, USA; 3Monash Health & Monash Univ, Australia; 4Federal Univ of Bahia, Brazil; 5Birmingham Heartlands Hospital, UK.

**Background:** Although HD presents numerous psychological and physical challenges for patients, they cope with dialysis therapy and its impact on quality of life (QoL) and mortality is poorly understood.

**Methods:** Patients from 6 DOPPS countries completed the Coping Strategies Inventory-Short Form (CSI-SF), which we found to be reliable and valid in those countries for measuring 4 coping strategies: problem-focused engagement (PFE) and disengagement (PFD), and emotion-focused engagement (EFE) and disengagement (EFD); and summary measures of engagement (actions to confront stressors) and disengagement (avoiding exposure to stressors). Outcome was QoL (from SF-12 and KDQoL-SF), depression symptoms (from the CES-D), and all-cause mortality. Mixed linear and logistic models were used to estimate coping effects, adjusting for country and potential confounders.

**Results:** In general and whatever the exposure to stressors). Outcomes were QoL (from SF-12 and KDQoL-SF), depression symptoms (from the CES-D), and all-cause mortality. Mixed linear and logistic models were used to estimate coping effects, adjusting for country and potential confounders.

**Conclusions:** Engagement strategies appear to be beneficial and disengagement detrimental for HD patients. A better understanding of the coping strategies used by patients may have prognostic implications and may help to improve disease management by providing tailored care for each patient.

**Funding:** Pharmaceutical Company Support - Agenem, Kyowa Hakko Kirin, AbbVie, Sandol Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DgGin, Shire, WiNe Institute, Societä Italiana di Nefrologia (SIN), PDOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx., Private Foundation Support

**TH-PO930**

**Intradialytic Aerobic Cycling Exercise Improve Inflammation Status, Endothelial Progenitor Cells and Bone Density in Patients with End Stage Renal Disease on Maintenance Hemodialysis**

**Chi-chao W1,2**

1Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center; Taipei, Taiwan; 2Dept of Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic Univ, New Taipei City, Taiwan.

**Background:** Inflammation, endothelial dysfunction and mineral bone disease play critical roles of morbidities and mortalities in the hemodialysis (HD) patients. Physical exercise can improve inflammatory status and bone density reverse protein-energy wasting (PEW) and bone loss. We investigate the effects of intradialytic aerobic cycling exercise (TACE) during HD.

**Methods:** Forty end-stage renal disease patients undergoing HD will be randomly allocated into an exercise or control group for 3 months. The cycling session consisted of 5 minute warm-up, 20 minutes cycling at desired workload and 5 minutes cool-down during the three weekly dialysis sessions. Biochemical markers, inflammatory cytokines and nutritional status as well as serum endothelial progenitor cells (EPCs) count, bone mineral density and functional capacity were checked.

**Results:** There were no statistically differences in the baseline characteristics between groups. Biochemical and anthropometric parameters revealed improvement in serum albumin, body mass index and inflammatory cytokines in the exercise group. Statistically significant changes in numbers of CD133/CD34/KDR cells were observed in exercise group, whereas EPCs increased significantly during the study. The patients in exercise group showed a significantly greater 6-minute walk test than at baseline. Subjects who were able to walk faster showed greater increases in EPCs than other subjects. Bone loss at the femoral neck was significantly greater in the control group compared with the exercise group which essentially showed no change. The bone mineral density (BMD) change at the lumbar spine (L1 to L4) was not significantly different between the treatment groups.

**Conclusions:** In conclusion, an intradialytic aerobic cycling exercise program can decrease inflammation, increase nutritional status and bone mass index, improve 6-minute walk distance, and increase the number of EPCs in HD patients.

**TH-PO931**

**Multicenter Trial of Aerobic Exercise in Maintenance Hemodialysis Patients**

**Misa Miura,1 Akihirayama,2 Shigeru Owada,3 Yo Hirayama,4 Osami Ito,5 Masahiro Kohzuki,6 1Dept of Health, Tsukuba Univ of Technology, Tsukuba, Ibaraki, Japan; 2Dept of Internal Medicine and Rehabilitation Science, Tokohu Univ Graduate School of Medicine, Sendai, Miyagi, Japan; 3Asao Clinic, Kawasawa, Japan.

**Background:** Hemodialysis patients show reduced physical function and greater risk of arteriosclerosis because of hypertension, metabolic disturbances, and vascular calcification. Meanwhile, exercise training in hemodialysis patients improves fitness, physical function, quality of life, and markers of cardiovascular disease such as arterial stiffness. This study aimed to determine whether aerobic training and electrical stimulation to skeletal muscles for 12 weeks could improve physical function and dialysis efficacy in patients with end-stage renal disease (ESRD).

**Methods:** This was a multicenter trial. A total of 35 ESRD patients on three occasions (20 males, 15 females; age: 70.2±11.7 years) were randomized to receive 12 weeks of aerobic training exercise, during hemodialysis session (Ex-group: n=19), electrical stimulation to the lower limbs (ES-group: n=6), or no specific intervention (Cont-group: n=10). The Borg
scale was used to control the intensity of training. At baseline and study completion, the primary outcome measures were grip strength, quad muscle torque, workout time, activities, dialysis efficacy, HDL, LDL, CRP, IL-6 and blood pressure.

Results: In the Ex-group, handgrip, quad torque, and workout time increased significantly (P<0.05). Dialysis efficacy, HDL-cholesterol, LDL-cholesterol, CRP, and blood pressure on the morning of the dialysis day also improved significantly (P<0.05). These effects were not observed in the Cont-group. In the Es-group, quad muscle torque and dialysis efficacy increased significantly (P<0.05). IL-6 decreased significantly (P<0.05), compared to the other two groups.

Conclusions: In this study, the safety and efficacy of training and electrical stimulation during hemodialysis were confirmed without sudden drop of blood pressure or any other side effects. Therefore, training during hemodialysis session for 12 weeks might improve physical function with specific whole-body effects as well as local effects in ESRD patients.

TH-PO932
Glycemic Markers and 2-Year Non-Diabetic Hemodialysis Outcomes from the Glycemic Indices in Dialysis Evaluation Study
Mark E. Williams,1,2 Neal Mittman,1,2 Lin Ma,3 Julia I. Brennan,1 Curtis D. Johnson,4 Franklin W. Maddux,5 Eduardo K. Lacson,1,5 Jesse Diabetes Center, Boston, MA; 2Kidney Care of Brooklyn and Queens, Brooklyn, NY; 3Presbyterian Medical Care North America, Walltham, MA; 4Spectra Laboratories, Rockleigh, NJ; 5Physician, Lexington, MA.

Background: The ongoing GIDE (Glycemic Indices in Dialysis Evaluation) study includes data on nonDM hemodialysis (HD) patients (confirmed by HgbA1c <6.5%). Because nonglycemic factors may lower HgbA1c levels in ESRD, we previously reported their glycemic status/1-year outcomes using alternative glycemic markers [albumin-adjusted and unadjusted fructosamine (AlbF;F) and glycated albumin (GA) or percent GA (%GA)]. We now report 2-year study data.

Methods: 970 nonDM HD patients from 26 FMCNA facilities with glycemic markers from Jan-March 2013 were followed until April, 2015. Baseline AlbF, F, GA and %GA were used to classify patients as high or low glycemia using thresholds of AlbF<94 mmol/L, F<285 mmol/L, %GA<15.7%, and GA<300 mg/L. Standard and Time-dependent (TD) Cox models with case-mix adjustment for age, sex, race, ethnicity, BMI, HD catheter and baseline comorbidity were used to determine associations between each glycemic index and hospitalization/death risk.

Results: While 1% had HgbA1c<7%, high glycemic status was more commonly detected using F (59%), AlbF (4%), GA (15%) and %GA (29%). Elevated AlbF was significantly associated with 2-year mortality [Standard Cox: Hazard Ratio (HR)=2.53, 95% CI (1.31, 4.92), p=0.006; TD Cox: HR=3.55, 95% CI (1.97, 6.38), p=0.00001 and hospitalization [TD Cox: HR=2.49, 95% CI (1.70, 3.67), p=0.0001]]. For all other glycemic markers, no such associations were evident at the proposed thresholds using adjusted analyses in the Cox model.

Conclusions: These data support our previous findings of an association between poor glycemic status (high AlbF) and hospitalization/mortality outcomes in nonDM HD patients. High AlbF-glycemic status may have prognostic implications in nonDM HD patients.

TH-PO933
Association of Change in Serum HDL Cholesterol with Mortality in Hemodialysis Patients: Role of Gender
Sheila Mazdasyani,1 Elami Streja,1 Tae Hee Kim,1 Connie Rhee,1 Steven M. Brunelli,2 Matt L. Kashyap,2 Nosratola D. Vaziri,1 Kamyrant Kalantar-Zadeh,1 Hamid Moradi,1,3 UC Irvine; 2DaVita Clin Research; 3VA Long Beach.

Background: Elevated high-density lipoprotein cholesterol (HDL) levels, though protective in the general population, can be associated with higher mortality in hemodialysis (HD) patients. Association of HDL change over time with mortality has yet to be examined. Based on previous studies, we hypothesized that upward trends in HDL levels may be associated with higher mortality risk in HD patients.

Methods: We examined HDL change over time in 24,400 incident HD patients receiving care from a large dialysis organization in 2007-2011. Association of delta HDL (HDL change between the 1st and 2nd 91st day interval from dialysis start) and HDL trajectory with all-cause mortality were examined using mixed effect and Cox regression models and adjusted for demographics, comorbidities and baseline HDL. Delta HDL was treated both as a continuous variable using restricted cubic splines and in categories of<6, 6-<12, 12 -<18 (Rej), 2, 6, =18 mg/dL.

Results: Patients were 65±15 years old, 44% female, 31% black, 66% diabetic with a mean baseline HDL 40.5±13.9 mg/dL and HDL change 1.7±10.4 mg/dL. While male patients had no significant change in HDL over time, females had a significant decrease in HDL (mean -0.6 mg/dL/year). A<26 mg/dL increase or decrease in delta HDL was associated with a 7% and 37%, respective increase in all-cause mortality compared to reference group. Delta HDL-mortality associations did not differ across gender.

Conclusions: Decreased HDL over time was associated with worse outcomes and increased HDL was paradoxically associated with higher mortality. While HD treatment can be associated with a decrease in HDL, this effect was magnified in younger females. The novel and intriguing role of age and gender in association of HDL and survival needs further evaluation.

Funding: NIDDK Support

TH-PO934
Differences in Perceived Kidney Disease Burden on Quality of Life by Race/Ethnicity in a Diverse Cohort of Hemodialysis Patients
Anna C. Porter,1 Rani Gallardo,2 Linda A. Schiffer,2 Denise M. Hynes,2,3,4 Dept of Medicine, Div of Nephrology, Univ of Illinois Hospital and Health Sciences System, Chicago, IL; 3Dept of Medicine, Div of Academic General Internal Medicine and Geriatrics, Univ of Illinois at Chicago, Chicago, IL; 4Inst for Health Research and Policy, Univ of Illinois at Chicago, Chicago, IL; 5Center of Innovation for Complex Chronic Healthcare, Edward Hines Jr., VA Hospital, Hines, IL.

Background: Low health-related quality of life (HRQOL) has been well-documented in patients with end-stage renal disease on hemodialysis (ESRD). While African Americans and Hispanics remain at increased risk for ESRD, HRQOL has been less well-described in these individuals compared to non-Hispanic whites.

Methods: Baseline HRQOL data was analyzed for participants enrolled in the Patient-Centered Medical Home for Kidney Disease study (PCMH-KD), a trial of a multidisciplinary, patient-centered primary care intervention in a population of hemodialysis patients at two dialysis facilities in Chicago. The Kidney Disease Quality of Life (KDQOL-36) instrument was used to assess HRQOL at baseline, and the following subscale scores were obtained: Physical, Mental, Burden of Kidney Disease, Symptoms and Problems, and Effects of Kidney Disease.

Results: Baseline data were available for 95 patients. Approximately, 52% of patients were African-American, and 45% were Hispanic. Significant racial/ethnic differences were observed among subscales of self-reported HRQOL.

<table>
<thead>
<tr>
<th>KDQOL Subscale</th>
<th>Mean Score for African American Participants</th>
<th>Mean Score for Hispanic Participants</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>35.8</td>
<td>34.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mental</td>
<td>51.4</td>
<td>47.1</td>
<td>0.040</td>
</tr>
<tr>
<td>Burden</td>
<td>57.4</td>
<td>33.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms/Problems</td>
<td>76.6</td>
<td>76.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Effects</td>
<td>74.9</td>
<td>66.8</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Conclusions: Hispanic patients with ESRD on HD report disproportionate burden and effects of kidney disease on HRQOL and worse mental HRQOL compared to African American patients with ESRD on HD. Further exploration of these disparities may lead to strategies for improvement of HRQOL in Hispanic patients.

Funding: Private Foundation Support
Relative Blood Volume and Mortality in Hemodialysis Patients

Linda H. Picciollo,1 Paul Balter,2 Mark Costanzo,3 Patrice B. Taylor,4 Claudio Mullon,5 Robert J. Kossmann.6
1Fresenius Medical Care North America (FMCNA), Waltham, MA; 2Renal Research Inst (RRi), New York, NY.

Background: A quality improvement project on fluid management using Crit-Line® Monitors (CLM) was conducted across multiple RRI facilities. Percent change in relative blood volume (RBV) was measured during routine hemodialysis (HD). Previous analyses of the same cohort have shown associations between RBV reduction and reduced hospital admission rate; the current analysis assesses mortality.

Methods: A retrospective analysis of HD treatments with RBV measurements was conducted over 6 months. RBV was calculated using: RBV= [(Hematocrit (admission rate; the current analysis assesses mortality.

Results: Patients were divided into RBV categories by 5% increments and compared on risk of deaths per patient months. Time to death was modeled with Cox proportional hazards model.

Conclusions: In a large cohort of HD patients with relative blood volume measured, patients with less reduction in percent change in relative blood volume at the end of dialysis had higher risk of death over 6 months when compared to patients with greater reduction. These patients may represent a subset of patients at high risk for adverse outcomes and may benefit from fluid management programs.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

The Effect of Altitude on Erythropoiesis-Stimulating Agent Dose, Hemoglobin Level, and Mortality in Hemodialysis Patients

Scott Sibbald,1 Donna E. Jensen,1 John Alan Laich,1 Sarb Senghildi,2 Bradley J. Maroni,2 Steven M. Brunelli,1 DaVita Clinical Research, Minneapolis, MN; 1Akebia Therapeutics, Cambridge, MA.

Background: Prior studies have shown that hemodialysis (HD) patients residing at higher elevations have lower erythropoiesis-stimulating agent (ESA) utilization, possibly due to activation of hypoxia-regulated genes. We sought to better understand the impact of altitude on dosing of anemia medications and mortality following 2011 changes to the US epoetin alfa label and reimbursement policy.

Methods: We studied a cohort of prevalent nonverteran HD patients (vintage >6 months) treated at a large dialysis organization between 1 Jan 2012 and 31 Dec 2012. Patients were categorized across categories of longitudinal hemoglobin (Hb) level, ESA and intravenous (IV) iron dose, and mortality risk using mixed linear models. Associations were adjusted for baseline demographic and clinical characteristics.

Results: Compared to altitude of 0-1499 ft, higher altitude was incrementally associated with higher mean Hb and lower mean ESA dose; mean IV iron utilization did not differ. Altitude >1500 ft (vs 0-1499 ft) was independently associated with lower mortality risk: incidence rate ratio (IRR) was 0.74 with 95% confidence interval (CI) 0.63-0.88.

Conclusions: Among contemporary HD patients receiving treatment at >1500 ft, higher altitude was independently associated with greater Hb level despite lower ESA doses and comparable IV iron utilization. Altitude of >4500 ft was independently associated with a 26% lower mortality risk.
Results: Among subjects treated with PBO (n=9) or sotatercept 0.3 mg/kg or sotatercept 0.5 mg/kg, adverse events were mostly mild/moderate, unrelated to study drug, similar in type/severity between groups, and generally consistent with subject medical histories. Two deaths occurred in the PBO group. There were no dose-dependent changes in home BP. In the 225-day treatment phase, Hb was ~11 g/dL in 33%, 33%, 63%, and 78% of subjects treated with PBO or sotatercept 0.3, 0.5, or 0.7 mg/kg, respectively. Paired QCTs obtained in 4, 6, 5, and 6 subjects treated with PBO or sotatercept 0.3, 0.5, or 0.7 mg/kg showed <15% progression of VC in 33%, 80%, 80%, and 100%, and >2% increase in femoral neck cortical BMD in 0%, 20%, 40%, and 75%, respectively.

Conclusions: Sotatercept appears to be well tolerated with an acceptable safety profile in HD, without increases in home BP. There are beneficial dose-related responses to sotatercept in Hb, VC, and BMD. A larger dataset, with an ongoing 14-day dose group, will further substantiate these results.

Funding: Pharmaceutical Company Support - Study was sponsored by Celgene Corporation.

TH-PO939
Impact of CKD-MBD Composite Score on Mortality and Hospitalization: Dialysis Outcomes and Practice Patterns Study (DOPPS)
Douglas S. Fuller,1 Paul Dluzniewski,2 Kerry Cooper,3 Brian D. Bradbury,4 Mark D. Danese,5 Bruce M. Robinson,6,7 Francesca Tentori,2,3,8 Arbour Research Collaborative for Health, Ann Arbor, MI;9 Amgen, Thousand Oaks, CA;10 Outcomes Insights, Inc., Westlake Village, CA;11 Univ of Michigan, Ann Arbor, MI;12 Vandebilt Univ, Nashville, TN.

Background: The biochemistries associated with chronic kidney disease-mineral and bone disorder (CKD-MBD), parathyroid hormone (PTH), calcium (Ca), and phosphorus (P), are physiologically interrelated. We evaluated the impact of combinations of CKD-MBD parameters on mortality rates in HD patients.

Methods: We identified DOPPS 3-5 (2005-2014) pts in the US, Canada, and Europe (France, Germany, Italy, Spain, Sweden, and the UK) with ≥2 mos of follow-up. We assessed demographic and clinical covariates in study miss 9-12 and used Cox models to generate risk scores (DOPPS 5) by region based on pts with CKD-MBD parameters in target (MBD 0; P 3.5-5.5 mg/dL, Ca 8.4-10.2 mg/dL, PTH 150-600 pg/mL) and to compare event rates, adjusted for DRS, of mortality and a composite of death or hospitalization between MBD 0 and pts with 2-3 values outside target (MBD 2+).

Results: MBD 2+: prevalence, primarily due to high PTH and P, was 22.8%, 29.5%, and 26.9% in the US, Canada, and Europe, respectively. PTH above target was higher in the US (52%) compared to Canada (42%) and Europe (28%). Compared to MBD 0, MBD 2+ was associated with moderately higher mortality in the US (52%) compared to Canada (42%) and Europe (28%). Compared to MBD 0, MBD 2+ was associated with higher health care costs. Despite these differences, the majority of patients had CKD-MBD parameters within target ranges.

Conclusions: CKD-MBD parameters vary by region, perhaps resulting in differential risk of adverse outcomes. Our findings in this international cohort highlight the importance of simultaneous, rather than independent, control of CKD-MBD parameters within clinical guidelines.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. CMS ESRD databases are available.

TH-PO940
US DOPPS Practice Monitor: Comparisons with CMS ESRD Databases
Douglas S. Fuller, Lindsay Zelpel, Keith McCullough, Brian Biber, Ronald L. Pisoni, Francesca Tentori, Bruce M. Robinson. Arbour Research Collaborative for Health, Ann Arbor, MI.

Background: Since August 2010, the Dialysis Outcomes and Practice Practices Practice Monitor (DPM; www.dopps.org/DPM) has leveraged its US Hemodialysis (HD) sample (now >200 facilities) to provide timely and detailed (>750 data tables) updates on national trends in HD care. Here we compare DPM estimates to available results from end-stage renal disease (ESRD) data sources collected by the Centers for Medicare and Medicaid Services (CMS).

Methods: Pearson correlations (r) were used to compare contemporary trends since Aug 2010 between DPM and the 2014 US Renal Data System Annual Data Report (ADR, through Dec 2012) and the Nov 2014 CMS Claims-Based Monitoring Project (CBMP, through Jun 2014). We also compared monthly DPM estimates with cross-sectional estimates from 2014 CrownWEB (CW, Dec 2013).

Results: DPM trends in ESA use and dose, IV iron use, and hemoglobin levels were highly correlated (r’s: 0.89-0.98) with ADR and CBMP trends. Compared to CW, DPM showed slightly higher fistula use, but slightly lower percent of patients with adequate Kt/V and URR values.

Table: Comparisons of US DPM national estimates to CMS ESRD data sources

<table>
<thead>
<tr>
<th>Reference Estimate</th>
<th>DPM Estimate (SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA use (%)</td>
<td>10.8 ± 1.3</td>
<td>0.035</td>
</tr>
<tr>
<td>ESA dose (%)</td>
<td>10.8 ± 1.3</td>
<td>0.035</td>
</tr>
<tr>
<td>ESA dose g/dL (%)</td>
<td>10.8 ± 1.3</td>
<td>0.035</td>
</tr>
<tr>
<td>IV iron use (%)</td>
<td>61.4 ± 1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean Hb (g/dL)</td>
<td>10.6 ± 0.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

TH-PO941
Reduced Free Triiodothyronine Is an Independent Predictor of Clinical Outcomes in Hemodialysis Patients with Low Albuminemia
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Background: Low free triiodothyronine (fT3) and free thyroxine (fT4) are both related to malnutrition, inflammation and mortality in dialysis patients. Upper-normal thyrotrin (TSH) levels are also associated with a higher risk of total mortality in hemodialysis (HD) patients. However, it remains unclear which of thyroid-related hormones is most useful in predicting clinical outcomes. So, we aimed this study to compare the prognostic value of different hormones in prevalent HD patients.

Methods: We enrolled 339 HD patients (age: 64±13 years old, time on HD: 129±14 months), and measured basal fT3, fT4 and TSH. We then followed the patients for the next 42 months, and assessed the impact of fT3, fT4 and TSH on all-cause mortality and cardiovascular (CV) events or hospitalization. Patients were divided into the 4 groups based on the quartiles of fT4, fT3 and TSH. The associations of basal levels with clinical outcomes were examined with Cox proportional hazards models adjusted for demographic and classical factors and comorbidities.

Conclusions: Distributions of CKD-MBD parameters varied by region, perhaps resulting in differential risk of adverse outcomes. Our findings in this international cohort highlight the importance of simultaneous, rather than independent, control of CKD-MBD parameters within clinical guidelines.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. CMS ESRD databases are available.
Low Socioeconomic Status and Co-Morbidity Are Associated with Limited Health Literacy in RRT Patients – Results from the ATTOM Study

**Background:** Limited health literacy (LHL) is a risk factor for poor outcomes in chronic disease patients. Studies with limited patient numbers in RRT patients associate LHL with low socioeconomic status (SES), comorbidity and ethnicity.

**Methods:** This cross-sectional study used baseline data from the ‘Access to Transplantation and Transplant Outcome Measures’ (ATTOM) cohort. ATTOM recruited incident dialysis and transplant patients aged 18-75 years in the UK during 2011-2013 and also with patients similar to those transplanted (matched controls). Health literacy was measured by the question ‘How often do you need someone’s help to read instructions, leaflets, or other written material from your doctor or pharmacy?’ answered on a scale from 1-Never to 5-Always. LHL was defined as a score greater than 2. The three groups were analysed for associations between LHL and demographics, SES factors and comorbidity, using univariate and multivariate analysis, p<0.05.

**Results:** 6842 patients were recruited: 2621 incident dialysis (ID), 2262 incident transplant (IT) and 1959 matched controls (MC). 6373/6842(93%) completed the health literacy assessment. Prevalence of LHL was 20% in the ID, 12% in the IT and 15% in the MC group. In univariate analyses, in all groups, English not as first language, Asian ethnicity, low educational level, unemployment, absence of car or home ownership, increased comorbidity by modified Charlson index and mental illness were associated with LHL. In adjusted models, in all groups, the following factors were associated with LHL in patients receiving dialysis or at the point of transplantation, independent of first language. LHL may impact upon patients’ ability to engage with shared decision making with LHL in patients receiving dialysis or at the point of transplantation, independent of first language (OR>3.0 compared to employed) and absence of car ownership (OR 1.7). Low level of education (OR>2 for no qualifications compared to any), unemployment (OR>3.0 compared to employed) and absence of car ownership (OR 1.7). Age and sex were not associated with LHL of adjustment.

**Conclusions:** These findings suggest that low fT3 became an independent predictor of clinical outcomes in ID patients with low albuminemia.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only**
The reduction was most prominent in patients with longer dialysis vintage, patients who were younger, and those with lower pre-dialysis b2m levels. Similar results were obtained by propensity score-matched analysis. We also found that b2m clearance >80% may reduce risk of CTS.

Conclusions: The incidence of first-time CTS as proxy for DRA decreased significantly from 1998 to 2010. Several factors may have contributed to this decrease, including improved dialysis methods.

TH-PO947
Twice Weekly Hemodialysis and Clinical Outcomes in the China DOPPS
Yuecheng Yan,1 Mia Wong,2 Jia Qi Qian,1 Brian Bierer,3 Mei Wang,1 Nan Chen,1 Bruce M. Robinson,4 Shuchi Anand,4 Shanghai Renji Hospital;4 Arbor Research;4 Shanghai Ruijin Hospital;4 Stanford Univ.

Background: Outcomes related to 2 times weekly hemodialysis (HD), substantially practiced in China, remain understudied. Small, single-center studies have indicated better preservation of residual kidney function (RKF) and similar survival for 2 vs. 3 times weekly HD. We used data from the China Dialysis Outcomes Practice Patterns study (DOPPS) to evaluate survival and hospitalizations by frequency of HD.

Methods: We studied 1,433 patients from 45 HD units in China (2012-2015). Cox regression was used to model the association of 2 vs. 3 times weekly HD with clinical outcomes adjusting for patient and treatment characteristics.

Results: 270 patients (19%) were undergoing 2 times weekly HD in China. Compared with 3 times weekly HD, patients on 2 times weekly HD were more likely to be female and have shorter time on dialysis (4.3 vs. 2.6 yrs), more urine output, shorter dialysis session length (238 vs. 250 min) and longer travel times to facility. They were less likely to have diabetes or cardiovascular disease. Insurance coverage was similar in the two groups. During follow-up (median=1.7 years), 184 (13%) deaths and 516 (38%) hospitalizations occurred. No differences in mortality or hospitalization were found between the two frequency groups (Table). No interaction was observed with vintage (p=0.43).

Table: Progressive adjustment of mortality with twice weekly dialysis, in China

<table>
<thead>
<tr>
<th>Frequency</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 times week</td>
<td>0.90(0.61-1.33)</td>
<td>0.61</td>
</tr>
<tr>
<td>3 times week</td>
<td>0.95(0.63-1.42)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*1393 patients, 184 events. 
*a, age, gender, BMI, standardized, and vintage.

Conclusions: In this multi-center study with well-characterized patient and treatment data, outcomes of 2 vs. 3 times weekly HD were similar. Thus, it is possible that among carefully selected patients 2 times weekly HD may provide acceptable outcomes. An additional study is also need due to residual confounding, small sample size, and the changes in results with progressive adjustments.

TH-PO948
Initiation of a Chronic Kidney Disease Case Manager Program Is Associated with Better Outcomes in Incident Hemodialysis Patients
Joseph A. Kuhn,1 Patrick Bridge, John W. Larkin, Hao Han, Sheetal Chaudhuri, Len A. Usvyat, Terry Ketchersid, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: The Renal Care Coordinator (RCC) Program places chronic kidney disease (CKD) case managers in the Nephrology Practice to co-manage late stage CKD (4 and 5) patients for an optimal outpatient start to Renal Replacement Therapy (RRT). This program is performed through both physical and virtual RCCs. We compared outcomes in patients starting hemodialysis (HD) who were previously enrolled in the RCC program to CKD patients cared for in the nephrology practice, but were not in the RCC program.

Methods: All CKD 5 patients who transitioned to end stage renal disease (ESRD) requiring RRT between 1/1/2012 and 10/1/2014 at the nephrology practices that adopted the RCC program were analyzed. We compared outcomes in patients enrolled into the RCC program versus patients considered to have a “Timely Referral” for dialysis (i.e. were followed in a
nephrology practice for 4 months before starting RRT), but received no RCC interaction. The albumin (Alb) and hemoglobin (Hgb) levels were collected at the first outpatient HD treatment. We also computed the hospital days of mortality and the first 120 days of HD.

Results: 1,404 CKD 5 patients were identified for the analysis, where 51% of the population was enrolled in the RCC. Patients in the RCC had a lower % of catheters, higher days of HD. We also computed the rates of hospital days and mortality in the first 120 days of HD treatment. We also computed the rates of hospital days and mortality in the first 120 days of HD. We also computed the rates of hospital days and mortality in the first 120 days of HD.

P<0.05 (*)

Conclusions: This analysis demonstrates that placement of CKD case managers is associated with better outcomes, including anemia, access type, nutritional status and hospitalization in the first 120 days of HD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-P0949

Extracellular Overhydration Measured by Multifrequency Bioelectrical Analysis Is Associated with Increased Postdialysis Systolic Blood Pressure in Hemodialysis Patients Hae Yeul Park, 1 Seok-hyoung Kim, 1 Ah Ran Choi, 1 Jung eun Lee, 1 Hyung jong Kim, 2 Hoon Young Choi, 3 Sung-Kyu Ha, 1 Hyeong cheon Park. 1 Nephrology, Gangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea; 2 Nephrology, Ross Medical Research Institute, Cleveland, Ohio; 3 Nephrology, University of Maryland School of Medicine, Baltimore, Maryland.

Background: Postdialytic hypertension is associated with increased morbidity and mortality for hemodialysis (HD) patients. Recent studies suggested that increased postdialysis extracellular volume may account for the rise in postdialysis systolic blood pressure (PDSBP).

Methods: Volume status assessments were performed during mid-week HD using multifrequency bioelectrical impedance (BIA, Inbody S10) in supine position. Demographic and routine biochemical data were collected and pre- and post-dialysis B-type natriuretic peptide (BNP) level was measured (Triage BNP test, Alere).

Results: We enrolled clinically stable 99 HD patients from 3 dialysis centers. Patients were divided into 3 groups based on a fall in SBP of 20mmHg or more (Hypotensive, 24.2%), an increased SBP of 10mmHg or more (Hypertensive, 32.3%), and a stable group (43.4%). The mean age was 55 ± 13.3 years in hypertensive, 58 ± 11.6 years in stable, and 62 ± 27.2 years in hypertensive group. Postdialysis BNP was 267 ± 251.1 pg/ml in hypertensive, 660 ± 913.9 pg/ml in stable and 212 ±197.8 pg/ml in hypertensive group. There were no differences in gender, dialysis prescriptions, and subjective global assessment score among the patient groups. The ECW/TBW ratio was significantly higher in the hypertensive group and positively correlated with PDSBP and delta SBP. The only independent risk factor affecting ECW/TBW ratio after dialysis was volume status.

Conclusions: HD patients who demonstrate increase in PDSBP should have their volume status reassessed and target dry weights adjusted using BIA, which is a promising new tool in assessing fluid status in patients on HD.

TH-P0950

Novel Phosphate Binder, Ferric Citrate Hydrate, Can Reduce Serum Phosphate Levels and Doses of Erythropoiesis Stimulating Agents in Japanese Patients on Hemodialysis Hironori Kuma, 1 Akihiro Nishimura, 1 Yosuke Umezaki, 1 Masafumi Sato, 2 Toru Kuma, 2 Daisuke Nishimura, 2 Taketoshi Uyama, 3 Yosuke Umezaki, 1,2,3 Nephrology, Nagoya University Hospital, Nagoya, Japan; 2 Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: Ferric citrate hydrate (FC) has been available in Japan as a phosphate binder for patients on dialysis (HD) since 2014 although its effects have not been evaluated in detail in such patients. The present study aimed to determine the effects of FC on serum phosphate levels and anemia control in patients on HD.

Methods: Thirty-eight outpatients (mean age, 62.5 ± 7.7; hypertension, n = 29 [75.3%]; diabetes, n = 19 [50.0%]; secondary hyperparathyroidism, n = 15 [39.5%]) on maintenance HD were treated with FC for 6 months to control hyperphosphatemia. Serum concentrations of phosphate, calcium, hemoglobin, and ferritin levels, transferrin saturation (TSAT), and weekly epoetin (EPO) dose were monitored during the study.

Results: Mean phosphate levels were significantly decreased from 7.05 ± 1.11 to 6.19 ± 0.91 (p < 0.0001) and 6.14 ± 1.16 (p < 0.05) and 6.01 ± 1.11 (p = 0.0035) mg/dL at one, three and six months, respectively. Calcium, hemoglobin and ferritin levels did not significantly differ during the same periods. Transferrin saturation was significantly increased (26.7 ± 10.9% vs. 22.0 ± 9.5%, p < 0.05) and the weekly EPO dose was significantly decreased (2750 ± 2699 vs. 6801 ± 7406 IU/week, p < 0.05) after six months of FC therapy.

Conclusions: FC can decrease serum phosphate levels and the weekly EPO dose. Therefore, FC is useful for treating hyperphosphatemia and renal anemia in Japanese patients on HD.

Background:

TH-P0951

Geographic Variation of Potentially Avoidable Readmissions in Hemodialysis Patients Daniel W. Ross, 1 Kamyar Kalantar-Zadeh, 1 Steven Fishbane, 3 Anna Mathews, 1 BPI Division of Nephrology, Hofstra North Shore --LIJ School of Medicine, New York, NY; 2 Harold Simmons Center for Kidney Disease Research and Epidemiology, Div of Nephrology, Univ of California, CA.

Background: In 2011 in the United States, 36.3% of prevalent hemodialysis patients were readmitted within 30 days of an index hospitalization. These rates are approximately twice that of the general U.S. Medicare population. While some readmissions to hospital are unavoidable, it is probable that a substantial number could be prevented. In the present study, we describe inter-state variability in 30-day potentially avoidable readmissions (PAR).

Methods: The United States Renal Data System (USRDS) was used to identify prevalent hemodialysis patients (vintage ≥90 days) with acute hospitalizations in 2008. Exclusion criteria were transfer to rehabilitation or skilled nursing facility, unknown dialysis start date, and renal function recovery. PAR were identified using a validated, computerized algorithm (SQLape), and displayed geographically by state using Pitney Bowes MapInfo.

Results: 250,606 index hospitalizations were identified, with 37% readmissions within 30 days (n = 84,279). Nationwide, 24% of index hospitalizations were followed by a 30-day PAR (64.9% of all readmissions) (n= 59,803). PAR ranged from 12% to 31% by state. The figure shows the geographic distribution of potentially avoidable readmissions.

Conclusions: There is inter-state variability in PAR among chronic hemodialysis patients and may be related to regional differences in practice patterns or patient demographics. Further characterization of risk factors associated with PAR is the focus of our ongoing research.

TH-P0952

Unravelling the Relationship Between Mortality, Hyponatremia, Inflammation and Malnutrition in Hemodialysis Patients: Results from the INTERNATIONAL MONDO Initiative Marike J.E. Dekker, 1 Daniëlle Marcelli, 2 Bernard J. Canaud, 3 Constantijn Konings, 4 Karel M. Leunissen, 4 Nathan W. Levin, 4 Jochen G. Raimann, 5 Frank van der Sande, 6 Len A. Ustyayt, 7 Peter Kotanko, 8 Jeroen Koornman, 9 Catharina Hospital Eindhoven, 10 Maastricht Medical Center, 11 Fresenius Medical Care; 12 Renal Research Inst.

Background: Hyponatremia is a risk factor for mortality in hemodialysis patients. However, it is not well known to which extent comorbidities, such as malnutrition, fluid overload and inflammation are related to hyponatremia and influence the association between hyponatremia and outcomes.

Methods: We studied 8892 patients from the European subset of the MONDO Initiative. Nutritional and fluid statuses were assessed by multifrequency bioimpedance spectroscopy. Based on pre-dialysis fluid status, fluid depletion was defined as an extracellular water volume < -1.0L and fluid overload > +2.5L. Malnutrition was defined as a lean tissue index below the 10th percentile of age- and gender matched healthy controls. Hyponatremia and inflammation were defined as serum sodium levels ≤ 135 mEq/L and C-reactive protein levels > 10 mg/L, respectively.

Results: Hyponatremia was predicted by the presence of malnutrition (odds ratio (OR) 1.48 (95%CI 1.30-1.69) and inflammation (OR 1.44 (95%CI 1.26-1.64)), but not by fluid depletion (OR 1.38 (95%CI 0.98-1.93)) or fluid overload (OR 0.99 (95%CI 0.85-1.14)). Malnutrition (hazard ratio (HR) 1.39 (95%CI 1.23-1.58)), inflammation (HR 2.31 (95%CI 2.04-2.62)), fluid overload (HR 2.17 (95%CI 1.90-2.47)) and hyponatremia (HR 1.63 (95%CI 1.39-1.90)) were independent predictors for all-cause mortality.

Conclusions: In hemodialysis patients hyponatremia is associated with malnutrition and inflammation but not with denarged fluid status. Hyponatremia maintained predictive for all-cause mortality after correction for malnutrition, inflammation and fluid status abnormalities. Hyponatremia may aid efforts to identify hemodialysis patients at increased risk of death.
TH-PO953

Low Serum Sodium Concentration at the Induction of Maintenance Hemodialysis Predicts Higher Risk of Mortality: Yokako Ohyama, Hideaki Shimizu, Daio Inaguma, Yoshiro Fujita. 1Nephrology and Rheumatology, Chubu Rosai Hospital, Nagoya, Japan; 2Nephrology, Red Cross Nagoya Daini Hospital, Nagoya, Japan.

Background: Low serum sodium concentrations are associated with an increased risk of death in the general population because of underlying diseases such as congestive heart failure and cirrhosis. However, some papers report hyponatremia itself further increases the mortality risk. The prevalence of hyponatremia and the mortality risk of hyponatremia at the induction of maintenance hemodialysis (HD) have not been reported before.

Methods: This study is a retrospective cohort study which date was collected from “Aichi Cohort study of Prognosis in Patients” (AICOPP) newly initiated dialysis. After the exclusion of peritoneal dialysis (PD) patients, this study enrolled 1395 patients (mean age; 68 ± 13 years, mean eGFR level; 54 ± 2.2 ml/min/1.73m²) who started maintenance HD between 10/1/2011 and 11/30/2013. We divided the cohort to 4 groups by serum sodium concentration at the induction of HD adjusted by serum glucose concentration (Severe hyponatremia: Na<130, Mild hyponatremia: 130≤Na<136, Normal:136≤Na≤145, Hypernatremia: Na>145 mEq/L). The proportional hazard model was used to examine the association between serum sodium level and mortality.

Results: The prevalence of hyponatremia, defined as Na<136 mEq/L and <130 was at 23% and 5%, respectively. During 15.5 months’ mean follow up, 159 patients (11%) died. The lowest Na group was significantly associated with higher risk of mortality (figure1). Patients with serum sodium levels of <130 mEq/L were more likely to have multivariable-adjusted mortality hazard ratios (95% confidence interval) of 2.34 (1.31-4.15) compared to patients with serum sodium levels of 136-145 mEq/L.

Kaplan-Meier curves

Conclusions: Hyponatremia at the induction of HD is an independent predictor of higher risk for mortality.

TH-PO954

Frequency of Hyperkalemia Events in Dialysis Patients in a Large Dialysis Organization: Akeem Yusuf,1 Yan Hu,1 Bhupinder Singh,2 Alex Yang,2 James B. Wetmore.1 1Chronic Disease Research Group, MMRF, Minneapolis, MN; 2ZS Pharma, Inc, Redwood City, CA.

Background: Hyperkalemia is a major problem in dialysis patients. It is associated with increased risk of cardiac arrhythmias and sudden cardiac death. However, few studies have examined frequency of hyperkalemia episodes in a large population of dialysis patients.

Methods: A cohort of patients receiving thrice-weekly HD in 2010 was constructed using data linked between USRDS and a large dialysis organization (LDO). Patients were followed from first serum K measurement until death, transplant, change in dialysis modality, change in dialysis K concentration, loss of Medicare eligibility, loss to follow up, or Dec 31, 2010. Hyperkalemia was defined by serum K levels 5.5-6.0 mEq/L at 0.1 mEq/L intervals. Time-dependent Cox proportional hazards modeling was used to estimate the association between hyperkalemia occurrence and all-cause and cardiovascular mortality.

Results: Hyperkalemia defined as serum K ≥5.7 mEq/L was associated with all-cause mortality (adjusted hazard ratio [AHR] 1.1, 95% CI 1.01-1.28, P = 0.037, compared to K ≥5.0 mEq/L) after adjustment for demographic and clinical factors in time-dependent models; the AHRs increased progressively as the threshold for hyperkalemia rose (AHRs 1.18, P = 0.014, for K=5.8 mEq/L; 1.29, P = 0.001, for K=5.9 mEq/L; 1.37, P = 0.0002, for K=6.0 mEq/L). The pattern of the point estimates was similar for cardiovascular mortality, although the results did not reach statistical significance (AHRs 1.09 for K=5.7 mEq/L, 1.13 for K=5.8 mEq/L, 1.20 for K=5.9 mEq/L, 1.28 for K=6.0 mEq/L).

Conclusions: Hyperkalemia is associated with all-cause mortality beginning at K level ≥5.7 mEq/L, with mortality risk point estimates increasing in ordinal fashion through K level ≥6.0 mEq/L. A similar pattern was observed in the point estimates for cardiovascular mortality. This study may have identified a threshold at which point serum K becomes dangerous.

Table: Number of events per 100 patient-months

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of events per 100 patient-months</th>
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</thead>
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<tr>
<td>Year</td>
<td>Events on day after</td>
</tr>
<tr>
<td></td>
<td>long interval</td>
</tr>
<tr>
<td>2007</td>
<td>28,769</td>
</tr>
<tr>
<td>2008</td>
<td>34,785</td>
</tr>
<tr>
<td>2009</td>
<td>34,567</td>
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</table>

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

Underline represents presenting author.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.
TH-PO956
A Multicenter, Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial of Nabumetone ER Tablets for the Treatment of Uremic Pruritus: Baseline Population Characteristics
Vandana S. Mathur,1 Jayant Kumar,1 Paul W. Crawford,1 Howard Halt,2 Thomas Sciascia.2 1MathurConsulting, Woodside, CA; 2Trevi Therapeutics, New Haven, CT. 1Renal Medicine Associates, Albuquerque, NM; 2Biostatistics, EdrivenConsulting, Wilmington, DE; 1Research by Design, Evergreen Park, IL.

Background: Uremic pruritus (UP) afflicts 30-40% of hemodialysis patients (HDP) and is associated with greater use of ESA and antibiotics. UP is hypothesized to be centrally-mediated via the reduction in endogenous κ/µ opioid ligand ratio. Nabumetone ER tablet (NAL), a κ-opioid agonist and µ-opioid antagonist, is being developed for treatment of UP.

Methods: 373 HDP with moderate or severe UP (Numerical Rating Scale, NRS itch intensity scores >4.5) were randomized to blinded placebo or NAL (60 or 120 mg BID) X 8-wks.

Results: Worsening itch intensity by baseline NRS quartile was monotonically associated with impaired QOL on all instruments as well as with sleep onset latency, anxiety, and depression, but not with age, gender, BMI, ethnicity, itch duration, IPTh, URR, or Kt/V. Black race appeared to be associated with higher NRS.

Conclusions: In addition to the 1st endpoint hypothesis that NAL will reduce itch intensity, the apparent associations between itch intensity and QOL measures at baseline warrant examination by treatment. Unblinded results will be presented.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

TH-PO957
International Variation of Characteristics of Health Literacy and Its Association with Mortality in Dialysis
Kerri L. Cavanaugh,1 Mia Wang,1 Ken Wallston,1 Russell Rothman,1 Ali AlSahow,2 Patricia De Sequera,1 Takeshi Hasegawa,2 2Brian Bieber,2 Brian M. Robinson,2 Ronald L. Pisoni,2 Francesca Tentori.1,2
1Humber University; 2Abor Research; 1Jahra Hospital; 2Hospital Infantia Leonor; 1Fukushima Medical University.

Background: In patients receiving hemodialysis (HD), low health literacy (LHL) is associated with greater use of emergency care, more hospitalizations and higher mortality. Little is known about the characteristics of LHL in HD patients outside of the United States.

Methods: A total of 11,476 DOPPS participants completed the Brief Health Literacy Screen (BHLS) [0-12]. Descriptive statistics were performed overall and by country. Participants characteristics were examined between three health literacy categories using mixed, GEE, and multinomial logistic models. Cox models were applied to examine associations of LHL with mortality adjusting for the above variables and also potential effects of study phase, country, and facility clustering.

Results: LHL prevalence varied across countries (Figure). LHL was more likely in patients who were older, female, unemployed and in those who had fewer years on HD, lower education, and lower income (all P for trend<0.001). LHL was significantly associated with mortality when examined as a continuous score (HR=1.05; 95%CI=1.03-1.08 for each point decreased) or as a category (HR=1.65; 95%CI=1.28-2.12 Low vs. High), and with mortality when examined as a continuous score (HR=1.05; 95%CI=1.03-1.08 for patients who were older, female, unemployed and in those who had fewer years on HD, lower education, and lower income (all P for trend<0.001). LHL was significantly associated with mortality when examined as a continuous score (HR=1.05; 95%CI=1.03-1.08 for each point decreased) or as a category (HR=1.65; 95%CI=1.28-2.12 Low vs. High), and with mortality when examined as a continuous score (HR=1.05; 95%CI=1.03-1.08 for)

Conclusions: LHL is common worldwide among HD patients. Variability in LHL prevalence across countries may be in part explained by cultural differences as well as health care systems. Vulnerable patients are at highest risk of LHL, and LHL is an independent predictor of mortality. Further examining by country the role of health system practices may help to overcome LHL-related barriers to patient engagement and improve outcomes in hemodialysis.

Funding: Pharmaceutical Company Support - The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. Additional support for specific projects and countries is also provided in Canada by Amgen, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support); in Germany by Hexal, DGN, Shire, WiNe Institute; for PDOPPS in Japan by the JSPD. All support is provided without restrictions on publications.

TH-PO958
Evaluation of a Vancomycin Weight-Based Dosing Protocol in Patients Undergoing High-Flux Hemodialysis
Katherine Desorges, Marieme N’Diaye, Robert Zoel Bell, Jean-Philippe Laferraine, Vincent Pichette, Michel Vallee.
Nephrology, Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.

Background: Hemodialysis patients are frequently subject to Gram-positive infections including Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus (MRSA). Vancomycin is an antibiotic of choice in this population to treat these infections. The objective of this project was to validate the performance of a pre formatted individual prescription protocol of vancomycin in its capacity to reach target vancomycin serum concentrations of 10 to 30 mg/L for Gram-positive infections and 15 to 20 mg/L for MRSA infections.

Methods: The records of 84 patients diagnosed with end-stage renal disease undergoing a 4-hour, three times weekly high-flux hemodialysis treatment were analyzed retrospectively. All patients received vancomycin according to a weight-based dosing protocol between 2011 and 2014. Patients < 70 kg received a 1000 mg loading dose followed by a 500 mg maintenance dose at each dialysis session. Patients between 70 and 100 kg received a 1500 mg loading dose followed by a 750 mg maintenance dose. Patients > 100 kg received a 2250 mg loading dose followed by a 1000 mg maintenance dose.

Results: We collected and analyzed 189 dosages of 84 patients. For all assays, 95.2% achieved levels between 10 and 30 mg/L and 50.3% achieved levels between 15 and 20 mg/L. Stratified by weight categories, for the 10 to 30 mg/L target, 93.3% of patients < 70 kg, 100% of patients between 70 and 100 kg and 89.5% of patients > 100 kg achieved the target serum concentrations. For the 15 to 20 mg/L target, 49.3% of patients < 70 kg achieved the target serum concentrations (mainly below), 61.3% of patients between 70 and 100 kg achieved the target serum concentrations and 31.6% of patients > 100 kg achieved the target serum concentrations (mainly higher, but below 30 mg/L).

Conclusions: The vancomycin weight-based dosing protocol achieved target serum concentrations of 10 to 30 mg/L in 95.2% of patients. However, because half the dosages of patients < 70 kg were below the target of 15 to 20 mg/L, vancomycin bolus and maintenance doses should be adjusted upward in this subgroup. No dose change is suggested in the other subgroups.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO959
Trends in Incident ESRD Counts Initiating Dialysis in Freestanding Facilities Have Regional Variation
David T. Gilbertson.1 Peer Kidney Care Initiative Investigators.1,2 CDRG, MRF, Minneapolis, MN; Peer Kidney Care Initiative.

Background: Overall rates of incident end-stage renal disease (ESRD) patients initiating dialysis in freestanding units have stabilized, and the growth in counts of incident ESRD patients began to slow by the beginning of this decade. We assessed trends in incident ESRD counts from 2004–2011, overall and geographically by the 9 US Census Divisions.
Methods: Data were ascertained from the Centers for Medicare & Medicaid Services ESRD database. For annual incident cohorts, we identified patients with their first outpatient dialysis within 3 months of initiating chronic dialysis in a freestanding facility.

Results: Yearly counts increased through 2010, with an average annual percent increase of 2.7% from 2004 to 2011. Between 2009 and 2011, this average percent increase was relatively unchanged (1.6%). However, there were regional differences, with increased New England Census Division experiencing the largest proportionate decrease in incident patients between 2009 and 2011, while the contiguous Middle Atlantic division averaged the highest increase during the same period by 2011.

Conclusions: Overall trends in dialysis incidence reveal substantial geographic variation that has not been explained, suggesting that an assessment based on overall U.S. counts may mask important regional differences. Whether these trends will continue in the face of increasing diabetes rates, an aging population and shifts in social demographic changes is uncertain and will require more detailed analysis.

Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renals Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota., Private Foundation Support

TH-PO960

Assocation of Intradialytic Hypoxemia with Hospitalization and Mortality: Results from a Large U.S. Hemodialysis Cohort

Nancy Ginsberg,1 Xiuling Ye,1 Stephanie Thijsen,1 Icahn School of Medicine at Mount Sinai, New York, NY; 1Renal Research Inst, New York, NY; 2Univ of Gruz, Austria; 3Univ of California - Santa Barbara, CA; 4Columbia University, New York, NY.

Background: While intradialytic hypoxemia is recognized since the early days of hemodialysis (HD), its associations with hard clinical outcomes have not yet been assessed.

Methods: We analyzed arterial oxygen saturation (SaO2) data obtained by Crit-Line™ monitor (CLM) in chronic HD patients treated between 1/2002 and 1/2015. An individual 6-month baseline with at least 10 CLM measurements preceded a 12-month follow-up. Prolonged intradialytic hypoxemia (PIH) was defined as SaO2 ≤ 90% for more than 1/3 of treatment time. Patients were stratified based on the presence or absence of PIH.

Results: We conducted Cox proportional hazards analysis with adjustment for age, gender, race, vintage, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes, albumin, hemoglobin, erythropoietin (EPO) dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain, post-HD systolic blood pressure, and ultrafiltration rate. PIH was associated with a higher hazard of hospitalization and mortality compared to patients without PIH (HR: 1.24, 95% CI: 1.11-1.38, p<0.001). The increases in hospitalization and mortality were most prominent in patients with both PIH and lower albumin and hemoglobin levels.

Conclusions: Prolonged intradialytic hypoxemia (PIH) is associated with increased risk for hospitalization and mortality. A better understanding of the pathophysiology of PIH, its clinical consequences and its medical management requires future basic and clinical research.

Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renals Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota., Private Foundation Support

TH-PO961

A New Poly methyl methacrylate Membrane (PMMA) Improves the Membrane Adhesion of Blood Components and Clinical Efficacy

Lauren J. Sexton,1 Donal J. Sexton,2 Scott Reule, Robert N. Foley, Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Though the management of scleroderma continues to evolve it is unknown whether the burden of ESRD from scleroderma has changed.

Methods: We examined United States Renal Data System data (N = N = 1,557,117) for the years 1995-2010 to calculate incidence rates and outcomes of ESRD due to scleroderma. We conducted Cox proportional hazards analysis with adjustment for age, gender, race, vintage, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes, albumin, hemoglobin, erythropoietin (EPO) dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain, post-HD systolic blood pressure, and ultrafiltration rate. PIH was associated with a higher hazard of hospitalization and mortality compared to patients without PIH (HR: 1.24, 95% CI: 1.11-1.38, p<0.001). The increases in hospitalization and mortality were most prominent in patients with both PIH and lower albumin and hemoglobin levels.

Conclusions: Prolonged intradialytic hypoxemia (PIH) is associated with increased risk for hospitalization and mortality. A better understanding of the pathophysiology of PIH, its clinical consequences and its medical management requires future basic and clinical research.

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TH-PO962

Outcomes of Infants Receiving Chronic Peritoneal Dialysis

Hongying Dai,1 Laurel K. Willig,1 Bradley Warady,1 1Nephrology, Children's Mercy Hospital, Kansas City, MO; 2Research Development and Clinical Investigation, Children’s Mercy Hospital, Kansas City, MO.

Background: Outcome data for infants receiving chronic peritoneal dialysis (CPD) is limited and has been reported primarily by small voluntary registries. The impact of treatment era has also been poorly studied.

Methods: The USRDS database was reviewed for demographic features and outcomes of patients who initiated CPD in the first year of age from 1990-2014.

Results: A total of 1,730 infants (575 £1 month and 1155 >12 months) who initiated CPD at £12 months from 1990-2014 were identified. Overall, 68% of the infants were male and the most common primary diagnoses were obstructive uropathy (31.8%) and congenital renal dysplasia/hypoplasia (29.9%). Mean age at initiation of CPD was 0.4 months (±0.3 months) in infants £1 month and 5.2 months (±3.1 months) in infants >12 months.

Conclusions: The new PMMA (NF) membrane may improve the QOL of chronic dialysis patients by stabilizing the platelet and peripheral circulation.

Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renals Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota., Private Foundation Support

TH-PO963

ESRD from Scleroderma in the United States 1995-2010

Donal J. Sexton,1 Scott Reule, Robert N. Foley, Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Whether the burden of ESRD from scleroderma has changed.

Results: ESRD rates due to scleroderma in 1995-1996 were 0.6 per million per year in the overall population, with higher rates in age 40-64 (9.0) and ≥ 65 (14.1) years, females (0.8) and African Americans race (0.9). Standardized incidence ratios declined between 1995-1996 and 2009-2010 in the overall population (ratio 0.55), in those aged 40-64 yrs (0.49), 65+ yrs (0.62), in male (0.56) and female sex (0.55), in white AA (0.37). Characteristics of ESRD from scleroderma included age 40-64 (57.9% Vs. 41.3% yrs.), female sex (76.6% Vs. 45.1%) and white race (78.1% Vs. 65.2%). 74.3% of patients with scleroderma died over a mean observation period of 3.3 years, while 16.9% were
listed for renal transplant and 10.1% received a renal transplant. With matching for age, sex and race, overall mortality rates were higher in scleroderma cases than controls (22.3 vs. 15.5 per 100 person-years, P < 0.001). Overall rates of listing for renal transplant (8.4 vs. 8.5 per 100 person-years, P = 0.92) and rates of transplantation (4.1 vs. 4.3 per 100 person-years, P = 0.66) were similar in scleroderma cases and controls.

Results: The incidence of ESRD from scleroderma appears to have declined in the United States since 1995. Mortality rates on RRT are higher in scleroderma cases than controls taken from ESRD from other causes. However, listing for and receiving a renal transplant were as likely in scleroderma patients as matched controls.

TH-PO964

Background: As the prevalence and mortality associations of protein-energy wasting (PEW) syndrome criteria in the MHD population are not well established, we examined these in 1480 MHD pts in the HEMO Study, a multi-center RCT to examine the effects of dialysis dose and dialyzer flux on mortality.

Methods: The prevalence of International Society of Renal Nutrition and Metabolism PEW criterion (listed in the table) at the 12 m follow-up visit were examined. Subsequent mortality associations were examined in Cox models adjusted for demographics, duration of ESRD, Kt/V and flux groups, smoking and alcohol use.

Results: There were 632 deaths / 3390 yrs of follow-up. The prevalence of PEW criterion varied widely: 0% for low body fat% to 64% for low DEI (figure).

<table>
<thead>
<tr>
<th>PEW Criterion</th>
<th>All-cause mortality HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Alb &lt; 3.5 (g/dl)</td>
<td>2.12 (1.68, 2.69)</td>
</tr>
<tr>
<td>Serum Chol &lt; 100 (mg/dl)</td>
<td>3.68 (2.46, 5.50)</td>
</tr>
<tr>
<td>BMI &lt; 23 (kg/m²)</td>
<td>1.51 (1.23, 1.86)</td>
</tr>
<tr>
<td>Wt loss &gt; 10%</td>
<td>1.95 (1.47, 2.58)</td>
</tr>
<tr>
<td>Muscle mass category</td>
<td></td>
</tr>
<tr>
<td>Low MAMC*</td>
<td>2.00 (1.60, 2.50)</td>
</tr>
<tr>
<td>Dietary protein intake (DPI) ≤ 0.60 (g/kg/day)</td>
<td>1.10 (0.80, 1.24)</td>
</tr>
<tr>
<td>Dietary energy intake (DEI) ≤ 25 (kcal/kg/day)</td>
<td>0.87 (0.72, 1.05)</td>
</tr>
</tbody>
</table>

*as none had body fat% < 10%, this variable could not be examined; 10% or more lower than the 50th percentile of reference population

Conclusions: As there is a wide variability in the prevalence of PEW criteria, the thresholds used in their definition need to be further refined. Dietary variables were not associated with mortality and the validity of these variables as PEW criteria also needs further study.

Funding: NIDDK Support

TH-PO965
Primary Care Physician Involvement in the Care of Chronic Dialysis Patients in the U.S. Vahakn B. Shahinhian, Deanna Chyn, Yi Li, John Z. Ayanian, Richard Hirth, William H. Herman, Rajiv Saran. Univ of Michigan.

Background: Current health reform efforts aimed at improving quality and value center around delivery of good primary care. However, national patterns of primary care physician (PCP) involvement along with a nephrologist in the care of chronic dialysis patients are unknown.

Methods: Patients on chronic dialysis during 2010-11 with Medicare as the primary insurer were identified using US Renal Data System (USRDS) data. PCP involvement was defined based on a claim for an outpatient (non-dialysis) visit with a physician specializing in family practice, general internal medicine or geriatrics. Patients were characterized with respect to two aspects of preventive care: influenza vaccination and diabetes care.

Results: The sample included 179,645 patients, 81,272 of whom were diabetic. In 2010, 59% of patients had evidence of PCP involvement based on 1 outpatient visit. Patients with PCP involvement were older and more likely to be female, white and with diabetes as cause of ESRD (Table). Rates of vaccination and diabetes care were higher in those with PCP involvement, even after adjustment (ORs: 1.48 [1.45-1.51] for vaccination and 1.53 [1.48-1.58] for a composite of diabetes care).

<table>
<thead>
<tr>
<th>Patient Characteristics or Delivered Care</th>
<th>PCP Involvement (1+ Visit in 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at ESRD (SD)</td>
<td>52.1 (17.6) vs. 57.8 (16.0)</td>
</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td></td>
<td>40.2</td>
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<td></td>
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<td>Race</td>
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<td>Primary Disease Causing ESRD</td>
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<td>35.8</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td>Influenza Vaccination</td>
</tr>
<tr>
<td></td>
<td>9.2</td>
</tr>
<tr>
<td>Diabetes-related care (among diabetic patients)</td>
<td>No (N=29,524) vs. Yes (N=51,748)</td>
</tr>
<tr>
<td>1+ HbA1C test</td>
<td>75.9%</td>
</tr>
<tr>
<td>1+ Lipid test</td>
<td>65.5%</td>
</tr>
<tr>
<td>1+ Diabetic eye exam</td>
<td>36.3%</td>
</tr>
<tr>
<td>All 3 tests</td>
<td>24.1%</td>
</tr>
</tbody>
</table>

By a more restrictive definition of ≥2 visits in 2010, 47% had PCP involvement; under a looser definition of ≥1 visit over 2 years (2010-11), vs 70%, had PCP involvement.

Conclusions: Even under the looser definition of PCP involvement, over one quarter of dialysis patients have no evidence of PCP involvement. Patients with PCP involvement have higher rates of preventive care, but further study should examine the impact on outcomes and costs.

Funding: NIDDK Support

TH-PO966
Are We Choosing Wisely? A Study of Colon Cancer Screening Practices Among Dialysis Patients in the United States Christopher A. Carlos, Chi-yuan Hus, Meda E. Pavkov, Nilka Rios Burrows, Vahakn B. Shahinhian, Rajiv Saran, Neil R. Powe, Kirsten L. Johansen. 1Univ of California, San Francisco, San Francisco, CA; 2Univ of Michigan, Ann Arbor, MI; 3Centers for Disease Control and Prevention, Atlanta, GA.

Background: Because estimated net gains in life expectancy are very small, the American Society of Nephrology recommended against routine cancer screening in asymptomatic dialysis patients. We aimed to determine how often colon cancer screening is performed in the U.S. and whether colon cancer screening is targeted toward healthier dialysis patients. Methods: We performed a retrospective cohort study of patients aged ≥50 years on dialysis between January 1, 2007 and September 30, 2012 using data from the United States Renal Data System (USRDS). Using multivariable Cox regression models, patients were divided into quartiles based on the risk of death and the likelihood of receiving a kidney transplant and, according to these quartiles of risk, we then assessed the likelihood of colon cancer screening (CCS) by fecal occult blood testing, sigmoidoscopy and colonoscopy from Medicare claims data.

Results: Of 391,616 patients, 13% received CCS over a median follow-up of 1.5 years (interquartile range 0.7-2.9). Screening was most common in patients with the lowest mortality risk (16%), compared with 9% of those with the highest mortality risk (HR 1.33;
Severe Sepsis Hospitalizations in Those on Maintenance Dialysis – National Trends and Outcomes
Ankit Sakhuja,1 Kianoush Banaei-Kashani,2 Hatem Amer,2 Robert C. Albright,1 Nephrology and Mayo Clinic.

Background: Severe sepsis (SS) is a life-threatening condition requiring early diagnosis and management. Incidence of SS is increasing in general population (GP) and mortality is declining; however, epidemiology and outcomes of SS have not been well studied in those on maintenance dialysis (MD). We designed this study to look at incidence and outcomes of SS in those on MD.

Methods: Using Nationwide Inpatient Sample database we included all hospitalizations (age ≥ 20 yr) with SS based on ICD-9-CM codes of severe sepsis, septic shock or blood stream infection with organ dysfunction from 2005 to 2010. Those on MD were identified based on ICD-9-CM codes. Age adjusted incidence of SS and mortality in subgroups was calculated by direct standardization to 2000 standard US population. Linear regression was used to assess trends over time and logistic regression to assess independent effect of MD on mortality.

Results: Of estimated 5,000,152 (95% CI: 4,798,520-5,201,784) hospitalizations with SS, 6.4% were on MD. Unadjusted incidence of SS was 145.4/1000 in MD compared to 3.5/1000 in GP with incidence rate ratio 40.9 (95% CI: 40.8-40.9). Age adjusted incidence of SS seems to be increasing in both subgroups though trend was not significant in MD (Fig 1).

Conclusions: Our findings suggest that screening was appropriately targeted to dialysis patients with longer life expectancies and away from those with the lowest chances of receiving kidney transplantation.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO967

Unadjusted in-hospital mortality is higher in MD (30.3% vs 26.2%; p<0.001). Age-adjusted mortality is decreasing in both subgroups though trend was not significant in MD. Age-adjusted mortality continues to be higher in MD (Fig 1). MD is an independent risk factor for mortality with OR 1.26 (95% CI: 1.23-1.29).

Conclusions: Hospitalizations with SS are over 40 times more common in MD. Mortality is higher in MD and being on MD is an independent predictor of mortality in those admitted with SS. Though incidence of SS seems to be increasing, there is a trend towards decrease in mortality even in MD.

TH-PO968

Trends in Colorectal Cancer Screening in U.S. End-Stage Renal Disease Population
Kevin C. Abbott,1 Chyng-Wen Fuw,1 Paul L. Kimmel,1 Paul W. Eggers,1 Div of Kidney, Urologic Hematologic Diseases, NIDDK, NIH, Bethesda, MD; 2Social & Scientific Systems, Inc., Silver Spring, MD.

Background: Screening for colorectal cancer (CRC) has been recommended for those over 50 years old. Medicare coverage of CRC screening began in 2000. Dialysis patient care is shared by many practitioners, perhaps leading to therapeutic nihilism and insufficient screening. CDC data show almost 2/3 of patients at risk report CRC screening. We determined rates of CRC screening in ESRD hemodialysis (HD) patients, compared to a 5% Medicare sample, and to assess secular trends.

Methods: We used data from the 2001-2011 USRDS to describe trends in percentages of HD patients receiving CRC screening tests per year. We limited our study population to patients with Medicare Part A and B as primary payer to ensure complete Medicare claims data for CRC screening. Current Procedural Terminology /Healthcare Common Procedure Coding System (CPT/HCPCS) codes identified Medicare physician and supplier billing data for screening: colonoscopy (G0105 and G0121), sigmoidoscopy (G0104), and fecal-occult blood test (F0BT; G0107, G0328, and 82270). We compared HD data to a 5% Medicare sample.

Results: Overall, the proportion of HD patients having CRC screening decreased from 6.1% annually in 2001 to 3.5% in 2011 due to decreased use of FOBT. There was a persistent increase in the proportion of patients with colonoscopy or sigmoidoscopy for CRC screening in the 11-year study period, from 0.3% to 1.0% annually. In most years, male, black and age 50-75 patients were more likely to receive colonoscopy or sigmoidoscopy than female, white, and other age subgroups. In 2006, the most recent available comparable year, CRC screening in HD patients was less than that of the general Medicare population; 0.8% vs. 1.6% annually for colonoscopy and sigmoidoscopy, 0.4% vs. 8.1% including FOBT.

Conclusions: Screening for CRC in ESRD HD patients is less frequent than in the general Medicare population, and considerably less than CDC recommendations. Differences in ascertainment methods (CDC uses self-report) may account for most of the disparity from CDC estimates.

Funding: NIDDK Support

TH-PO969

Increasing Prevalence of Withdrawal from Dialysis: Trends from 2004-2011
James B. Wiener,1 Peer Kidney Care Initiative Investigators.2 CDCRG, MMRF; 2Peer Kidney Care Initiative.

Background: Voluntary withdrawal from dialysis, which frequently occurs when a patient perceives dialysis as having become unduly burdensome, is an area of increasing interest. How early withdrawal, defined as that occurring within 1 year of dialysis initiation, has changed over the past decade has not been fully explored.

Methods: Patients initiating dialysis between 2004 and 2011 were selected from the Centers for Medicare & Medicaid Services End-Stage Renal Disease (ESRD) database. Information on withdrawal was ascertained from the ESRD Death Notification Form by the presence of code 104 (“withdrawal”) in the 1st or 2nd position. The unadjusted cause-specific monthly mortality rate (deaths per 100 pt-years) was calculated for patients initiating in each year.

Results: Annual incidence counts ranged from 87,174 (2004) to 100,665 (2011). Overall, during the first year of dialysis, the withdrawal rate was highest soon after initiation, peaking at month 2 for all years except 2004. Rates then decreased until approx. month 9, stabilizing through month 12. Additionally, early rates more than tripled over the study period, from 1.9 per 100 pt-years at month 2 in 2004 to 5.9 in 2008 to 6.4 in 2011.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: Withdrawal rates are high in the weeks immediately after dialysis initiation, a pattern more marked in recent years. Because patients who withdraw soon after initiation may be suboptimal dialysis candidates, future work should focus on determining whether a tailored approach, designed to identify individual patient goals and present the risks and benefits of dialysis and viable alternatives such as conservative care, might provide optimal patient-centric care.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic Inc., DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care. In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, MN, Private Foundation Support

TH-PO970
The Dialysis Sodium Gradient – A Modifiable Risk Factor for Fluid Overload

Background: Fluid overload in patients on conventional hemodialysis is a frequent complication associated with increased hospitalizations, cardiovascular morbidity and all-cause mortality. There are multiple patient and physician-related factors that lead to fluid overload. Individualizing dialysate sodium prescription and minimizing the sodium gap are potential modifiable risk factors.

Methods: We performed a cross-sectional study on 111 prevalent stable conventional hemodialysis patients at the McGill University Health Center. The associations of sodium gradient with various hemodialysis parameters of fluid status including interdialytic weight gap, ultrafiltration (UF) rate, blood pressure (BP), intradialytic hypertension and intradialytic hypotension were analyzed.

Results: The mean serum sodium gradient was 4.6 ± 3.6 mEq/L with a mean pre-dialysis sodium of 137.4 ± 2.5 mEq/L and a mean dialysate sodium of 142.0 ± 3.6 mEq/L. There was a direct correlation between sodium gradient and interdialytic weight gain percentage (IDWG), ultrafiltration (UF) rate, blood pressure (BP), intradialytic hypertension and intradialytic hypotension were analyzed.

Sodium Thiosulfate Therapy Calcific Uremic Arteriolopathy: Mortality Outcomes with and without
Therapy
Chamberlain L. Obialo, Alexander Quarselle. Dept of Medicine, Morehouse School of Medicine, Atlanta, GA; Clinical Research Center, Morehouse School of Medicine, Atlanta, GA, Venezuela.

Background: Calcific uremic arteriolopathy (CUA) or Calcinosis is commonly seen in patients with end stage kidney disease (ESKD) and carries a high mortality risk. There is no definitive therapy for this condition but promising results have been reported in patients treated with intravenous sodium thiosulfate (STS). However, the mortality advantage of therapy with STS over therapy without STS remains unknown.

Methods: We retrospectively reviewed our ESKD patient’s records over a 10-year period and identified 45 biopsy confirmed cases of CUA. Associations between patients who received STS therapy and those who did not and various categorical end points were assessed using the Pearson chi-squared tests while differences in continuous end points were examined using Mann-Whitney- U tests. Survival analysis utilized Kaplan-Meier plots. All statistical tests were two-sided, and level of significance set at 0.05.

Results: The mean age of the 45 cases was 63, 60% female, mean body mass index was 34 and mean dialysis vintage was 4 years. Of the 45 cases, 23 (51%) received STS while 22 (49%) did not. The mean serum albumin, phosphorus and parathyroid hormone was 2.8 g/dl, 6.7 mg/dl and 989 pg/dl respectively. One – year mortality was 22% in STS vs. 50% in no STS cases, p = 0.05. The overall survival of the patients over the 2- year study period was significantly superior in the recipients of STS than in those who did not receive STS, p = 0.03.

Patients who did not receive STS were also more likely to have major surgeries than those who received STS, 86% vs. 52%, p = 0.01.

Conclusions: Sodium thiosulfate therapy appears to confer both short term and long term survival advantage over no STS. We encourage hospitals and dialysis companies to procure and make this agent more available to physicians.

Funding: Clinical Revenue Support

TH-PO972
Effect of High-Dose and High-Flux Hemodialysis on Markers of Inflammation in the HEMO Study
Kristen L. Nowak,1 Tom Green,2 Jian Ying,2 Alfred K. Cheung,2 Michel Chonchol,1 1Univ of Colorado Denver; 2Univ of Utah.

Background: Hemodialysis treatment induces markers of inflammation, which could affect clinical outcomes. This study sought to determine whether high-dialysis dose and high-flux dialysis would improve markers of inflammation compared with standard dialysis dose and low flux dialysis.

Methods: The HEMO Study was a randomized multicenter study of the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum high sensitivity C-reactive protein (hs-CRP, pre-specified primary outcome for this set of analyses) and interleukin-6 (IL-6) were measured in stored serum samples in 1,846 HEMO participants. For each inflammatory marker we used a joint multi-state modeling approach to estimate the proportion of patients in 5 ordered states (S) over 3 annual assessments while accounting for mortality: S1=deceased (score=0), S2=alive in highest quartile (score=1), S3=alive in 2nd quartile (score=2), S4=alive in 3rd quartile (score=3), and S5=alive in lowest quartile (score=4). The average rank was computed over 3 yrs of follow-up and compared between the randomized groups.

Results: Randomized patients had high rates of coexisting conditions: 45% had diabetes, 80% had a history of cardiac disease. Characteristics of the patients in the two dose groups were similar, as were the characteristics of those in the two flux groups. The state distribution of hs-CRP in each year by dose (KTV) group and by flux group for hs-CRP are shown in Figure 1.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Comorbidity Data Source May Impact SMR/SHR Calculation

Jiannong Peng, 1  Jie Li, 2  Jiannong Peng, 1

TH-PO973

Comorbidity Data Source May Impact SMR/SHR Calculation

Jiannong Peng, 1  Mahesh Krishnan, 2  Jincheng Zhou, 1  Kimberly M. Nieman, 1  Yi Peng, 1  David T. Gilbertson, 1

CDRG, MMRF, MPLS, MN; 2 DaVita Healthcare Partners, Denver, CO.

Background: Standardized mortality and hospitalization ratios (SMRs and SHRs) are used to measure dialysis facility performance, with adjustment for demographics and comorbidities derived from the end-stage renal disease (ESRD) Medical Evidence (ME) Report. Sensitivities are low for ME-based comorbidities. We investigated the effect on SMR and SHR calculations by comparing ratios adjusted for claims-based comorbidities.

Methods: Using the USRDS ESRD database, we included US hemodialysis patients who initiated dialysis July 1-December 31, 2006-2010, had Medicare as primary payer, were aged ≥ 66 years, and had no prior transplant (TX). Patients were followed from dialysis initiation to the earliest of death, TX, modality change, or 1 year. SMRs and SHRs were calculated for patients in for-profit/non-profit and rural/urban facilities for ME-based and claims-based comorbidity, separately. Cox models were used for expected number of deaths and piecewise Poisson models for expected number of hospitalizations. Agreement of comorbidity between the two sources was measured by a kappa statistic.

Results: 73,950 incident hemodialysis patients were included. Kappas for comorbidity agreement were low, less than 0.5, except for diabetes (0.77). Percent of patients with claims-based comorbidity was similar for for-profit and non-profit facilities; ME-based comorbidity was lower for for-profit facilities. Differences between ME-based and claims-based SMR/SHR, claims-based ratios decreased 0.9%/0.6% for for-profit and 1.0%/0.7% for urban facilities and increased 3.4%/2.8% for non-profit and 5.9%/4.1% for rural facilities.

Conclusions: Comorbidity data source may impact performance evaluation. The impact is larger for smaller groups, and may increase with prevalent patients included.

Funding: Pharmaceutical Company Support - DaVita Clinical Research, DaVita HealthCare Partners Inc., Denver, Colorado

TH-PO974

Thematic Analysis of the Medical Records of a National Cohort of Patients Who Initiated Maintenance Dialysis: 2000-2009

Susan P.Y. Wong, 1  Elizabeth Vig, 1  Nilka Rios Burrows, 2  Chuan-fen Liu, 1  Desmond Williams, 2  Paul L. Hebert, 1  Ann M. O’Hare, 1

1Univ of Washington; 2Center for Disease Control.

Background: Little is known about how decisions to initiate dialysis take shape in clinical practice.

Methods: We performed a qualitative thematic analysis of the medical records of patients who initiated maintenance dialysis to understand factors that impact decisions to initiate maintenance dialysis as they occur in clinical context. We analyzed key care processes, patient-provider interactions and patient and/or provider concerns and considerations relevant to the decision to initiate dialysis as documented in the electronic medical records of a national random sample of patients for whom the decision to initiate maintenance dialysis was made at the Department of Veteran Affairs between 2000 and 2009 (n=1,691).

Results: We identified three dominant, overlapping themes pertaining to the decision to initiate dialysis: 1) dialysis initiation as process, which describes the decision to initiate dialysis as integrated with other treatment decisions and unfolding over time rather than an isolated decision occurring at a fixed point in time; 2) sources of momentum for dialysis initiation, which describes factors that appeared to hasten the process of dialysis initiation and included hospitalization for acute illness and efforts to optimize patients’ clinical status for future medical interventions; and, 3) push-pull dynamics between patients and providers, which describes the sometimes adversarial relationship between patients and providers during the process of dialysis initiation in which patients were often portrayed by providers as “resistant” to dialysis initiation while providers appeared paternalistic and safety conscious in their approach towards treatment decisions.

Conclusions: Our analysis of the medical record underscores the complexity of treatment decisions about dialysis initiation in real-world clinical settings and supports a re-conceptualization of dialysis initiation as a process that unfolds over time rather than as a discrete treatment decision occurring at a fixed point in time.

Funding: Other U.S. Government Support, Veterans Administration Support

TH-PO975

Trends in 30-Day Readmission Rates in Dialysis Patients During an Era of Medicare Payment Policy Changes, 1996-2012

Allan J. Collins, 1  Peer Kidney Care Initiative Investigators.

1MMRF; 2Peer Kidney Care Initiative.

Background: High hospital readmission rates, which may indicate inadequate quality of care and result in unnecessary expenditures, have been a recent focus for Medicare. Medicare has enacted payment-related policy changes: freezing the inpatient payment rate (1997), expanding “disproportionate share” hospital payments (early 2000s), tying

hsCRP did not differ significantly between dose (p=0.83) or flux groups (p=0.53). Similar results were obtained for IL-6.

Conclusions: Over 3 years, neither high-dose nor high-flux dialysis exhibited a beneficial effect on markers of inflammation.
reimbursement for outpatient hemodialysis services to the number of monthly visits (2004), introducing the new Medicare prospective payment system (2011), and instituting the “hospital payment penalty” (2012). Given evidence demonstrating links between these changes and readmission rates in the general population, we sought to examine changes in 30-day readmission rates in dialysis patients 1996–2012.

Methods: Data were obtained from the Centers for Medicare & Medicaid Services End-Stage Renal Disease database. Dialysis patients were assessed for discharges from short-term or critical access hospitals. Thirty-day readmission rates were calculated, without adjustment for differences in patient case-mix or hospital characteristics.

Results: All-cause readmission rates increased modestly over the period studied except for 2012. The rate was 32.8% in 1998; the rate increased to 34.6% in 2005, fell to 34.1% in 2009, and peaked at 34.8% in 2010. Discharge data in the first 6 months of 2012 showed further decrease (32.8%). In comparison, other studies show that the rate in the general Medicare population was generally stable 2007-2011 (19.0%), and decreased in 2012 (18.4%).

Conclusions: Thirty-day readmission rates were substantial in dialysis patients compared with general Medicare patients, possibly reflecting case-mix. How public policy changes may have affected potentially avoidable readmissions should be more fully explored. Cause-specific readmission rates might provide a better reflection of quality of care and should be examined.

Funding: Pharmaceutical Company Support - Financial support for Peer is provided by 13 participating dialysis provider organizations: American Renal Associates, Atlantic Dialysis Management Services, Centers for Dialysis Care, DaVita HealthCare Partners, Dialysis Clinic, Inc. (DCI), DSI Renal, Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Renal Ventures Management, Satellite Healthcare, The Rogosin Institute, and U.S. Renal Care.

In collaboration with the Chief Medical Officers of these organizations, the Peer Kidney Care Initiative is operated by the Chronic Disease Research Group, a division of the Minneapolis Medical Research Foundation, in Minneapolis, Minnesota. Allan Collins, MD, FACP, is the Executive Director of Peer. Allan Collins serves as a co-investigator on Phase I and II studies for DaVita Clinical Research., Private Foundation Support

TH-PO976

The Impact of Volume Status on Nocturnal Hypoxemia in Patients Undergoing Maintenance Hemodialysis Farhana Yousaf, Mittesh K. Patel, Sherbeth Marie C. Young, Chaim Charytan, Alla Goldberg, Bruce S. Spinowitz. New York Hospital Queens, flushing, NY.

Background: Hemodialysis patients experience changes in volume status according to hemodialysis schedule. Excess fluid volume may shift to the neck upon assuming a head-down position during overnight dialysis leading to edema of the soft tissues and peripharyngeal edema. We explored the impact of volume status on nocturnal hypoxemia in the hemodialysis population.

Methods: Following local IRB approval, adult hemodialysis patients who were undergoing regular chronic hemodialysis (HD) for at least 3 months were consented to complete two nights of nocturnal oximetry using Pulsox 300i wristwatch. HD night was defined as the night of HD treatment whereas non-HD night was defined as the night on which no HD was performed. The first hour of recording was deleted in efforts to capture changes and readmission rates in the general population, we sought to examine changes in 30-day readmission rates in dialysis patients 1996–2012.

For the 5 most common causes of hospitalization, the principal cause for readmission was in the same category as the initial admission, accounting for 18-32% of readmissions.

Conclusions: Thirty-day hospital readmission in Medicare recipients on dialysis is frequently linked to rehospitalization caused by the same underlying conditions. Additional research is warranted to further explore this phenomenon and develop preventive strategies.

TH-PO977

Hospital Readmission within 30 Days of Discharge Among Adults Receiving Dialysis Lorenzo D. Dalrymple, Barbara A. Grimes, Patrick S. Roman, Yi Mu, Danh V. Nguyen, Kirsten L. Johansen. 1 UC Davis; 2 UCSF; 3 UC Irvine, San Francisco VA.

Background: Hospital readmission is common in adults receiving dialysis. Few studies have examined the timing or causes of 30-day hospital readmissions.

Methods: We used the USRDS to examine adults initiating dialysis Jan 2009 through Dec 2010 who had Medicare as the primary payer. The cohort was followed from day 90 of dialysis for up to one year, with censoring for death, renal recovery or transplant. We classified the principal cause of the index hospitalization and hospital readmission using Clinical Classification Software.

Results: Our cohort consisted of 103,381 patients. During follow-up, 50,639 patients experienced 89,728 index hospital admissions; 5% resulted in in-hospital death. Of the 85,284 live hospital discharges, 25,792 (30%) were associated with 30-day readmission. The median time to readmission was 11 [5; 19] days. Leading causes of readmission by cause of index hospitalization are in Table 1.

Table 1. Causes of 30-Day Readmission

<table>
<thead>
<tr>
<th>Cause of Readmission</th>
<th>Leading Cause</th>
<th>2nd Leading Cause</th>
<th>3rd Leading Cause</th>
<th>4th Leading Cause</th>
<th>5th Leading Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause</td>
<td>N=99728</td>
<td>Septicemia</td>
<td>CHF</td>
<td>DM</td>
<td>HTN</td>
</tr>
<tr>
<td>Complication of device, implant or graft</td>
<td>N=14195</td>
<td>Septicemia</td>
<td>DM</td>
<td>CHF</td>
<td>HTN</td>
</tr>
<tr>
<td>Septicemia</td>
<td>N=6409</td>
<td>Complication of device, implant or graft</td>
<td>DM</td>
<td>Pneumonia</td>
<td>CHF</td>
</tr>
<tr>
<td>HTN*</td>
<td>N=5380</td>
<td>HTN</td>
<td>Complication of device, implant or graft</td>
<td>CHF</td>
<td>DM</td>
</tr>
<tr>
<td>CHF††</td>
<td>N=322</td>
<td>CHF</td>
<td>HTN</td>
<td>Complication of device, implant, graft</td>
<td>Fluid and electrolyte disorders</td>
</tr>
<tr>
<td>DM‡‡</td>
<td>N=496</td>
<td>DM</td>
<td>Complication of device, implant or graft</td>
<td>Septicemia</td>
<td>HTN</td>
</tr>
</tbody>
</table>

*HTN: Hypertension with complications and secondary hypertension; CHF: Congestive heart failure - nonhypertensive; †DM: Diabetes mellitus with complications

For the 5 most common causes of hospitalization, the principal cause for readmission was in the same category as the initial admission, accounting for 18-32% of readmissions.

Conclusions: Thirty-day hospital readmission in Medicare recipients on dialysis is frequently linked to rehospitalization caused by the same underlying conditions. Additional research is warranted to further explore this phenomenon and develop preventive strategies.

TH-PO978

Racial/Ethnic and Age Differences in Cause-Specific Deaths Among U.S. Dialysis Patients Alison J. Yu, Keith C. Norris, Alfred K. Cheung, Guofen Yan. 1 Univ of Southern California; 2 UCLA; 3 Univ of Utah; 4 Univ of Virginia.

Background: Recent research reported that Hispanics have the lowest all-cause mortality, African Americans (AAs) intermediate, and Whites the highest among U.S. dialysis patients over 30 years old. The objective of this study is to examine whether this risk pattern varied depending on the cause of death.

Methods: The study included 1,255,640 adult incident dialysis patients between 1995 and 2010 in the USRDS, with no prior kidney transplantation. We examined 5 major cause-specific deaths: cardiovascular (CVD), infection, malignancy, others, and unknown. Cause-specific hazards for each cause-specific death were compared among AAs, Hispanics, and Whites for overall and stratified by age groups.

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Results: After adjustment for multiple covariates (Table), compared with Whites, in all age groups, Hispanics consistently had lower risks of cause-specific deaths for all major causes examined (HRs<1), while AAs also had lower risks except for the cause of infection, for which AAs had significantly higher risks in age groups of 50-70 years (HRs from 1.07-1.94).

Table. Adjusted cause-specific hazard ratios (HRs) for AAs and Hispanics vs. Whites

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>CVD</th>
<th>Infection</th>
<th>Malignancy</th>
<th>Others</th>
<th>All-cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>Hispanic</td>
<td>AA</td>
<td>Hispanic</td>
<td>AA</td>
</tr>
<tr>
<td>18-30</td>
<td>0.99*</td>
<td>0.52</td>
<td>1.94</td>
<td>0.81</td>
<td>0.52</td>
</tr>
<tr>
<td>31-40</td>
<td>0.85</td>
<td>0.60</td>
<td>1.51</td>
<td>0.95*</td>
<td>0.82*</td>
</tr>
<tr>
<td>41-50</td>
<td>0.74</td>
<td>0.60</td>
<td>1.07</td>
<td>0.79</td>
<td>0.75</td>
</tr>
<tr>
<td>51-60</td>
<td>0.69</td>
<td>0.63</td>
<td>0.83</td>
<td>0.71</td>
<td>0.86</td>
</tr>
<tr>
<td>61-70</td>
<td>0.74</td>
<td>0.70</td>
<td>0.84</td>
<td>0.81</td>
<td>0.82</td>
</tr>
<tr>
<td>71-80</td>
<td>0.78</td>
<td>0.78</td>
<td>0.98*</td>
<td>0.90</td>
<td>0.92</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.84</td>
<td>0.84</td>
<td>1.07</td>
<td>1.01*</td>
<td>1.06*</td>
</tr>
</tbody>
</table>

Note: all significant at p<0.05 except the ones indicated by *.

Conclusions: The racial difference observed in all-cause mortality, in which Hispanics have the lowest risk, AAs intermediate, and Whites the highest, was also noted for major cause-specific deaths in most age groups, except for the cause of infection. Both younger and older AAs are at the greatest risk of death due to infection. Further studies are needed to explore the specific reasons responsible for the higher risk of infection-related death in AAs.

Funding: NIDDK Support

TH-PO979
Dialysis Therapy and Mortality in Older Heart Failure Patients with Advanced Chronic Kidney Disease: The Kaiser Permanente MATCH Study

David Law, Sijie Zheng, Sharina Belani, Jingrong Yang, Thida Tan, Juan Daniel Ordonez, Susan Kim, Alan S. Go. Kaiser Permanente Northern California.

Background: Heart failure (HF) and chronic kidney disease (CKD) often coexist and those with both have much worse outcomes than having either alone, with limited data to guide optimal management. We evaluated the outcome of dialysis therapy in a diverse elderly cohort with HF and advanced CKD.

Methods: In Kaiser Permanente Northern California, a large integrated healthcare system, we identified members ≥70 years with HF and estimated glomerular filtration rate (eGFR) £20 ml/min/1.73 m² between 2008-2012 and no prior renal replacement therapy, cancer, cirrhosis or organ transplant. Through 2013, we identified patients who started chronic dialysis and individually matched controls who were alive on the dialysis start date of the matched case along with age, gender, diabetes status, and high-dimensional propensity score to start dialysis. Demographics, clinical features and drug use were obtained from electronic records. We calculated rates of death through 2013 and examined the impact of dialysis on mortality using Cox regression.

Results: We identified 334 eligible HF-CKD cases who initiated dialysis and 899 matched control patients ≥20 years old matched on HF characteristics. Mean age was 80.1±4.8 yrs, with 51% women, 33% black and 72% diabetic. Case and control patients were well-matched across characteristics, except for controls being less likely to be Hispanic or have proteinuria, or to receive alpha blockers or thiazide diuretics; and more likely to have prior intracranial bleeding, liver disease, dementia and higher blood pressure, hemoglobin and mean eGFR (16.4 vs. 12.0 ml/min/1.73 m²). Incidence of death was 32 per 100 py in combined case and control patients. Among matched patients, after further adjustment for residual differences in patient features, dialysis was independently associated with a 47% lower rate of death (hazard ratio 0.53, 95%CI:0.41-0.67).

Conclusions: In older adults with HF and advanced CKD, dialysis was independently associated with a lower mortality. Randomized trials are needed to determine the net outcomes of dialysis related to both length and quality of life in the elderly with HF.

Funding: Private Foundation Support

TH-PO980
Gender, Poverty, and Dialysis Mortality in Adults with Sickle Cell Disease


Background: Chronic dialysis patients with sickle cell disease (SCD) have increased mortality compared with the general US dialysis population. The contributions of gender and neighborhood poverty to dialysis mortality in SCD patients are largely unknown.

Methods: Using USRDS data, we linked all US adults with SCD who initiated dialysis between 1995-2012 with zip-code level US Census neighborhood data. We performed multivariable Cox regression models with adjustment for age, dialysis type, BMI, and diabetes status to compare mortality between men and women, stratified by neighborhood poverty level. Neighborhoods with ≥20% of households living below the federal poverty level were defined as poor.

Results: The study cohort included 1,681 SCD patients on dialysis with 52% male, 94.7% black, mean age 42.5, and 55.9% living in poor neighborhoods. 1-, 5-, and 10-year mortality in this population were 26.1%, 67.9%, and 85.5%. Overall, men had similar mortality to women (aHR: 0.96, 95% CI: 0.86-1.07, p=0.45). However, men living in poor neighborhoods had a higher risk of death than women (aHR: 1.20, 95% CE: 1.04-1.40, p=0.015). (Figure 1) The median survival time from dialysis initiation for poor men with SCD was 2.37 years. In comparison, the median survival time for poor men without SCD was 3.77 years.

Figure 1. Dialysis Mortality in Sickle Cell Disease Patients by Gender and Neighborhood Poverty

Conclusions: Men with SCD who live in poor neighborhoods were at highest risk of death. Efforts to address socioeconomic barriers may be an important target for improving survival in this population.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO981
Peritoneal Dialysis (PD) Patient Outcomes Under the Dialysis Prognostic Payment System (PPS)

Marc Turecmen, Regina M. Baker, Jeffrey Pearson, Chad M. Cogan, Parma Mukhopadhyay, Elizabeth L. Cope. Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: The use of PD was expected to be incentivized by the expanded Medicare PPS that was implemented in 2011. There is early evidence under the PPS of additional incident ESRD patients and dialysis facilities using PD (Hirth et al 2013; Turecmen et al 2014). More widespread PD use could have implications for PD outcomes due to potential changes in PD selection or in the experience of dialysis providers with PD. This study assessed PD patient outcomes before and after the new PPS was implemented.

Methods: This study included n=36,582 incident ESRD patients for whom PD was identified as the intended initial dialysis modality on the CMS ESRD Medical Evidence Form during 2008-12. We evaluated 1-year PD technique failure and PD patient mortality using data from Medicare claims, the Standard Information Management System, CRWNWeb, and the CMS Death Notification Form. PD technique failure was ascertained when hemodialysis was used for at least 60 days.

Results: Selection of PD increased from 5.8% to 8.4% of incident patients between 2008 and 2012 (see Figure).

Conclusions: Men with SCD who live in poor neighborhoods were at highest risk of death. Efforts to address socioeconomic barriers may be an important target for improving survival in this population.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO982
key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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During this period, 1-year PD technique failure decreased from 18.8% to 16.1% of patients and 1-year PD patient mortality decreased from 9.4% to 8.6% (see Figure). Outcomes were relatively stable or improving across patient age, race, and Hispanic ethnicity subgroups and for patients in both urban and rural areas.

**Conclusions:** In the context of expanding PD use under the new PPS, there is no early evidence of worsening overall PD patient outcomes or of growing disparities in PD patient outcomes by demographic group or by urban/rural location. Instead, there were lower levels of PD technique failure and PD patient mortality in the initial years of the new payment system.

**Funding:** Other NIH Support - NIA, Private Foundation Support

### TH-PO982

**Cognitive Impairment and Mortality in Adults on the Kidney Transplant Waitlist**  
**Mara McAdams-DeMarco, Hao Ying, Israel O. Olorundare, Dorry L. Segev. Johns Hopkins.**

**Background:** Older adults with poor cognitive function are at increased mortality risk. It is unclear whether ESRD patients of all ages with cognitive impairment are at increased mortality risk of while on the kidney transplant (KT) waitlist.

**Methods:** 918 ESRD patients being evaluated for and waitlisted for KT (no previous listings) at Johns Hopkins were enrolled in a prospective cohort study (11/2009-5/2014). The Modified Mini Mental Status (MMS), a test of global cognitive function (range 0-100, higher scores represent better function) was assessed at KT evaluation. Global cognitive impairment was defined as MMS score<80). Mortality risk by MMS score and cognitive impairment (separately) was estimated using an adjusted Cox proportional hazards model; participants were censored at the waitlist removal, time of KT or administrative end of follow-up.

**Results:** At KT evaluation, the mean (SD and range) age was 54 (14; 18-86), 57% were male, and 46% were African American. The mean (SD and range) MMS score was 82.6(11, 47-100) and 52% were classified as having cognitive impairment. 45 participants died over an average of 1.7 years of follow-up. Mortality risk was greater for adults on the KT waitlist who had worse MMS scores (1 point decrease in MMS score: HR=1.05, 95% CI: 1.02-1.08, P=0.003) and those with cognitive impairment (HR=2.51, 95% CI: 1.91-3.33, P<0.001) versus no impairment.

**Conclusions:** Among adults ESRD patients, impairment in global cognitive function more than doubled the risk of waitlist mortality. A simple screener for global cognitive function scores at the evaluation for first listing would not only identify adults with ESRD who have unrecognized cognitive impairment but also identify a high-risk population.

**Funding:** Other NIH Support - NIA, Private Foundation Support

### TH-PO983

**Indications, Technique, and Outcome of Plasmapheresis in a Large Pediatric Dialysis Center**  
**Rainer Büscher, Lülbert Lübbers, Anja K. Büscher, Peter F. Hoyer. Pediatric Nephrology, Univ of Duisburg-Essen, Pediatrics II, Essen, Germany.**

**Background:** Plasmapheresis (PP) is a established therapeutic option for various indications in pediatric patients. However, there are only few reports with only little information on clinical outcome.

**Methods:** We performed a retrospective analysis involving 86 children and adolescents undergoing PP in our pediatric dialysis unit from 1997 to 2013.

**Results:** Within the observation period, 86 children (41 male), mean age 8.7±3.2 years (3 months to 18.9 years) received PP for a total of 652 sessions (1-33 sessions/patient; mean 6.4±3.1 sessions/patient). Most patients (30.2%) were treated for hematologic disorders. Complications during PP included encephalitis (5.5%), renal failure (1.2%), peritonitis (0.9%), and death (0.5%).

**Conclusions:** In the context of expanding PD use under the new PPS, there is no early evidence of worsening overall PD patient outcomes or of growing disparities in PD patient outcomes by demographic group or by urban/rural location. Instead, there were lower levels of PD technique failure and PD patient mortality in the initial years of the new payment system.

**Funding:** Other NIH Support - NIA, Private Foundation Support

### TH-PO984

**Who Makes the Best Exit Site: Nephrologist or Surgeon?**  
**Vaihbrah S. Keskar, Mallory B. Byiani, Brian Blew, Jeffrey Warhen, Brendan McCormick. The Ottawa Hospital, Univ of Ottawa, Ottawa, ON, Canada.**

**Background:** Buried peritoneal dialysis (PD) catheters are placed months before dialysis is needed and the exit site is created at the initiation of dialysis by the nephrologist. In contrast, the exit site of an unburied catheter is created by the surgeon at the time of insertion. Our PD unit uses both methods of catheter placement. We undertook this study to compare the outcomes of the two methods of exit site creation.

**Methods:** The charts of all patients who initiation PD between Jan 2012 and Dec 2013 were reviewed. At each clinic visit, exit sites were graded by the PD nurse into standard predefined groups: perfect, good, equivocal and infected. Primary outcome was the frequency of perfect exit sites at 2, 6, and 12 months after initiation of PD. Secondary outcomes were exit site infections, peritonitis and technique failure due to exit site infection.

**Results:** 119 patients started PD during the period of interest and 114 remained on PD at 2 months. 52 patients had buried catheters externalized at the time of starting PD (group A) and 62 patients had unburied catheters (group B). Group A had more males (71% vs 48%), had higher mean age (65±14 vs 59±15) and had most of the patients as incident dialysis patients. Diabetic nephropathy was the most common underlying disease in either group (61.53% and 51.61%). Group B had a higher frequency of perfect exit sites at 2 months but this difference disappeared by 6 and 12 months. There was a trend towards more exit site infections in Group A but this did not translate into more technique failure.

**Conclusions:** Buried catheters are less likely to have perfect appearance at two months compared to unburied catheters; however this is no longer significant at six and 12 months. The trend towards more exit site infections with buried catheters suggests that there may be clinical consequences of the tissue trauma at time of exteriorization. Consideration should be given to the use of prophylactic antibiotics at exteriorization.

### TH-PO985

**Prevention of Peritoneal Dialysis Catheter-Related Infections – A Multicenter Randomized Controlled Trial**  
**Mercedes L. Veja, Paula López, Carmen Felipe, Jose Ramon Rodriguez-Palomares, Gloria Del peso, Francisco Javier Alfiajo, Fernando Tornero, Mar'a Jose Fernandez Reyes, Ana M. Tato, Maria Rosario Luque, Jose M. Portoles. Grupo Centro Diálisis Peritoneal, Spain.**

**Background:** Peritonitis, tunnel and catheter exit site (CES) infections are the most serious complications of peritoneal dialysis (PD). We studied the effect of antibiotic ointment (EU/DRAC: 2009-016835-36) on catheter-related infections (CRI) and morbidity.

**Methods:** Allocation was stratified in blocs of 4 centers. Ointment containing 2% colistin, tobramycin, amphotericin B and 4% vancomycin or normal saline were applied to the CES over 1 year. Follow-up period was 3 months after the last dose. Exit site infection (ESI) was defined as erythema, edema or local pain with purulent secretion and positive culture. Antimicrobial therapy was given according to local protocols.

**Results:** 140 patients were included, 6 didn’t meet entry criteria. Characteristics and dialysis parameters of the 65 in the control group (CG) and 69 intervention group (IG) patients were comparable.

**Conclusions:** In the context of expanding PD use under the new PPS, there is no early evidence of worsening overall PD patient outcomes or of growing disparities in PD patient outcomes by demographic group or by urban/rural location. Instead, there were lower levels of PD technique failure and PD patient mortality in the initial years of the new payment system.

**Funding:** Other NIH Support - NIA, Private Foundation Support

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

**Underline represents presenting author.**

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Mean study duration was 0.6 (IG) vs 0.6 (CG) years (ns). 26 episodes of CRF (11 ESL, 4 tunnel, 11 peritonitis) occurred in the CG and 12 in the IG (3 ESL, 0 tunnel, 9 peritonitis) (p=0.001). Etiology of ESI was Staphylococcus aureus (x7), Corynebacterium spp., Pseudomonas aeruginosa, E. coli, Serratia spp., caulase-negative S. (x2) and 1 negative culture in the CG and S. aureus (x1), 1 Gram-negative bacillus and 1 negative culture in the IG. Systemic or topical antibiotics were given for ESI in 11 (CG) and 2 patients (IG) (p=0.01), respectively. Hospital admissions were 23 (CG) and 15 (IG). Local side effects were significantly increased in the IG.

Conclusions: Local prophylaxis with a broad-spectrum antimicrobial ointment is associated with a significant reduction in ESI and systemic antibiotic use without associated bacterial resistance. Significant local side effects were observed.

Funding: Private Foundation Support

TH-PO986

Association Between Plasma Fibroblast Growth Factor-23 and Carotid Artery Atherosclerosis in Peritoneal Dialysis Patients

Nanmyi Liu
Jinmin Hospital of Shanghai.

Background: We investigate the association between plasma fibroblast growth factor-23 (FGF-23) level and carotid artery atherosclerosis of 125 stage 5 chronic kidney disease (CKD5) patients, who are doing continuous ambulatory peritoneal dialysis (CAPD) at renal division of Shanghai Jinmin Hospital in China.

Methods: A retrospective cohort study of individuals 15 years of age and older, divided into two cohorts according to carotid intima-media thickness (CIMT): C. normal cohort (CIMT<0.9mm) and CIMT thickening cohort (CIMT>0.9mm). Plasma FGF-23 concentrations were determined by ELISA. CIMT thickness and atherosclerotic plaques were measured by carotid ultrasound.

Results: Of the 125 PD patients, the CIMT was thickened in 82 patients (65.6%). Compared with the CIMT normal patients, plasma FGF-23 concentration was significantly increased (p=0.01) in the CIMT thickening cohort (Table 1). Linear regression analysis discovered an obvious positive correlation between plasma FGF-23 and CIMT (r=0.416, P=0.006) (Table 2). Multiple regression analysis indicated that plasma FGF-23 level was independent risk factor for CIMT (β=0.421, t=2.607, P=0.003) (Table 3).

Conclusions: The level of plasma FGF-23 was positively correlated with CIMT and played an important role in development of carotid artery atherosclerosis in peritoneal dialysis patients.

Funding: Government Support - Non-U.S.

TH-PO987

Atherogenic Index of Plasma Is Associated with Insulin Resistance in Non- Diabetic Peritoneal Dialysis Patients

My June Lee,1 Jae Eun Im,2 Meiyan Wu,2 Tae ik Chang,2 Tae-Hyun Yoo.1 1Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 2Brain Korea 21 PLUS, Severance Biomedical Science Inst, Yonsei Univ College of Medicine, Seoul, Korea; 3Dept of Internal Medicine, NHIC Ilsan Hospital, Gyeonggi-do, Korea.

Background: Insulin resistance (IR) is an independent risk factor for cardiovascular morbidity and mortality. Although many factors including uremia, chronic inflammation, and abnormal adipokine levels are known to contribute to the development of IR, the role of pro-atherogenic lipoprotein on IR remains unknown in peritoneal dialysis (PD) patients. Therefore, we investigated the independent association between pro-atherogenic lipoprotein and IR in non-diabetic PD patients.

Methods: We conducted a cross-sectional study in 75 non-diabetic PD patients. Pro-atherogenic lipoprotein was assessed by the atherogenic index of plasma (AIP, log transformed triglyceride to high-density lipoprotein cholesterol ratio). IR was determined by homeostatic model assessment-IR (HOMA-IR). Patients were divided into the higher transformed triglyceride to high-density lipoprotein cholesterol ratio). IR was determined by homeostatic model assessment-IR (HOMA-IR). Patients were divided into the higher

Conclusions: IR was determined by homeostatic model assessment-IR (HOMA-IR). Patients were divided into the higher

Funding: Other U.S. Government Support

TH-PO990

Impact of Patient-Centred Automated Peritoneal Dialysis User-Interface on Operator Learning and Confidence

Catherine Firnnek, Mary Gellens, James A. Slood. Medical Affairs, Baxter Healthcare, Deerfield, IL.

Background: Automated peritoneal dialysis (APD) is an underutilized therapy for patients with end-stage renal disease (ESRD). The perception patients may not be able to manage their own treatment setups comes into play in choice of this treatment modality. Improvements to cyclergist technology may help to further simplify therapy for patients,
reducing barriers to uptake. This study aimed to determine whether a cycler-embedded, patient-centric interface offered an enhanced user experience compared to a conventional APD cycler.

Methods: 30 study participants (ages 29-84, mean 50 yrs, 67% male) diagnosed with ESRD were randomized into two groups using cycler with patient-centric user interface with advanced technology in development and a conventional APD cycler. Participants evaluated both cyclers on 2 non-consecutive days using a different cycler each day. Each participant was given a brief orientation, setup task, training session, break, followed by a setup task and questionnaire. Study results were analyzed via Fisher’s exact, Mann-Whitney and Exact binomial tests.

Results: The cycler with patient-centric user interface and advanced technology (in development) scored better on reduced reliance on printed instructions (p=0.001). Patients committed fewer deviations on the cycler in development vs the conventional cycler (2 of 19 vs 14 of 19 respectively) after training (p=0.004), including disinfecting hands (p=0.02) and line handling (p=0.01), and were more confident that they set up the cycler according to specifications (p=0.043). The new cycler scored higher in overall preference among study participants: The cycler with a patient-centric user interface was rated easier to learn (p=0.005) and to use (p=0.016), and users felt more confident operating the new cycler at home compared to conventional cycler interface.

Conclusions: A cycler with embedded, patient-centric interface was rated higher in terms of overall reliance on instructions, task competency, ease of use and learning, preference and overall confidence of using the cyclers. These findings indicate that APD cycler learning and confidence can be enhanced with a patient-centric user-interface.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

THI-P0991
Single-Site Trans-Umbilical Peritoneal Dialysis Catheter Insertion
Mangalakumar Veerarasamy, Nephrology, KMCH, Coimbatore, Tamilnadu, India.

Background: Traditional laparoscopic peritoneal dialysis catheter placement requires two ports incision and this could lead to complications like leak and hernia at the port sites. We describe a novel approach of using single-site trans-umbilical ports that is associated with small scar (less than 1 cm) and reduced complications.

Methods: Under general anaesthesia pneumoperitoneum was created as per standard method. One 10mm port and one 5mm port was inserted through trans-umbilical route to guide peritoneal dialysis catheter insertion. Hernial orifices were inspected and if there was any adhesion present that was released to facilitate free fluid movement. The catheter was inserted through a small incision 1 inch below umbilicus. The catheter was positioned in the pouch of Douglas using lap instrument passed through the trans-umbilical port. The other end of catheter was tunnelled in the standard manner and brought out through the trans-facial port. The latter prevented the omentum migration or any mechanical complication that might require catheter reposition or change. Peritoneal dialysis catheter was inserted through a single-site trans-umbilical port. Hernial orifices were inspected and if there was any adhesion present that was released to facilitate free fluid movement. The catheter was inserted through a small incision 1 inch below umbilicus. The catheter was positioned in the pouch of Douglas using lap instrument passed through the trans-umbilical port. The other end of catheter was tunnelled in the standard manner and brought out through the trans-facial port. The latter prevented the omentum migration or any mechanical complication that might require catheter reposition or change. Peritoneal dialysis catheter was inserted through a single-site trans-umbilical port. Hernial orifices were inspected and if there was any adhesion present that was released to facilitate free fluid movement. The catheter was inserted through a small incision 1 inch below umbilicus. The catheter was positioned in the pouch of Douglas using lap instrument passed through the trans-umbilical port. The other end of catheter was tunnelled in the standard manner and brought out through the trans-facial port. The latter prevented the omentum migration or any mechanical complication that might require catheter reposition or change. Peritoneal dialysis catheter was inserted through a single-site trans-umbilical port. Hernial orifices were inspected and if there was any adhesion present that was released to facilitate free fluid movement. The catheter was inserted through a small incision 1 inch below umbilicus. The catheter was positioned in the pouch of Douglas using lap instrument passed through the trans-umbilical port. The other end of catheter was tunnelled in the standard manner and brought out through the trans-facial port. The latter prevented the omentum migration or any mechanical complication that might require catheter reposition or change.

Conclusions: A combined method of Single-site port placement, omentectomy and loop fixation of intra-abdominal segment of catheter offers the following advantages: small incision, hence risk of leak when catheter was used early after placement is low. The risk of hernia through port site is reduced and small scar will be welcome to image conscious patients. If there was any adhesion present that could be released with minimal trauma to peritoneum. Omentum was folded and pulled upwards to the left upper guardant and fixed to anterior abdominal wall using a trans-facial loop. The latter prevented the omentum wrapping diathesis catheter and causing malfunction. Then the port site was closed in three layers (Video available).

Results: 10 cases underwent catheter insertion with this approach (Male 7, Female 3) and the mean follow up period is 11 months. None of them developed leak or catheter migration or any mechanical complication that might require catheter reposition or change.

Conclusions: A combined method of Single-site port placement, omentectomy and loop fixation of intra-abdominal segment of catheter offers the following advantages: small incision, hence risk of leak when catheter was used early after placement is low. The risk of hernia through port site is reduced and small scar will be welcome to image conscious patients. If there was any adhesion present that could be released with minimal trauma to peritoneum. Omentum was folded and pulled upwards to the left upper guardant and fixed to anterior abdominal wall using a trans-facial loop. The latter prevented the omentum wrapping diathesis catheter and causing malfunction. Then the port site was closed in three layers (Video available).

THI-P0992
Peritonitis and Survival following PD Catheter Insertion in Infants
Joshua Zaritsky, Coral D. Hanevold, Troy Richardson, Jonathan Rodean, John P. Lawlor, Raymond P. Quigley, Alicia Neu, Bradley Warady.

SCOPE Collaborative, CHA, Overland Park, KS.

Background: Chronic peritoneal dialysis (PD) is the dialysis modality of choice for children. However, there are limited outcome data in those who undergo PD catheter (cath) insertion in the 1st year of life. Using data from the Children’s Hospital Association Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (ESRD) Collaborative (SCOPE), we examined peritonitis rates and survival in 156 infants who had a PD cath placed in the 1st year of life. We describe a novel approach of using single-site trans-umbilical ports that is associated with small scar (less than 1 cm) and reduced complications.

Results: In hospital and overall peritonitis rates during the 1st year post cath insertion were 1.73 and 0.76 per-patient-year, respectively. Gran + organisms were responsible for 38.7% of infections (figure); 28% were culture negative. Polycystic kidney disease and pulmonary hypoplasia were more frequent in infants with peritonitis, whereas anuria did not differ between groups (table). Use of a cuffed catheter or plastic adaptor, nephrectomy prior to or concurrent with cath insertion, and G-tube insertion after cath placement were more common in pts with peritonitis, while number of cuffs, surgical technique, cath use within 14 days and cath revision did not differ between groups. Infants with peritonitis had longer initial hospital stays and lower survival compared with those without peritonitis.

THI-P0993
Risk Factors for All-Cause Unexpected Hospitalization After Peritoneal Dialysis Catheter Implantation
Zi Li, Zita C. Abreu, Joanne M. Bargman.

1Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China; 2Nephrology, Toronto General Hospital Univ of Toronto, Toronto, ON, Canada.

Background: Implantation of the peritoneal dialysis catheter (PDC), usually an elective procedure, may necessitate unexpected hospitalization due to multiple co-morbidities and inherent instability of the end-stage renal disease patient. This information is important for administrative planning for a PD program. However, information on hospitalization after PDC implantation is limited and details about the reason for hospitalization are lacking.

Methods: We performed a prospective cohort study in consecutive patients who underwent PDC implantation at a single institution from 2007 to 2013. Clinical characteristics of enrolled patients, technique of the implantation procedure and all-cause unexpected hospitalization and morbidity within 14 days after implantation were analyzed.

Results: A total of 246 patients receiving 252 PDC implantations during the 6 years were studied. After 39 procedures (15.5%), patients had an unexpected hospital stay due to operative complications (33.3%), worsening of comorbid disease (35.9%), or a single-night hospital stay for observation (30.8%). Compared to discharged patients, the unexpected hospitalization ones were older (P=0.001), had higher rates of previous episodes of heart failure (P<0.006) and heart disease (P<0.001), had more use of general anesthesia (P=0.046), had more added procedures during the implantation (P=0.02) and had more episodes of flow obstruction and peritonitis (P=0.012 and P<0.001). Multivariable logistic regression showed that age, cardiac morbidity, use of general anesthesia, PDC flow problems and peritonitis after implantation were independent predictors of all-cause unexpected hospitalization.

Conclusions: For the first time, our study has analyzed the rate of unexpected hospitalization after PDC implantation and identified the salient risk factors. Increased focus to identify patients at greatest risk for hospitalization, evaluation of processes of care, and implementation of preventive strategies may be helpful to reduce unplanned hospitalization after catheter insertion.
TH-PO994
Early Mechanical and Infective Complications in First Time Blind, Bedside, Midline Percutaneous Tenckhoff Catheter Insertion with Ultra Short Break-in Period: Setting New Standards
Succes Anjana,1 Ninoo G. George,2 Santosh Varughese.1 1Nephrology, Christian Medical College, Yellore, Tamil Nadu, India; 2Nephrology, Bilroth Hospitals, Chennai, Tamil Nadu, India.

Background: There are no large studies that have looked into ultra-short break-in period with blind, bedside, midline approach of Tenckhoff catheter insertion. Methods: 286 consecutive adult patients underwent catheter insertion for chronic peritoneal dialysis at our centre from January 2009 to December 2013. Those with history of midline laparotomy scars and hernias were referred for open surgical insertion. 245 patients (86.3%) underwent the percutaneous and 39 patients (13.7%) underwent surgical insertions. Results: The mean break-in period for the percutaneous group (PG) was 2.68 ± 2.63 days and for the surgical group (SG) was 11.19 ± 6.96 days, p <0.001. Poor catheter outflow was present in 22 (9%) of PG and in 4 (10.3%) of SG (p= 0.80).Primary catheter non-function was present in 24 (9.8%) of the PG and in 4 (10.3%) of the SG (p = 0.73). Catheter survival at one year was 164/241 (85.1%) in the PG. The various outcomes are: 

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Percutaneous N=245</th>
<th>Surgical N=39</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed Catheter Insertion,n(%)</td>
<td>2(0.8)</td>
<td>0</td>
<td>0.74</td>
</tr>
<tr>
<td>Poor outflow,n(%)</td>
<td>22(9)</td>
<td>4(10.3)</td>
<td>0.8</td>
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<tr>
<td>Diastole leak,n(%)</td>
<td>16(6.5)</td>
<td>6(15.4)</td>
<td>0.055</td>
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<tr>
<td>Mesoenteric tear,n(%)</td>
<td>2(0.8)</td>
<td>0</td>
<td>0.74</td>
</tr>
<tr>
<td>Paralytic ileus,n(%)</td>
<td>0</td>
<td>1(2.6)</td>
<td>0.01</td>
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<tr>
<td>Exit site bleeding,n(%)</td>
<td>10(4)</td>
<td>0</td>
<td>0.69</td>
</tr>
<tr>
<td>Early peritonitis,n(%)</td>
<td>5(2.1)</td>
<td>0</td>
<td>0.49</td>
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<tr>
<td>Overall early mechanical complication,n(%)</td>
<td>40(16.3)</td>
<td>11(28.2)</td>
<td>0.07</td>
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<tr>
<td>Primary catheter non-function,n(%)</td>
<td>24(9.8)</td>
<td>4(10.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Mortality,n(%)</td>
<td>68(241/28.2)</td>
<td>17(36/47.2)</td>
<td>0.02</td>
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<td>Catheter survival at one year,n(%)</td>
<td>164/184/89.1</td>
<td>29/35/28.9</td>
<td>0.29</td>
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<tr>
<td>Median patient survival(years)</td>
<td>45/95/CL28.5-57.5</td>
<td>35/95/CL24-46</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Figure: Relevance of systolic blood pressure to vascular events and cause-specific mortality, by prior vascular disease or raised troponin.

Conclusions: The significantly shorter break-in period and smaller wound incisions reduce hospitalization and the need for bridging hemodialysis as well as having good patient and catheter outcomes.

TH-PO995
Comparing Outcomes of Percutaneous Peritoneal Dialysis Catheter Insertion by Nephrologist versus Open Surgical Insertion – Large Single Centre Experience
Louise E. Ross, Bhirgu Raj Sood. South West Thames Renal and Transplantation Unit, Carshalton, Surrey, United Kingdom.

Background: Several studies suggest that percutaneous insertion of peritoneal dialysis (PD) catheters by nephrologists improves the uptake of PD. Percutaneously inserted PD catheters by nephrologists improves the uptake of PD. Percutaneously inserted catheters in the percutaneous versus open surgical group. PD catheters requiring manipulation or replacement within the first year due to a functional problem was comparable in the percutaneously inserted catheters (9.2% versus 12.9%; p=0.327). There were no major complications in the form of visceral perforation or major hemorrhage in either group.

Conclusions: In our study, we found that infection related complications were better with percutaneous PD catheter insertion and mechanical failure rate was comparable to open surgical PD catheter insertion. We in our practice we have found that percutaneously inserted PD catheters are a safe means of increasing patient access to PD, enabling more patients to have a home-based therapy.

TH-PO996
Shared Decision-Making in Chronic Kidney Failure: The Retrospection of First Stage Dialysis Patients in India
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Background: To date, little is known about the extent to which patients with chronic kidney failure feel involved in decision-making regarding the life-changing dialysis treatment. Previous studies on mortality yielded equivalence of peritoneal (PD) and hemodialysis (HD). However, only 5% of the patients in our study revealed, that although many patients are eligible for both options and entitled to unbiased counselling. Methods: In a nationwide multicenter study with federal funding (“CORETH-project”), we surveyed 781 patients on dialysis since 6 to 24 months with regard to their rating of shared decision-making (SDM) with their physician concerning the choice of renal replacement therapy. We used the “Shared Decision-Making Questionnaire” (Kriston et al., 2010), which is a highly reliable and well accepted measure. Furthermore, patients indicated the dominating reason for choosing their treatment as well as their treatment satisfaction (TS). Results: Data were compared between propensity score-matched groups of patients (p=0.7 vs p=0.246). Results: PD patients rated all aspects of SDM (for example, consideration of patient preferences or shared weighing of options) significantly more positive than HD patients (SDM-total score, p<.0001). PD patients predominantly (73%) indicated their independence as a motivation for the choice, whereas HD patients were largely (30%) subject to medical decisions only. Moreover, compared to HD, PD patients were more satisfied with the information received (p=.013). The SDM- and TS-total scores correlated significantly positive in the matched overall sample (r= .19, p<.0001). Conclusions: Our findings highlight awareness for an unbiased nephrological counseling-culture and provide indications for a successful SDM-process when choosing dialysis modality. According to the results, an effective SDM can pave the way for dialysis patients’ quality of life and treatment success. Funding: Government Support - Non-U.S.

TH-PO997
Depression and Cognitive Impairment in Peritoneal Dialysis: A Multi-Center Cross-Sectional Study
Jie Dong,1 Hai-chon Pi,2 Zaying Xiong,2 Jianlin Xiao,1 Hao Gui,1 Liang Liu,1 Yue-Ping Ren,1 Xing Bo,1 Liying Du,3 Zhao-xia Zheng.1 1Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China; 2Renal Div, Peking Univ Shenzhen Hospital, Shenzhen, China; 3Renal Div, The Second Hospital of Anhui Medical Univ, Hefei, Anhui, China; 4Renal Div, The Second Affiliated Hospital of Harbin Medical Univ, Harbin, Heilongjiang, China; 5Renal Div, Handan Central Hospital, Handan, Hebei, China.

Background: Depression and cognitive impairment have been identified as independent risk factors for mortality in peritoneal dialysis (PD) patients. The relationship between depression and cognitive functions in PD patients was investigated in this multi-center cross-sectional study. Methods: Study design: multi-center cross-sectional study. Setting & Participants: A total of clinically stable 458 patients who performed PD for at least 3 months from 5 PD units were included in this study. Only 5% of the patients in Germany choose PD, even though many patients are eligible for both options and entitled to unbiased counselling. Outcomes: Global and specific cognitive impairment. Measurements: Global cognitive function was measured by using the Modified Mini-Mental State Examination (3MS), specific cognitive function by executive function, immediate memory, delayed memory, visuospatial skill and language ability by subtests of Repeatable Battery for the Assessment of Neuropsychological Status. Depression was diagnosed if the depression severity index>0.5 by using Zung’s Self-rating Depression Scale. Results: The prevalence of depression and cognitive impairment evaluated by 3MS were 52% and 28.4% respectively. Patients with mild or moderate/severe depression had higher prevalence of general cognitive impairment, executive dysfunction, impaired immediate and delayed memory. After adjusting for demographic, comorbidity data and clinical parameters, depression scores were independently associated with lower scores of 3MS, immediate and delayed memory, and language ability, and longer completion time of Trails A and B. Even mild depression and HD independently predicted higher risk of CCI, executive dysfunction, impaired immediate and delayed memory after multivariable adjustments. Conclusions: Even mild depression plays an important role in global and specific cognitive functions in PD patients. Funding: Government Support - Non-U.S.

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Proposed Model for the Care of Hospitalized Peritoneal Dialysis Patients

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Background: Peritoneal dialysis (PD) has been prescribed throughout the United States, yet the optimal model of care for hospitalized PD patients remains unknown. With a growing interest in home modalities and emphasis on quality, it is imperative that we identify an effective and efficient way to care for this patient population during hospitalization.

Methods: We describe a model successfully implemented at Vidant Medical Center (VMC) in 2008. Prior to this date, the primary hospital nurses performed PD care. Due to the high risk, low volume nature of inpatient PD, this resulted in inconsistent care as well as decreased physician, nursing, and patient satisfaction. In 2008, an inpatient PD nursing team was created. This team, consisting of nephrology nurses with specialized PD training, is managed by VMC’s self-maintained dialysis unit. Staffed with 2 nurses during the day and 1 nurse at night, they provide 24-hour care through the hospital, including the ICU and ED.

Responsibilities include patient education, exit site care, catheter flushes, and all manual and automated PD exchanges. Upon discharge, the outpatient unit is contacted to ensure appropriate transition back to the outpatient setting.

Results: This model provided several benefits: 1) PD treatments are consistently completed and charted, 2) Increased physician, nursing, and patient satisfaction, 3) Continuity of care, and 4) Cost reduction (personnel and supplies). Since inception, this team has grown to 13 nurses. During FY2014, 2568 (1572 adult / 996 pediatric) PD treatments were performed, the majority CAPD. To ensure appropriate utilization of nursing resources, most are cross-trained to perform hemodialysis.

Conclusions: In conclusion, the creation of a specialized nursing team has been instrumental in optimizing the care of our hospitalized PD patients. This sustainable model provides effective, efficient care and should be considered for implementation for hospitals providing PD services.

TH-PO999

Elderly Peritoneal Dialysis Compared with Elderly Hemodialysis Patients and Younger Peritoneal Dialysis Patients: Competing Risk Analysis of a Korean Prospective Cohort Study

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Background: The outcomes of peritoneal dialysis (PD) in elderly patients have not been thoroughly investigated. We aimed to investigate the clinical outcomes and risk factors associated with PD in elderly patients.

Methods: We conducted a prospective observational nationwide adult end-stage renal disease (ESRD) cohort study in Korea from August 2008 to March 2013. Among incident patients (n=830), patient and technical survival rate, quality of life, and Beck’s Depression Inventory (BDI) scores of elderly PD patients (≥65 years, n=95) were compared with those of PD patients aged ≤49 years (n=205) and 50–64 years (n=192); and elderly hemodialysis (HD) patients (n=315). The patient death and technical failure were analyzed using cumulative incidence function.

Results: The patient survival rate of elderly PD patients was inferior to that of younger PD patients (P<0.001). However, the technical survival rate was similar (P=0.097). Compared with elderly HD patients, the patient survival rate did not differ according to dialysis modality (P=0.987). Elderly PD patients showed significant improvement in the BDI scoring compared with the PD patients aged <49 years (P=0.033). Low albumin, anemia, peritonitis, and low residual renal function were significant risk factors for the PD patient survival; and peritonitis was a significant risk factor for technical survival. Furthermore, low albumin and hospitalization were significant risk factors of patient survival among the elderly.

Conclusions: The overall outcomes were similar between elderly PD and HD patients. PD showed the benefit in BDI and quality of life in the elderly. Additionally, the technical survival rate of elderly PD patients was similar to that of younger PD patients. Taken together, PD may be a comparable modality for elderly ESRD patients.

TH-PO1000

Phosphorus Control and Phosphate Binder Pill Burden During Real-World Use of Sucroferric Oxyhydroxide in Peritoneal Dialysis Patients

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Background: Achieving serum phosphorus (sPhos) control can be a challenge for dialysis patients (pts). This retrospective database analysis examined the real-world effectiveness of sucroferric oxyhydroxide (SO), an iron-based phosphate binder (PB), in adult peritoneal dialysis (PD) pts.

Methods: A cohort of PD pts prescribed SO as part of routine clinical care at FMCNA clinics was analyzed. Pts had ≥1 sPhos measured during SO and had been previously treated with sevelamer, calcium acetate, calcium carbonate or dual therapy. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and PB pills per day (PPD) were assessed 3-months before SO (baseline) and 3-months during SO (follow-up).

Results: Pts (n=328) were, on average, 53 years old, with a dialysis vintage of 3.9 years. At baseline, 56% of pts used sevelamer, 29% calcium acetate, 11% calcium carbonate, and 5% dual therapy. Pts in-range increased from 13.5 to 23.8% (76% increase). Mean sPhos decreased from 6.92 to 6.67 mg/dl, p<0.001. PB PPD was reduced from 8.4 to 3.8 pills (4.6 fewer pills, p<0.001). There was no significant change in sCa (9.1 to 9.0 mg/dl) or iPTH (335 to 555 pg/ml). TSAT and FER increased from 35.4 to 36.6% and 752.1 to 814.9 mg/ml, respectively. In pts not receiving IV iron (n=127), TSAT and FER did not change significantly (36.3 to 37.3% and 797.9 to 743.3 mg/ml, respectively).

Conclusions: In this large cohort of PD patients prescribed sucroferric oxyhydroxide as part of routine clinical care, a significant reduction in serum phosphorus (p<0.001) and a 76% increase in patients achieving in-range serum phosphorus (p<0.001) was observed. This was accomplished with a mean of 3.8 pills per day, a reduction of 4.6 pills (p<0.001).

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO1001

Laparoscopic Findings of Visceral Peritoneal Injury in Patients Treated with Neutral pH Peritoneal Dialysis Solution Yudo Tanno, Nanae Matsuo, Izumi Yamamoto, Yasuuki Nakada, Ichiro Ohkido, Kettaro Yokoyama, Takashi Yokoo. Div of Kidney and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Encapsulating peritoneal sclerosis (EPS) is caused by a visceral peritoneal lesion, i.e., intestinal tract adhesion and encapsulation, it is important to evaluate changes in the visceral peritoneum. It has been reported that there was a decreasing trend of peritoneal injury with the use of PD solution with neutral pH as compared with acidic pH in the histopathological evaluation of the parietal peritoneum; however, there is no report evaluating changes in the visceral peritoneum, which is essentially important and should be evaluated. We previously reported laparoscopic approach for evaluation of EPS (KI 2012) in patients treated with PD solution with acidic pH. In this study, we examined macroscopic findings of the visceral peritoneum in patients treated with neutral pH solution alone for 4 years or more by laparoscopy.

Methods: 19 patients underwent laparoscopy at the time of PD catheter removal. Duration of PD in these patients was 64±18.8 months. Clinically, none of these patients had developed EPS by the time of the investigation. The findings of both parietal and visceral peritoneal tissues were categorized according to color changes, presence of neovascularizations and adhesions.

Results: It was found that longer the duration of PD, the worse the peritoneal injury. Although changes in the parietal and visceral peritoneum had heterogeneous distributions, the changes in the visceral peritoneum were milder, showing a discrepancy with the findings of the parietal peritoneum. As compared with laparoscopic findings in patients treated with PD solution with acidic pH, the degrees of color changes, presence of neovascularizations, and adhesions were all mild, however, severe adhesions were noted in patients with a history of PD peritonitis.

Conclusions: Although changes in the visceral peritoneum resulting from the use of PD solution with neutral pH show a decreasing trend as compared with acidic pH, there is a certain level of peritoneal change, suggesting the possibility of progression of peritoneal deterioration by long-term continuous use.

TH-PO1002


Background: Encapsulating peritoneal sclerosis (EPS) is the more dangerous complication of peritoneal dialysis (PD). The EPS can occur during PD (classic EPS), after kidney transplantation (TX) or rapid shift to hemodialysis (HD) as the mode of renal replacement therapy (RRT).

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

Underline represents presenting author.
Methods: Single-center retrospective analysis of PD transplanted patients in 35 years. Evaluation of the characteristics of the ESP presentation. Results: From July 1979 to December 2014, 173 PD patients underwent kidney transplantation (TX). They were diagnosed 5 cases (2.9%) of ESP: one after 6 months from the TX (typical posttransplant ESP), but the other 4 cases have occurred after more than 2 years after the kidney transplantation (maximum 207.2), and at least a long time of TX (median 227 ± 24 months, range 207-259), also after many years of cessation from the last period in PD. The median time of PD was 71±31 months (range 36-99). Two patients died after 10 and 41 months after diagnosis, respectively and after 332 and 367 months in RRT. In our center during the same period other 21 ESP cases (2.8%) were occurring among the 747 PD patients never transplanted. No cases of ESP was manifested after direct transfer from PD to HD. Conclusions: in our experience ESP prevalence in transplanted PD patients is not greater than that transplanted PD patients. In patients for many years in RRTs, ESP occurs even after a long time of the cessation of DP, especially after many treatments and long periods in PD. It is possible that the PD is acting only as a side event on the tissues affected by fibrotic processes formed for a long time in RRTs and/or due to the immunosuppressive therapy. To its features this form can be defined “composite ESP” and should also be considered in PD patients transplanted since many years.

TH-PO1003

Delta Neutrophil Index Is a Predictive Marker of Catheter Removal in Peritoneal Dialysis Patients with Peritonitis

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Background: Severe and prolonged peritonitis leads to peritoneal membrane failure and is the most common cause of technique failure in patients treated with peritoneal dialysis (PD). Recent studies reported that delta neutrophil index (DNI), which reflects the fraction of circulating immature granulocytes in the blood, is a practical severity marker of infection. This study investigated whether DNI could be a predictive marker of catheter removal PD patients with peritonitis.

Methods: Patients treated with PD peritonitis at Severance Hospital between January 2012 and January 2015 were enrolled. Demographic data, clinical, and laboratory parameters including DNI were collected at the time of peritonitis. DNI was calculated by automatic analyzer.

Results: A total of 125 PD peritonitis episodes in 92 patients were investigated. The mean age was 59.1 ± 12.0 years and 55 (44.0%) were male. PD catheter was removed in 31 (24.6%) patients. The median value of DNI in patients undergone PD catheter removal was significantly higher compared to that of patients who maintained PD catheters [DNI (interquartile range) 3.30 (0.0-6.50) vs. 0.70 (0.0-22.5), P<0.001]. DNI is significantly associated with percentage of segmented neutrophil (r=0.28) and serum albumin (r=-0.32), and dialysate leukocyte counts (r=0.20), but not with C-reactive protein (CRP) levels (r=-0.08). Multivariate logistic regression analysis revealed that DNI was an independent predictor for PD catheter removal in patients with PD peritonitis (odds ratio=1.08, 95% confidence interval=1.01-1.12, P<0.04) after adjustment for serum albumin, CRP, leukocyte count of dialysate effluent, and septic shock. The area under the ROC curve (AUC) of DNI for PD catheter removal was 0.69 (P<0.001), whereas the AUC of dialysate leukocyte count was not statistically significant (0.52, P=0.70).

Conclusions: DNI levels reflected the severity of peritonitis. Higher levels of DNI could be an independent predictor for PD catheter removal in patients with PD peritonitis.

TH-PO1004

Peritonitis Rates Among African Americans and Caucasians Undergoing Peritoneal Dialysis

Acceia Muqri, Russell Griffin, Eric L. Wallace. Univ of Alabama at Birmingham.

Background: African Americans (AA) are under-represented in the prevalent peritoneal dialysis (PD) population in the United States. There is relatively little conclusive data to explain the cause of this. One explanation is that AA may have higher rates of peritonitis than Caucasians leading to increased technique failure. This study aimed to determine if AA have higher rates of peritonitis than Caucasians. Despite this, technique survival between races did not differ. This study does not support the hypothesis that the underlying cause of decreased prevalent AA PD patients is due to increased technique failure from disproportionate peritonitis rates.

TH-PO1005

Factors Associated with Peritoneal Dialysis Technique Failure: A Single Center Study

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Background: To review peritoneal dialysis (PD) technique survival and assess factors associated with PD technique failure at our center.

Methods: We performed a retrospective analysis of 315 patients with PD catheters placed between 01/2001 and 09/2009, reviewing medical records for demographic and clinical information. Primary outcome was PD technique failure, defined as permanent discontinuation of PD due to infectious or non-infectious complications, inadequate dialysis, or miscellaneous factors such as pain. Patients were followed at least 36 months after PD initiation. Survival analysis was performed using Kaplan-Meier methods. Covariates influencing survival were analyzed using Cox proportional hazards regression models.

Results: There were a total of 70 failures, 31 (44.3%) related to infectious complications, 22 (31.4%) to non-infectious complications (e.g. obstruction, leaks), 8 (11.4%) to inadequate dialysis, and 9 (12.9%) to miscellaneous factors. Overall survival at 36 months was 78.81%. Covariates significantly affecting technique failure include prior HD (1.83; 1.14-2.92), non-infectious complications (1.82; 1.28-2.59), DM (1.62; 1.00-2.63), HIV (2.52; 1.01-6.24), peritonitis (1.95; 1.29-3.12), and exit site infections (1.79; 1.09-2.92). Previous abdominal surgeries (90; 0.78-1.0) and BMI (1.005; 0.97-1.04) were not significantly associated with failure.

Conclusions: This is one of the largest single center studies of its type from a US PD program. It shows excellent 3 year PD technique survival, better than reported in similar studies. Our results confirm that diabetes mellitus, PD related infections, and non-infectious mechanical problems are independent risk factors for PD technique failure. Conversely, BMI, abdominal surgeries, and demographic characteristics such as race and gender do not have significant association and should not be considered barriers to PD initiation.

Funding: Clinical Revenue Support

TH-PO1006

Effect of Early Peritonitis on Clinical Outcomes

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Background: Infection is a source of significant morbidity and mortality for peritoneal dialysis (PD) patients. Previous studies suggest that early peritonitis is associated with shorter technique survival; however these studies are limited by small samples, restricted generalizability, and a lack of standardized definitions. We used data from a large dialysis database to determine if the timing of the first peritonitis episode is associated with adverse clinical outcomes.

Methods: US and Canadian data from 1996 to 2005 in the Baxter POET (Peritonitis, Organisms, Exits sites, Tunnel infections) database was analyzed. Patients who developed peritonitis within 6 months of PD initiation were identified as cases. Controls were patients whose first peritonitis occurred after 6 months. Patients who never developed peritonitis or who were on PD for less than 6 months were excluded. Patients were censored at the clinical inpatient, transfer to hemodialysis, or death.

Results: 920 cases and 2607 controls were identified.

Conclusions: AA when compared to non-AA, trended towards a higher risk of peritonitis than Caucasians. Despite this, technique survival between races did not differ. This study does not support the hypothesis that the underlying cause of decreased prevalent AA PD patients is due to increased technique failure from disproportionate peritonitis rates.
early mortality, occurrence of coronary heart disease and stroke, and incidence of peritonitis.

Secondary outcomes included all-cause mortality, cardiovascular and cerebrovascular
mortality, occurrence of coronary heart disease and stroke, and incidence of peritonitis.

Methods: In this retrospective cohort study, 348 incident PD patients (aged 48.2
± 15.5 years, 62% men) at Peking University Shenzhen Hospital from 2000 to 2014 were
included. BMI was calculated with height and weight first recorded within 2 to 6 months
after initiation of PD. Patients were categorized according to the World Health Organization
recommendation for Asians. All patients were followed until October 31, 2014. Primary
outcome was technical failure, defined as death or permanently transferred to hemodialysis.
Secondary outcomes included all-cause mortality, cardiovascular and cerebrovascular mortality,
incidence of coronary heart disease and stroke, and incidence of peritonitis. Data were analyzed using Cox proportional hazards models.

Results: BMI in this cohort was 22.1 ± 3.0 kg/m². During 2.5 (interquartile range:
1.0-4.0) years, 60 cases of technical failure occurred. Incidence of technical failure was higher in patients with low BMI (13.4/100 person-years) than those with normal BMI (5.2/100 person-years) and with high BMI (6.3/100 person-years). After adjustment of
date of age, sex, education, primary disease, and heart failure, hazard ratios (95% confidence
intervals) were 3.60 (1.53, 8.45) and 0.93 (0.49, 1.76) for patients with low and high BMI,
respectively, as compared to those with normal BMI. Similarly, the low BMI group had
significantly higher rates of total as well as cardiovascular and cerebrovascular mortality
than the normal BMI group, but such relationships did not exist in the high BMI group. No
associations of BMI with occurrence of coronary heart disease and stroke and incidence of
peritonitis were observed.

Conclusions: In incident PD patients, low BMI is associated with technical failure,
all-cause mortality, and cardiovascular and cerebrovascular mortality.

Funding: Government Support - Non-U.S.

TH-PO1008

The Association Between Body Mass Index and Mortality in Peritoneal Dialysis Patients

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Background: Unlike the general population, a higher body mass index (BMI) was consistently found to be a strong predictor of decreased mortality in patients with end-stage renal disease who receive maintenance hemodialysis (HD). This phenomenon has been referred to as the “Obesity paradox” or “reverse epidemiology.” Similar tendency has been observed in several studies with peritoneal dialysis (PD) patients, but the studies have reported conflicting results. We conducted this study to evaluate the association between BMI and all-cause mortality in PD patients.

Methods: A systematic search was conducted for published studies in Medline, EMBASE, and the Cochrane library databases from 1970 to April 2015. We identified studies

<table>
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<th>Late (n=2607)</th>
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<tr>
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<td>25</td>
</tr>
<tr>
<td>% Other *</td>
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Presented as %, *= mean, * = failed transplant or moved from another unit

Patients with early peritonitis had a significantly higher peritonitis rate than controls (1.26 and 0.67 episodes/person-year, p<0.001). Early peritonitis was also associated with shorter technique and patient survival.

Conclusions: Our results suggest that patients with early peritonitis are at increased risk of adverse clinical outcomes such as future infection, technique failure, and death.

TH-PO1009

Is Obesity a Poor Prognostic Factor in Incident Peritoneal Dialysis Patients?

Hynju Jeong Cho,1 Hyo Jin Kim,1 Miseon Park,2 Dong Ki Kim,1 Kwon Wook Joo,1 Yon Su Kim,1 Curie Ahn,1 Kook-Hwan Oh.1 Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Clinical Research Inst, Seoul National Univ Hospital, Seoul, Korea.

Background: Obesity is associated with an increased risk of death in the general population. Previous studies have demonstrated a discrepancy in the impact of body mass index (BMI) on mortality among peritoneal dialysis (PD) patients. We examined the effect of BMI on patient and technique survival in a prospective, incident PD cohort at a single center.

Methods: Subjects who started PD between 2000 and 2012 were enrolled in the study. Demographic and laboratory data were prospectively collected. Patients were categorized into four BMI groups: obese, ≤25 kg/m², overweight, 23.0–24.9 kg/m², normal, 18.5–22.9 kg/m² (reference category); and underweight, <18.5 kg/m². Patient and technique survival were compared using Cox proportional hazards models.

Results: A total of 632 incident PD patients were included in final analysis. The median follow-up period was 40 months (interquartile range, 19-64 months). Kaplan-Meier survival curve, patient survival was not statistically different among all BMI categories (p = 0.641, by log-rank test). The hazard ratio (HR) adjusted for age, sex, diabetes, comorbidities, albumin, hemoglobin for patient survival was not significant among BMI groups (p = 0.837). In contrast, technique survival was significantly poorer in obese patients than in patients having a normal BMI (p = 0.029, by log-rank test). The HR for technique failure was significantly greater for obese PD patients in comparison with the reference category [1.8, 95% confidence interval (CI): 1.2 to 2.8, p = 0.008]. The reasons for technique failure included recurrent peritonitis (34%), inadequate dialysis (17%), mechanical problem (17%) and refractory exit-site/tunnel infection (11%) in obese patients.

Conclusions: In our PD patients, patient survival was similar in all BMI categories. Therefore, obese patients should not be discouraged from receiving PD purely on the basis of BMI. However, technique survival was significantly poorer for obese PD patients. Further study is warranted to improve technique survival in obese patients.

TH-PO1010

Phosphate Clearance in Peritoneal Dialysis: Residual Renal Function and Dialysis Modality

Carmen Gonzalez corvillo,1 Mariangales Rodriguez Perez, Alejandro A. Suarez benjumea, Nuria Areste, Mercedes Salgueira lazo. Nephrology, Virgen Macarena-Rocio, Sevilla, Spain.

Background: Evaluate urinary and peritoneal excretion of phosphate and related factors in peritoneal dialysis(PD). Analyse phosphate clearance depending on PD modality and peritoneal membrane type.

Methods: Observational study, in a sample of 37 PD patients. Mean age 60±14 years. 24 patients on APD(16CCPD,8NIPD) 13 on CAPD.Mean Kt/ V: 1.8±0.6. Mean residual renal function(RRF):6.3±4.6 ml/min.Transmembranous peritoneal transport:6high(H),26high-average(HA) and Slow-average(LA).Renal and peritoneal phosphate clearance(ultrafiltration (UF) and diffusion(D)) was analyzed.Urinary and dialysate P-Cr. Weekly peritoneal P clearance(WPCl).Serum P/PTH.Use and dosage of phosphate binders and vitaminD analogs.

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

Underline represents presenting author.

330A
Results: Mean total P clearance=460±192mg/dl. Mean renal P clearance=286±201mg/dl and renal urine clearance=250±198mg/dl, respectively. When we analyzed Group A (18.4±1.2 weeks) and Group B (22.5±0.9 weeks) and by D 194:85±24/hr(1%). Mean urine and dialyze P concentration were 0±0.15 and 0.59±0.24 Mean WPCI=31.1±13.1/l/week. Mean serum P 4.5±1mg/dl and THPD24±166ppg/ml. 80±9% of patients were on Sevelamer and 22±calcium based binders.45% were on a vila min (P<0.03). Positive correlation between peritoneal clearance and UF (r=0.46, p<0.001) as well as between RRF and P elimination (r=0.53, p<0.001) was observed. WPCI was higher in patients on CAPD than on APD/39,47±27 vs 21±13/l/week p<0.05) being the many difference subjects performed to continuous vs discontinuous modalities (Kidney Int. 2013). It is still unexplained what factors predict RRF loss in the PD patients using BDPS. We investigated the relationship between clinical parameters at PD initiation and the change of RRF in the PD patients using BDPS. Methods: The data from patients who started PD as their first dialysis modality from 2001 to 2014 at The University of Tokyo Hospital were collected retrospectively. All patients were treated by automated PD (APD) using BDPS. To identify predictors of RRF decline, we analyzed data including clinical parameters measured at PD initiation. Residual GFR was calculated as the average of 24-hour urinary urea and creatinine clearances. The rates of urine volume and residual GFR decline were calculated by the least squares linear regression formula. The outcome of dialysis modality change was defined as switching to hemodialysis (HD) or combined therapy of PD and HD due to RRF loss. Results: 96 patients were analyzed in this study. On multiple regression analysis, the decline rates of urine volume and residual GFR were significantly correlated with proteinuria at PD initiation. When patients were divided into two groups according to urinary protein level, Kaplan-Meier analysis revealed the lower proteinuria group had higher persistence rate of APD and lower rate of dialysis modality change (Log rank; p = 0.011 and 0.004, respectively). On ROC analysis, urinary protein predicted the need of dialysis modality change within 2 years after PD initiation with statistical significance (AUC [95%CI]=0.78 [0.66-0.90]). Conclusions: Proteinuria at PD initiation may predict RRF loss and the need of dialysis modality change in the APD patients using BDPS.

TH-PO1012

Background: Although urgent start (US) peritoneal dialysis (PD) and traditional start (TS) PD have similar outcomes, it is not known if differences in outcomes exist based on race. The objective of this study was to determine if differences in PD outcomes exist when stratified based on race and type of PD start.

Methods: Retrospective data from an electronic database on incident PD patients collected between November 2012 and March 2015 was analyzed. Patients were analyzed by race and modality start: 3 groups-4 groups: Non-Asian (AA), Non-AA US, AA US and Non-AA US. Chi-square analysis was used to compare categorical variables, while ANOVA was used to compare means across groups. Exact mid-p was used to compare rates of hospitalization, peritonitis and catheter revisions. Survival curves were used to evaluate the probability of hospital free, peritonitis free, and technique survival. Patients were censored in the technique survival analysis for death or transplant.

Results: 114 patients were started on PD during the study period, 33 of which were US. When comparing US to TS, patients were matched for age, gender, and average days on PD. There were no significant differences in the incidence of infections, or technique failure, timing of peritonitis, timing of peritonitis, technique failure, catheter revision or hospitalization rates between TS and US groups. Sub-group analysis based on race stratification showed that age at PD start was younger in AA TS vs Non AA TS (50±13 vs 60±14 years respectively, p=0.02). 60% of AA TS patients were 60% more likely to have technique failure than Non-AA US (p<0.03). Peritonitis rates for AA TS, Non-AA TS, AA US, and non-AA US were 0.3, 0.14, 0.33, 0.36 per patient year respectively; catheter revision rates were 0.49, 0.3, 0.42 and 0.5 per patient year respectively with no significant difference among the subgroups.

Conclusions: There were no significant differences in outcomes among TS and US groups when stratified by race. Although AA TS patients have the least technique failure and hospitalization rates while AA TS have the highest, no significant differences were noted among race when stratifying by modality.

TH-PO1013

Background: In-center HD and PD are the 2 most common types of dialysis utilized in US. Few studies have examined characteristics of patients who changed dialysis modality. Kaiser Permanente Northern California is an integrated health care delivery system with 3.7 million members. We retrospectively examined the characteristics and disease burden of patients who switched from PD to HD.

Methods: Retrospective examination of EMR from Jan 2009 – Oct 2014. Disease burden was assessed by internally developed comorbidity point score, which predicts negative outcomes in the next 12 months, based on documented comorbidities and hospitalizations.

Results: From 2010-2014, dialysis population in our integrated health system increased from 4005 to 4491 patients, and PD population decreased from 621 to 1033. In this period, 11% of patients initiated dialysis modality switching. Majority of mode changes occurred within a year after dialysis initiation. 8% of HD patients switched to PD and 24% of PD patients switched to HD. Majority of patients who switched from HD to PD do so within 6 months of initiation. They have less comorbidities than those who stay on HD. They have a higher comorbidity score when they switch to PD but lower than repeated switching of those who switched from PD to HD. They were younger than those remaining on HD. Most patients who switched from PD to HD did so within a year. They have more comorbidities than those who stay on PD and have a higher comorbidity score when they switch to HD, even higher than the repeat score of those who switch from HD to PD. The difference in co-morbidity scores between the first and second measurement is higher in the PD to HD pattern. They have similar age to those who didn’t switch.

Conclusions: Patients who switched from HD to PD remain at approximately the same comorbidity score before and after switch. Comorbidity scores of patients who switched from PD to HD significantly increased, suggesting that change was influenced by decline in their overall condition. In our patient population, the switch from HD to PD is likely a patient’s decision, while the switch from PD to HD may be due to inability to continue PD.

TH-PO1014
Impact of Pre-Dialysis Immunosuppressive Treatment Time on Infectious Complications and Survival of Systemic Lupus Erythematosus (SLE) Patients on Peritoneal Dialysis Junbog Shi, Joanne M. Bargman. Dept of Nephrology, Peking Univ Third Hospital, Beijing, China; Div of Nephrology, Univ Health Network, Toronto General Hospital, Toronto, ON, Canada.

Background: SLE patients on peritoneal dialysis (PD) have a significant risk of infectious complications and poor outcomes.However, few studies have examined the relationship between pre-dialysis exposure to immunosuppressive (IS) therapy and the outcome of PD therapy. The objective of this study was to investigate whether pre-dialysis IS treatment time influences the infectious complications and outcomes of SLE patients on PD.

Methods: Twenty-six SLE patients were treated with PD in a major academic centre from May 1996 to May 2014. Demographics, diagnostic tests and IS treatment, comorbid conditions, hospitalizations. Few studies have examined characteristics of patients who changed dialysis modality.

Results: Two patients were lost to follow-up during the study period. Therefore, a total 24 patients were included for analysis. The SLE patients with longer duration of predialysis IS (n=17) were older than patients with shorter pre-dialysis IS (n=7) (83.6±11.0 vs 27.1±7.8, P<0.05), but there were no significant differences in sex, race, PD duration, PD sub-modality and biochemistry between the two groups (P<0.05). Seven patients died during the follow-up period and all the deaths were from the group with longer-pre-dialysis IS time (P>0.05). Three patients died from infections, two patients from cardiovascular disease, and two had sudden death at home. However, there were no significant differences in the incidence of other infections, or hospitalizations, infectious complications, hospitalizations and clinical outcomes during the study period were collected. Three years was chosen as the discriminant between longer and shorter duration of IS therapy.

Conclusions: SLE patients undergoing PD with longer pre-dialysis exposure to IS drugs have a greater mortality that appears to be related to both infectious and noninfectious causes. Although incident to PD, they should be considered a high-risk subgroup.

TH-PO1015
Predicting Peritoneal Dialysis Prescriptions with a Fast Peritoneal Equilibration Test Using PD Adequest J. Ken Levold, 1 Baris U. Agar, 2 James A. Sloand, 1 Mary Gellens, 2 1 Medical Products (Renal), Baxter Healthcare Corporation, Deerfield, IL; 2 Medical Products (R&D), Baxter Healthcare Corporation, Round Lake, IL.

Background: The fast peritoneal equilibration test (PET) is often used to determine parameters for peritoneal transport status, but its accuracy in predicting parameters of peritoneal dialysis (PD) therapy adequacy using computer software, like PD Adequest, has not been quantified. In the current study, the ability of a new version of PD Adequest was
examined to 1) compare mass transfer-area coefficients (MTACs) for urea, creatinine and glucose during fast and standard PETs and 2) use those parameters to predict PD therapy prescription adequacy.

**Methods:** Data from 104 PD (41 CAPD, 63 APD) patients who underwent a 4-hour standard PET and an overnight exchange with the same glucose concentration were used to determine the presented dialysis parameters. Calculated MTAC values for standard PET were compared with those for fast PET by using only data obtained at 4-hours during the standard PET and assuming a 200 mL residual volume in the prior exchange. The calculated membrane parameters were used to predict net ultrafiltration (UF), urea Kt/V and creatinine clearance (CrCl), and those predictions of therapy adequacy were also compared with the mean of 3 actual measurements of net UF, Kt/V and CrCl for each patient.

**Results:** Median urea, creatinine and glucose MTACs were 20.9, 10.1, and 9.1 mL/min during standard PET, and 21.0, 10.1 and 9.0 mL/min during fast PET; the corresponding median urea and creatinine clearance differences between MTACs for urea, creatinine and glucose were 0.6, 0.3 and 0.6 mL/min. Comparing predictions using standard and fast PETs, 81% of net UF were within 150 mL, 94% of Kt/V were within 0.1wk and 93% of CrCl were within 2 L/wk/1.73m². The percent of predicted and actual measured values of net UF within 300 mL, Kt/V within 0.2 wk and CrCl within 0.8 L/wk/1.73m² were 64%, 63% and 77% for standard PET and 38%, 64% and 77% using fast PET; these differences were not statistically significant.

**Conclusions:** These results suggest that the predictions of PD therapy adequacy using PD Adequest are clinically equivalent when either fast or standard PET is employed. **Funding:** Pharmaceutical Company Support - Baxter Healthcare Corporation

**TH-PO1016**

The Residual Diuresis Increases in Erythropoiesis in PD Patients

**Background:** Anemia in ESRD is attributed to impaired erythrocyte formation due to erythropoietin and iron deficiency. The accelerated clearance of erythrocytes may at least partially be due to enhanced erytpysis, a suicidal death of erythrocytes characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine(PS)-externalization at the erythrocyte (RBC) surface. Exposed PS is recognized by macrophages that engulf and degrade the affected cells. Little is known about mechanisms underlying enhanced erythropysis in ESRD. At least in theory, erythropysis may be stimulated by some uremic toxins. The present study investigated erythropysis in peritoneal dialysis (PD) patients.

**Methods:** 46 PD patients (31 M, mean age:64±14yrs) and 17 healthy subjects (CTR) were enrolled. All measurements were made in isoethal RBCs. PS exposure was estimated from FITC-AnnexinV binding by flow cytometry.

**Results:** 27 patients were treated with CAPD and 19 with APD. The mean length of treatment was 39±29months. The PS externalization on surface was significantly higher in PD patients than in CTR (2.6%, 1.6±3.7 versus 0.8%, 0.7±1.3, p<0.01). The median percentage of erythropysis showed no significant differences between patients with(n=18) and without diabetes, treated with CAPD or APD and with a negative or positive (n=18) history of peritonitis. Erythropysis showed significantly lower levels in PD patients with residual diuresis (n=23) than in patients without (3.7%, 2.6±5.6 versus 5%, 3.1±6, p=0.03). A significant negative correlation was observed between percentage of erythropysis and Body Composition Monitor-BCM for hydration status (Spearman’s rho=-0.4, p<0.05). There was no a statistically significant relationship between erythropysis and months of PD, urea albumin and creatinine levels.

**Conclusions:** In conclusion, erythropysis has been shown to be significantly higher in PD patients than CTR. Our data suggest that the type and the length of PD treatment do not enhance erythropysis. On the contrary, the loss of residual diuresis lead to a significant increase of erythropysis: the residual diuresis may contribute to the elimination of potential uremic toxins that induce increased erythropysis.

**Funding:** Private Foundation Support

**TH-PO1019**

Dialysate Losses of Vitamin 25(OH)D in a Cohort of Patients Treated with Peritoneal Dialysis Juen Carlos Ramirez-Sandoval, Maria Luisa Safar-Boueri, Jorge Jesus Silva, Olynka Vega-Vega, Ricardo Corea-Rotter, Reynero Fagundo, National Medical Sciences and Nutrition Inst Zubiran, Mexico City, Mexico.

**Background:** Peritoneal dialysis (PD) is associated with 25(OH)vitamin D deficiency. To our knowledge, there are no cohort studies about 25(OH)vitamin D dialysate losses in PD.Observative: To characterize 25(OH) vitamin D losses in peritoneal effluent (PE) and their relation with changes in serum 25(OH)vitamin D levels during 4 months in a cohort of incident PD patients.

**Methods:** 52 patients with <6 mths but >1 mth on PD were invited from 2011 to 2014. Those with severe infections, hospitalizations, and oral intake of D3 or D2 during follow up were excluded. Basal vitamin 25(OH) D in 24h PE and serum were measured. After 4 months, a 2nd assessment was performed. The principal outcome was the change in serum vitamin 25(OH) D levels.

**Results:** 43 patients were included, 22 (51%) men, median age was 39y (Interquartile range [IQR] 31-62), 29 (68%) had diabetes and 29 (67%) had some degree of renal residual function during all study. After 4 months of PD initiation, all patients had vitamin 25(OH) D levels <20 ng/mL, 13 of them with levels less than 10 ng/mL.

<table>
<thead>
<tr>
<th>Characteristics, (n=43)</th>
<th>Initial</th>
<th>After 4 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25(OH)D, ng/mL</td>
<td>14.2 ± (10.3-28.2)</td>
<td>8.6 (8.9-31 ng/mL)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peritoneal effluent 25(OH)D, ng/mL, losses, mg/d*</td>
<td>13 (9-17)</td>
<td>*Not all detectable at this timepoint</td>
<td>10 (6-20)</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>521 (343-845)</td>
<td>590 (288-791)</td>
<td>0.6</td>
</tr>
<tr>
<td>Ca, mg/dL</td>
<td>9.2 (8.5-9.6)</td>
<td>9.14 (8.5-9.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>P, mg/dL</td>
<td>4.9 (3.6-6.1)</td>
<td>5.4 (3.8-6.1)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The mean decrease of vitamin 25(OH)D levels was 5.8 ng/mL/month (IQ 2.9-3.9 ng/mL). Basal PE losses in mg/d and delta in serum vitamin 25(OH)D had a significant correlation

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

Underline represents presenting author.

**332A**
Fungal Peritonitis in the Standardizing Care to Improve Outcomes in Dialysis Not Associated With Peritoneal Transport Status in the Same Individual

**Background:** Recent studies have reported that peritoneal protein excretion (PPE) during peritoneal dialysis (PD) therapy is associated with cardiac disease and patient survival. However, little is known regarding the extent to which PPE can be influenced by PD prescription or peritoneal transport status.

**Methods:** The aims of this study were to compare PPE in the same individual with different PD prescriptions of either continuous ambulatory PD (CAPD) or nocturnal intermittent PD (NIPD), and to evaluate the correlation between PPE and dialysate to plasma creatinine ratio (D/P Cr). Seventeen patients, of whom 58.8% were male, were included in the study. A peritoneal equilibration test was performed and the amount of total protein (TP) loss in the dialysate was measured during CAPD or NIPD therapy in the same patient.

**Results:** The mean age of the patients was 59.4 ± 18.0 years, body mass index was 21.5 ± 3.4, serum TP (s-TP) was 5.8 ± 0.8 g/dL, serum albumin (s-Alb) was 3.0 ± 0.7 g/dL, C-reactive protein (CRP) was 0.4 ± 0.7 mg/dL, and D/P Cr was 0.76 ± 0.15. During NIPD therapy, PPE was correlated with peritoneal clearance ($\gamma = 0.63$, p = 0.006), effluent volume ($\gamma = 0.69$, p = 0.002), and PPE to effluent volume ratio ($\gamma = 0.80$, p = 0.000), but not with s-TP, s-Alb, CRP, or D/P Cr. During CAPD therapy, PPE was negatively correlated with s-TP ($\gamma = -0.62$, p = 0.007) and s-Alb ($\gamma = -0.58$, p = 0.014), positively correlated with effluent volume ($\gamma = 0.50$, p = 0.037) and PPE to effluent volume ratio ($\gamma = 0.72$, p = 0.001), but not with CRP or D/P Cr. On comparing NIPD and CAPD, there was no difference in effluent volume (7341 mg vs. 7209 mg, respectively); however, both PPE and PPE to effluent volume ratio were significantly lower during NIPD than during CAPD (5586 mg vs. 7779 mg (p = 0.004) and 0.74 mg/mL vs. 1.09 mg/mL (p = 0.044), respectively).

**Conclusions:** The current study demonstrated that PPE and PPE to effluent volume ratio were lower during NIPD than during CAPD in the same individual, independent of the peritoneal transport status.

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**TH-PO1022**

Relation of Central and Brachial Blood Pressure to Volume Status in Peritoneal Dialysis Patients

**Background:** Euvolemia is an important predictor of outcome in peritoneal dialysis (PD), but chronic subclinical volume overload occurs frequently in PD patients. Even though volume overload is associated directly with hypertension, blood pressure (BP) not always reflect volume overload. Central BP has been shown to be a better predictor for target organ damages compared with brachial BP in general population. In this study, we evaluated comparative values of central BP and brachial BP for determining volume status in PD patients.

**Methods:** We enrolled 52 prevalent PD patients, and accessed variable status using Body Composition Monitor (BCM). Central BP was estimated using radial artery tonometry, and brachial BP measurement at office and 24-hour ambulatory blood pressure monitoring (ABPM) were performed. Volume overload was defined as an overhydration (OH) $\geq$ 1.1 L.

**Results:** Average office central systolic BP (cSBP), office brachial systolic BP (sSBP), and ambulatory brachial systolic BP (24-ssSBP) were 139.8±26.3, 140.7±19.2, and 142.5±22.0 mmHg, respectively. In overall, 41(78.8%) patients were in volume overload status. A stronger association of central BP with volume overload compared with brachial BP was observed in the receiver operating curve analysis (area under the curve (AUC) of cSBP, sSBP, and 24-ssSBP was 0.87±0.06, 0.78±0.09, and 0.83±0.06 respectively). In multivariate analysis adjusted for age, sex, PD vintage, diabetes, and cardiovascular disease, the odds ratio (OR) for central BP (OR 1.110; 95% CI 1.019-1.210) was higher than those for brachial BP (OR 1.085; 95% CI 1.014-1.161 for sSBP and OR 1.194; 95% CI 1.021-1.173 for 24-ssSBP).

**Conclusions:** Office central BP was more strongly related to volume status than out-of-office ambulatory brachial BP as well as office brachial BP, suggesting that central BP was more valuable than brachial BP in assessing volume status in PD patients.

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**TH-PO1023**

Novel Regimen for Intrapерitoneal Cefazolin and Ceftazidime in Peritoneal Dialysis Patients

**Background:** Current guideline suggested that intraperitoneal (IP) antibiotics should be administered only in a long peritoneal dialysis (PD) dwell (>6 hours), which is not always practical because the long dwell might result in low ultrafiltration and volume overload. The objectives of this study were to develop a novel regimen for IP antibiotics in short dwell (<2 hours) during the automated PD cycling and examine the dialysate and plasma level of the most used empirical antibiotics for PD-related peritonitis, cefazolin and ceftazidime.

**Methods:** In the novel regimen, cefazolin and ceftazidime (20 mg/kg each) were added in a 5-liter bag of 2.5% dextrose PD fluid which was placed on the warmer of the PD cycling machine. Another 5-liter bag of PD fluid was connected to the machine, off the warmer. Patients underwent 5 exchanges of 2-liter PD fluid over 10 hours by the PD cycling machine without last fill or additional dwell. Cefazolin and ceftazidime concentrations in plasma and dialysate were determined by high performance liquid chromatography.

**Results:** Six PD patients without peritonitis were participated in the study. Dialysate cefazolin and ceftazidime were consistently high throughout the PD session in all patients (26-360 mg/L). Plasma cefazolin and ceftazidime exceeded the minimal inhibitory concentration (MIC) for susceptible organisms (8 mg/L) in 2 hours (cefazolin 28.5±8.0 and ceftazidime 12.5±3.4 mg/L at 2 hours), peak at 10 hours (51.1±14.1 and 23.0±5.2 mg/L) and then sustained well above the MIC at 24 hours (42.0±9.8 and 17.1±3.1 mg/L).

**Conclusions:** The novel regimen for IP cefazolin and ceftazidime in short dwell (<2 hours) during the automated PD cycling could provide adequate dialysate and plasma concentration and would become a standard regimen for peritonitis in PD patients already using PD cycling machine as well as those who temporarily need shorter dwells during peritonitis due to increasing peritoneal solute transport.

**Funding:** Government Support - Non-U.S.
Is Automated Peritoneal Dialysis Better Than Continuous Ambulatory Peritoneal Dialysis in Quality of Life, Depression, and Renal Treatment Satisfaction? A Prospective Multicenter Propensity-Matched Study

**Methods:** Incident patients initiating APD and CAPD were prospectively enrolled from nationwide multicenters in Korea. HRQOL, depression, and renal treatment satisfaction were assessed at 1 and 12 months after the start of dialysis by Kidney Disease Quality of Life Short Form 36 (KDQOL-36), Beck’s Depression Inventory (BDI), and Renal Treatment Satisfaction Questionnaire (RTSQ), respectively. The mean changes of scores in APD and CAPD were compared by propensity score matching analysis.

**Results:** All 260 incident patients starting peritoneal dialysis (PD) from 11 centers were included in this study. A total of 170 patients were matched from 208 patients who completed all questionnaires and did not change PD modality during the 1-year follow-up period. The total scores at 1 month showed better HRQOL for APD than CAPD patients in symptom, patient satisfaction, pain, and social function domains. No differences were observed between the two groups in total scores of KDQOL-36 at 12 months. However, CAPD patients had a significantly greater improvement in symptom and social function domains. A significant improvement also occurred in BDI and RTSQ in CAPD patients.

**Conclusions:** APD is not better than CAPD in HRQOL, depression, and renal treatment satisfaction during initial first one year on dialysis. The relative positive effect of CAPD compared with APD on improvement of HRQOL, depression, and renal treatment satisfaction was confirmed.

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**TH-PO1025**

Thyroid Functional Disease and Mortality in a National Peritoneal Dialysis Cohort

**Background:** Peritoneal dialysis (PD) patients have a high prevalence of thyroid dysfunction which may be due to 1) peritoneal effluent losses (vast majority of thyroid hormone is protein-bound) and 2) frequent exposure to povidone-iodine cleaning agents leading to iodine-induced hypo- and hyperthyroidism. In the general population thyroid dysfunction is associated with higher risk of cardiovascular (CV) disease and death. There has not been study of the association between hypo- or hyperthyroidism defined by TSH with mortality in PD patients.

**Methods:** We examined the association of thyroid functional status with all-cause mortality in a 5-year national cohort (1/2007-12/2011) of PD patients with at least one TSH measure. Thyroid functional status was defined as: hyper-, eu-, and hypothyroidism (TSH <0.5, 0.5-5, >5mIU/L). We examined time-dependent and baseline thyroid function to determine short- and long-term exposure–mortality associations, respectively, using Cox models with 3 adjustment levels: unadjusted, case-mix, and case-mix+laboratory adjusted.

**Results:** Among 1484 patients, 7% and 18% had hypo- and hyperthyroidism, respectively. In time-dependent analyses, hypo- and hyperthyroidism were each associated with higher mortality, suggesting short-term risk in PD patients. Further studies are needed to determine if CV pathways are implicated, and if thyroid-modulating therapies ameliorate mortality in this population.

**Conclusions:** Time-dependent hypo- and hyperthyroidism were each associated with higher mortality, suggesting short-term risk in PD patients. Further studies are needed to determine if CV pathways are implicated, and if thyroid-modulating therapies ameliorate mortality in this population.

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**TH-PO1026**

A Tale of APOL1 Mutation and Parvovirus Infection

**Introduction:** We present a case of a first trimester pregnant woman with nephrotic range proteinuria and fetal demise in the setting of an acute parvovirus infection. Kidney biopsy revealed collapsing FSGS, and exome sequencing revealed mutations in APOL1. The relationship between Parvovirus and FSGS is one that clinicians might overlook, and perhaps may play a more prominent role in these progressive cases especially with APOL1 mutations.

**Case Description:** 37 yo Caribbean female presented at 8 weeks gestation with progressive swelling. Her daughter developed fifth’s disease one month prior. On presentation her BP was 146/95, HR 77 with pitting edema. Her creatinine was 6.3, BUN 43, albumin 1.5, and spot pt/ct 20.8. Parvovirus PCR was 2000 copies. Biopsy demonstrated collapsing FSGS secondary to Parvovirus B19 [Fig 1A 1B]
The hope was that this injury would improve with improvement in titers, so IVIG was started. A follow up PCR showed improvement to 200 copies but she remained nephrotic with proteinuria of 20-60 g. Re-biopsy revealed significant scarring and dialysis was initiated [Fig IC]. Patient is now being evaluated for transplant. Given the unusual severity of this case, and her possible African ancestry, a genetic susceptibility to podocyte injury was entertained. Whole exome sequencing identified the patient to have two APOL1 risk alleles.

**Discussion:** Parvovirus has been linked with collapsing FSGS, and in one study viral PCR was detected in 78% of kidney tissue with this diagnosis. The combination of B19 infection and APOL1 mutation likely made our patient particularly susceptible to injury. Our case raises the question of how often subclinical parvovirus infection may be involved in collapsing FSGS, and highlights how subtle and devastating it can be to the life of a prior healthy young woman.

**TH-PO1027**

**Podocyte Myeloid Bodies withoutConfirmed Genetic Mutation in a Female: Fabry’s Disease?**

Pravir V. Baxi,1 David J. Cimbaluk,2 David G. Warnock,3 Robert J. Descheny,4 William Luke Whittier,5 \*Nephrology, Rush Univ MC, Chicago, IL; 5Pathology, Rush UNC, Chicago, IL; 6Nephrology, UAB, Birmingham, AL; 7Genetics, Mt Sinai, New York, NY.

**Introduction:** Fabry’s disease (FD) is a X-linked lysosomal storage disorder caused by deficient alpha-galactosidase activity. A renal variant has been described with the R363H mutation. Due to random X-chromosomal inactivation, heterozygous females can present a diagnostic challenge. We report a case with a renal limited presentation, biopsy findings characteristic of FD but a negative whole blood DNA analysis.

**Case Description:** A 46-year-old Hispanic woman was evaluated for proteinuria. She was asymptomatic with no prior medical history or family history, and no exposure to silica, amiodarone, or hydroxychloroquine. Her exam was unremarkable: no neuropathy, skin changes, or corneal dystrophy. ScCr was 0.6 mg/dL, UA 2+ protein with P/C ratio of 1.94 g/L. Biopsy revealed diffuse enlargement of the podocytes with a foamy cytoplasmic appearance and on EM, prominent podocyte lamellated lipid inclusions with foot process effacement and minimal endothelial deposits.

**Figure 1:** Podocyte myeloid bodies; yellow line denotes foot process effacement, red star shows limited endothelial inclusion. Alpha-galactosidase activity was 0.187 U/L (lower limit of nl) and genomic sequencing of the GLA gene was negative. EKG, Echo, cardiac MRI, and brain MRI with and without gadolinium were nl.

**Discussion:** We present a pt with renal limited manifestations mimicking FD in the absence of known toxic exposure and a negative whole blood DNA mutation analysis. Treatment with enzyme replacement is not warranted without a positive genetic analysis. This case highlights the variable genotypic and phenotypic presentation, and raises the possibility that tissue-specific mosaicism could explain phenotypic variation in females with Fabry’s Disease.

**TH-PO1028**

**Relapsing Thrombotic Microangiopathy following Persistent Intravenous Use of Reformulated Oxycodone**

Melissa S. Nataatmadja,1,2,3 Baxi V. Pravir,4 Warnock, David G.,5 Descheny, Robert J.6, Whittier, William Luke.5

**Introduction:** Thrombotic thrombocytopenic purpura (TPP), with normal ADAMTS13 activity has recently been observed in persons injecting OxyContin (oxymorphone). This report supports the use of oxymethylene oxide (PEO), a tamper-proof coating added to the reformulated Oxycodone and Opna ER, as the causative agent, as TMA has now been observed following the use of two different medications but with the same PEO coating. Additionally, our case is the first to demonstrate relapse of TMA following persistent intravenous drug use of oxymethylene oxide. Given the rarity of this illness, it is possible that an unidentified genetic or immunologic susceptibility causes some individuals to develop TMA in response to these drugs, whilst others do not. We encourage clinicians to consider IV drug use in all patients presenting TMA, as treatment approach may differ and the role of plasma exchange is not yet clear.

**TH-PO1029**

**Iplilimum Associated Kidney Injury**

Andinet Gizaw, Jason M. Kidd, Nephrology, VCUHS, Richmond, VA.

**Introduction:** Melanoma is the most fatal form of skin cancer. Patients without surgically resectable disease require chemotherapy. Iplilimumab; a human monoclonal antibody against anti-CTLA-4 is an Immunomodulation agent, with proven benefit in overall survival in patients with unresectable, advanced (Stage 3) Melanoma. Cytotoxic T Cell Lymphocyte Antibody 4 (CTLA-4) is a negative regulator of T-Cell mediated anti-tumor immune response working as immune check points (down regulation). We present a case of acute kidney injury due to interstitial nephritis and minimal change disease from this drug.

**Case Description:** A 53-year-old woman with metastatic breast cancer, right atrial mass, status post resection, was seen for evaluation of acute kidney injury and nephrotic range proteinuria. He developed lower extremity swelling with rash about 02 weeks after receiving a third dose of ipilimumab. He had a baseline serum creatinine of 1.2mg/dL. At the time of consultation, his serum creatinine was 2.97mg/dL, 9 grams of proteinuria on 24 hours collection and serum albumin of 2.2. He was initially fluid resuscitated, however, creatinine increased to 5.2 mg/dL and he became oliguric. Urine microscopy was without casts and serology markers were negative. Renal biopsy was performed that showed an interstitial cast nephritis without giant cell interstitial inflammation and severe edema. Among most half of glomeruli were globally sclerotic, the others had minimally altered composition. Immunofluorescence was unremarkable. Electron microscopy showed diffuse effacement of podocyte foot processes. He was treated with high dose (2mg/kg) steroid and oral diuretics. Renal function has returned to his prior baseline and has a nephrotic proteinuria.

**Discussion:** This describes a case of nephrotic syndrome and interstitial nephritis related to the monoclonal antibody, Iplilimumab. Interstitial nephritis has been described with this drug before. However, this is the first case to our knowledge of the administration of Iplilimumab leading to acute kidney injury from interstitial nephritis and severe proteinuria from diffuse foot podocyte process effacement. Prompt recognition of this presentation is necessary to preserve renal function.


**TH-PO1030**

**Kappa Light Chain-Associated Crystal-Storing Tubulopathy, Podocytopathy, and Histiocytosis in GI Tract, in a Patient with Multiple Myeloma**

Michifumi Yamashita,1,2 Albert Q. Lam,3 Joseph V. Bonventre,2,3 Vanesa Bijo,2,4 \*Pathology, Brigham and Women’s Hospital, Boston, MA; 3Renal Division, Brigham and Women’s Hospital, Boston, MA; 4Harvard Medical School, Boston, MA.

**Introduction:** Multiple myeloma manifests with variety forms of kidney disease, such as amyloidosis, cast nephropathy, and light chain deposition disease. Among them, crystal-storing disease is a rare entity. We report an interesting case of a patient with extramedullary IgGk multiple myeloma, who presented with crystal-storing histiocytosis in GI tract, and subsequently developed crystal-storing tubulopathy and podocytopathy.

**Case Description:** A 65-year-old man with type 2 DM and HTN was found to have a 1 cm largeecal polyp on screening colonoscopy in 2009. The polyp showed diffuse infiltration by a plasma cell neoplasm and crystal-storing histiocytosis with k light chain (LC) restriction. At that time, the patient showed intact bone marrow, normal renal function and proteinaemia of 0.5 g/L. He was subsequently closely followed with endoscopy, SPEP, and renal function tests. In 2014, he developed nephrotic range proteinuria (>4g/24h), slightly rising Cre to 1.12 mg/dL, and increased serum free k LC (216 mg/L). Kidney biopsy was performed, revealing many proximal tubular epithelial cells containing PAS-positive PAS-negative granular materials in the cytoplasm. The glomeruli were unremarkable except for mild mesangial expansion. No significant immune deposits were present in glomeruli or tubulointerstitium, but there was slightly stronger background IF reactivity for k LC than l LC on frozen tissue sections. IF studies on protease-digested paraffin sections revealed strong k LC reactivity of the materials aggregated in the tubular epithelial cells and podocytes, whereas l LC was negative. EM revealed extensive intracytoplasmic accumulation of crystalline material of rhomboid and rectangular shapes in proximal tubular cells and podocytes.

**Discussion:** LC-associated crystal-storing disease is a rare kidney disease. To our knowledge, this is the first reported case of coexisting crystal-storing tubulopathy, podocytopathy, and histiocytosis in the GI tract in a patient with multiple myeloma.
Case Report of Obstructive Nephrolithiasis Secondary to Atazanavir

Dina Abdulwahab, Anusheer C. Shirali.

Introduction: Atazanavir, a protease inhibitor used in the management of human immunodeficiency virus (HIV), is associated with crystalluria and nephrolithiasis. While crystalluria is seen in 10-20% of patients on atazanavir treatment, frank nephrolithiasis is less common. We report a case of nephrolithiasis associated with atazanavir in an HIV patient on long-term highly active anti-retroviral therapy (HAART).

Case Description: A 56-year-old male with a past medical history of HIV on HAART, using dolutegravir, lamivudine, and abacavir to treat his HIV, presented with obstructive uropathy. His HAART regimen was switched to dolutegravir, lamivudine, and abacavir.

Discussion: This case clearly showed: (1) for the first time, Parvovirus B19 particles in glomeruli immunohistochemically and ultrastructurally, (2) Parvovirus B19 infection systemically and histologically preceding CG, and (3) when CG developed, serum Parvovirus B19 titer significantly decreased which could not be explained by the kidney tissue by EM or IHC. The evidence suggests that the direct or the indirect association between Parvovirus B19 infection and CG in kidney allograft.

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Relapse of Kappa Restricted Chronic Lymphocytic Leukemia Associated with a Lambda Restricted Plasma Cell Clone Causing Renal Amyloidosis

Sunil Smita Mahendrakar, Anushree C. Shirali.

Introduction: Chronic lymphocytic leukemia (CLL) has been associated among many malignant diseases. Rarely, it has been associated with amyloidosis either as the sole clone responsible, or in association with a plasma cell clone possessing the same light chain. A 72-year-old man with ESRD due to DM and HTN, status post kidney transplantation. Delay in diagnosis and xanthine oxidase inhibitor treatment predisposes to recurrent disease in renal allograft, with allograft loss in over 25% cases. Though APRT is ubiquitous in all cells, extrarenal symptoms are uncommon in affected individuals. Our patient presented with crystalline keratopathy resolving completely after kidney transplantation.

Case Description: A 66 year old male, diagnosed with kappa-restricted CLL in 2009 achieved complete remission after 6 cycles of fludarabine, cyclophosphamide and rituximab. 5 years later, he presented with foamy urine, generalized swelling, and weight gain. Serum creatinine was 1.1. Initial spot urine protein / creatinine ratio showed proteinuria of 5g/g which later increased to 10g/g. During the previous year serum albumin fell from 3.8 to 1.5 g/dL, and the white blood cell count rose from 7.4 to 30 x10^9/L. During the previous year serum albumin fell from 3.8 to 1.5 g/dL, and the white blood cell count rose from 7.4 to 30 x10^9/L. While the lymphocyte frequency rose from 45% to 88%, serum free light chains were 45.1mg/L lambda, 21.5 mg/L kappa with a ratio of 0.48. Kidney biopsy showed AL-amyloidosis with immunofluorescence positive for lambda. Due to discrepancy in the clonality of previous circulating CLL expansion (kappa restricted) and renal amyloidosis (lamba restricted), a bone marrow biopsy was done. This showed a relapse of CLL with low level (<10%) plasma cell dyscrasia. Flow cytometry confirmed that the relapsed CLL population was kappa-restricted while the clonal plasma cell population expressed lambda. After 8 months of treatment with velcade, dexamethasone and revlimid, he showed minimal improvement in proteinuria.

Discussion: Though the co-existence of clonal plasma cells and CLL is known, the temporal association of this patient’s nephritic syndrome secondary to amyloidosis from a unique plasma cell clone expressing a different light chain supports the hypothesis that, in CLL, sharing the same microenvironment as non-tumor cells may activate bystander B-cells to express free light chains and in this case lead to amyloidosis.

Recurrent 2,8-Dihydroxyadenine Deposition Successfully Treated with Kidney Transplantation

Pamela A. Duran, Mohamran Narayanaj, Div of Nephrology, Yale Univ School of Medicine, New Haven, CT.

Introduction: Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive purine metabolism disorder where adenine is oxidized by xanthine dehydrogenase to 2,8-dihydroxyadenine (2,8-DHA), forming insoluble urinary crystals, nephrolithiasis, CKD and ESRRD. Literature reveals diagnosis of APRT deficiency is rare before kidney transplantation. Delay in diagnosis and xanthine oxidase inhibitor treatment predisposes to recurrent disease in renal allograft, with allograft loss in over 25% cases. Though APRT is ubiquitous in all cells, extrarenal symptoms are uncommon in affected individuals. Our patient presented with crystalline keratopathy resolving completely after kidney transplantation.

Case Description: A 41 y/o Caucasian female with recurrent 2,8-DHA nephrolithiasis since age 23 was maintained on Allopurinol. Clinical course was significant for obstructive uropathy requiring multiple stent placements, continued decrement in renal function and bilateral hydronephrosis. Treatment with xanthine oxidase inhibitor was initiated to prevent recurrent transplant kidney stone disease. She developed crystalline keratopathy, xanthine oxidase inhibitor treatment predisposes to recurrent disease in renal allograft, with allograft loss in over 25% cases. Though APRT is ubiquitous in all cells, extrarenal symptoms are uncommon in affected individuals. Our patient presented with crystalline keratopathy resolving completely after kidney transplantation.

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Recurrence of CLL in a Patient with X-Linked Immunodeficiency Syndrome with Paraneoplastic Tumor-induced Osteomalacia (TIO) in Small Cell Carcinoma

M. Ahmed, Suneet Verma, Mandeep Samra, Jennine Michaud, Donghong Cai, Michael Yudd.

Introduction: Small cell carcinoma (SCCA) with diffuse sinusoidal pattern. Despite PO4 replacement, hypophosphatemia was found. Serum FGF-23, 577 RU/ml. No lab findings of Fanconi Syndrome . CT showed pulmonary weight loss. Labwork showed normal renal function, serum phosphorus (PO4) 0.8 mg/dl, immunohistochemical staining for FGF-23 in SCCA.

Discussion: Immunostaining of tumor cells from the lung and liver were positive for FGF-23. This is the first case with documented elevated serum FGF-23 and positive FGF-23 immunostaining of SCCA. Tumor-induced osteomalacia (TIO) is usually associated with benign tumors of mesenchymal origin, rarely with adenocarcinoma or small cell carcinoma. The syndrome is characterized by renal PO4 wasting due to excess FGF-23 from the tumor, leading to hypophosphatemia. There are at least 10 cases of SCCA with paraneoplastic PO4 wasting. Only for 1 case with documented elevated FGF-23 associated with tumors other than mesenchymal tumors: 2 cases of stage D2 prostate adenocarcinoma, one with metastatic colon cancer, and one with stage 4 ovarian cancer. All of these were advanced, metastatic disease. Of these, only the metastatic colon cancer case was documented with FGF-23 immunohistochemical staining in the hepatice metastases. Our case is the first case of FGF-23-positive immunostaining in tumor cells of small cell CA.

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Minimal Change Disease Diagnosing Relapsing Mantle Cell Lymphoma

Juan Calderon, Mark A. Perazella. Nephrology, Yale Univ School of Medicine, New Haven, CT.

Introduction: Glomerular lesions are linked with hematologic malignancies, with minimal change disease (MCD) commonly associated with Hodgkin’s lymphoma. Diagnosis of the underlying hematologic disorder often precedes development of the glomerulopathy; however, in rare cases, MCD precedes discovery of the lymphoma by several months. We present a case of a new onset nephrotic syndrome and AKI in association with undetected relapsing mantle cell lymphoma (MCL).

Case Description: A 74 yo man with history of stage IV mantle cell lymphoma in remission developed AKI and new onset edema. Chemotherapy completed 1 year prior to presentation induced complete remission on bone marrow and follow-up PET scans. On presentation he denied B symptoms, had no new lymphadenopathy, and only noted decreased appetite. The patient was edematous and hypertensive. Serum Cr was 2.4 mg/dl up from 1.3 mg/dl. High-grade, non-quantifiable urine protein was noted by the lab. Urine sediment was remarkable for numerous granular casts, oval fat bodies, and few uric acid crystals. Serum uric acid was 13.2 mg/dl. Therapy for tumor lysis syndrome was instituted due to concern for relapsing lymphoma in the setting of AKI. However, PET/CT scan was completely normal with no evidence for lymphoma. Furthermore, LDLH was within normal limits. Kidney biopsy revealed normal glomeruli on light microscopy with acute tubular injury. EM revealed global effacement of foot processes. A diagnosis of MCD with focal tubular injury was made and steroid therapy was started. Peripheral flow cytometry and later a bone marrow biopsy confirmed a 23% tumor burden compatible with relapsed MCL.

Targeted chemotherapy for MCL was initiated.

Discussion: We present the first report of MCD associated with relapsing MCL. Oncologic surveillance including PET scan failed to detect recurrent MCL. BM biopsy and flow study was pursued following the diagnosis of MCD. Initial therapy with steroids alone was associated with a reduction in proteinuria. This improved further with therapy directed at the relapsed MCL suggesting a pathophysiological relationship between these two disorders. Clinicians must remain cognizant of the possibility of malignancy when a suspicious glomerular lesion develops.

Renal Osteodystrophy

Hitarth S. Dave, Daniel E. Carl. Dept of Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ School of Medicine, Richmond, VA.

Introduction: It is believed that mineral metabolism changes start as early as stage II chronic kidney disease (CKD). The spectrum of CKD-mineral and bone disorder (MBD) ranges from low-turnover anemic disease to high-turnover osteitis fibrosa.

Case Description: A 37-year-old female with end-stage renal disease (ESRD), currently undergoing hemodialysis, presented complaining of a 1-day history of inability to eat or drink. Prior to presentation, she had noticed 2-week history of difficulty speaking, and 8-month history of increasing facial size. On presentation, the blood pressure was 180/68 mm Hg, and the oxygen saturation 98% while breathing ambient air. The physical examination revealed significant bony hypertrophy of the maxilla and mandible with edema of the overlying soft tissue. Computed tomographic (CT) scans of the maxilla and mandible showed severe expansion of the mandible and hard palate with complete replacement of the osseous matrix and surrounding mass effect on the maxillary sinuses and oropharynx. This improved further with therapy directed at the relapsed MCL suggesting a pathophysiological relationship between these two disorders. Clinicians must remain cognizant of the possibility of malignancy when a suspicious glomerular lesion develops.

5-Oxoprolinuria: A Rare Cause of High Anion Gap Metabolic Acidosis due to Acetaminophen Ingestion

Aravind Manshadian, 1,2 Sreesh G. Iyengar, 1 Seyed-ali Sadjadi, 1 Lisa Aimee Hechanova. 1 Nephrology, Loma Linda Univ, Loma Linda, CA; 2 Nephrology, Jerry L Pettis Memorial Veterans Medical Center, Loma Linda, CA.

Introduction: Acquired 5-oxoprolinuria is a rare cause of high anion gap metabolic acidosis, with excessive accumulation of citrulline. It largely goes unrecognized because an assay for 5-oxoprolinuria is not widely available. The malnourished and chronically ill women with history of chronic acetaminophen ingestion are commonly affected. Acetaminophen levels are rarely in toxic range.

Case Description: A 57-year-old woman with a history of adipsia dolorosa was admitted for acute osteosclerotic. She was chronically taking acetaminophen containing aspirin. Her acetaminophen level was not elevated. Usual causes of anion gap acidosis were ruled out. Finally, a urine organic acid screen showed elevated 5-oxoprolinuria levels. Acetaminophen containing pain medication was stopped; she was given IV hydration and sodium bicarbonate. Her anion gap metabolic acidosis would quickly resolve.

Discussion: Acute and chronic acetaminophen ingestion can lead to high levels of 5-oxoprolinuria. The pathophysiology behind acquired 5-oxoprolinuria has been mostly explained by reduced glutathione in prior case reports. 5-oxoprolinuria is an intermediate in the gamma-glutamyl pathway, the metabolic cycle responsible for creating glutathione and shuttling amino acids into the cytosol. When glutathione levels are diminished, feedback inhibition ceases, causing an overproduction of 5-oxoprolin. Sepsis, amongst others eutologies, have been implicated in glutathione depletion. 5-oxoprolinuria clinically presents with altered mental status. One of the key aspects of diagnosing this disorder is the detection of 5-oxoprolin in urine. N-acetylcycteine may be an effective treatment that acts to restore intracellular glutathione levels. Extracellular fluid expansion with dextrose containing saline promptly improves symptoms. In conclusion, 5-oxoprolinuria should be considered in any patient with unexplained metabolic acidosis and recent acetaminophen ingestion. Overlooking the diagnosis can be costly.

Severe Tubulointerstitial Nephritis with Lymphoid Follicles in Sjögren’s Syndrome

Maiko Nagata, Takehiko Kawaguchi, Mao Watanabe, Takafumi Yamakawa, Moritoshi Kadomura, Hiroshi Kitamura, Toshiyuki Imasawa. Internal Medicine, National Hospital Organization Chiba-East-Hospital, Chiba, Japan.

Introduction: Patients with Sjögren’s syndrome (SS) are at increased risk for the development of lymphoma. The presence of acute tubular injury and lymphoid hyperactivity in SS may predispose patients to the development of lymphoma neoplasm. However, biopsy specimens from some of these patients do not meet histologic criteria for frank malignancy. We report a rare case of severe tubulointerstitial nephritis with lymphoid follicles in SS.

Case Description: A 66-year-old woman, who had developed general malaise for a few years, was admitted to our hospital, because of the rapid rise in the serum creatinine
Scleroderma renal crisis was diagnosed according to the pathology result. Lisinopril 20 mg once daily was started and a continued deteriorating leading to hemodialysis.

Discussion: Recognizing the early signs of kidney injury is important to initiate the treatment scleroderma renal crisis (SRC). Physicians should suspect for SRC once patients have signs of acute kidney injury regardless of elevated blood pressure or creatinine.

TH-PO1042

Acetaminophen Associated 5-Oxoproline Acidosis in an Anuric End-Stage Renal Disease Patient Michael Plam,1 Leslie F. Thomas,2 Christine Snozek,3 1Internal Medicine, Mayo Clinic, Phoenix, AZ; 2Nephrology, Mayo Clinic, Phoenix, AZ; 3Laboratory Medicine & Pathology, Mayo Clinic, Scottsdale, AZ.

Introduction: Also known as pyrogulatamic acid, 5-oxoproline is an intermediary in glutathione antioxidant metabolism. Reports of acetaminophen associated 5-oxoproline high–anion gap metabolic acidosis (HAGMA) has been slowly growing in the literature but remains under recognized in clinical practice.

Case Description: A 57 year old male with anuric end-stage renal disease (ESRD) was admitted for confusion and hypotension secondary to sepsis from infected lower extremity ulcers, poor oral intake, and excessive peritoneal dialysis. Laboratory evaluation revealed a depressed bicarbonate level of 17 mEq/L and an elevated albumin–corrected anion gap of 30 mEq/L. Despite correction of an elevated L–lactate with fluid resuscitation and antibiotics, his HAGMA persisted. An exhaustive investigation was unable to find a convincing etiology including common–ly attributable organic acids, D-lactate, paraproteinemia, toxic exposures, and medications. Further inquiry revealed a protracted course of therapeutic acetaminophen ingestion with a weighted average daily dose of 1.3 grams in the four weeks leading to presentation. Serum 5-oxoproline was elevated to >100.0 mmol/L (normal <2.5 mmol/L). Serum acetaminophen was undetectable. All medications and medications containing medications were subsequently stopped. His clinical course improved with supportive care and he was discharged home. After 5 weeks of acetaminophen cessation, his serum 5-oxoproline normalized to 27.1 mmol/L with anion-gap and bicarbonate levels returning to baseline.

Discussion: To our knowledge, we report the first case of acetaminophen associated 5-oxoproline acidosis in an anuric ESRD patient. Risk factors are thought to be related to glutathione deficiency which in turn favors the 5-oxoproline pathway of the γ-glutamyl cycle and results in accumulation. These risk factors include reactive acetaminophen metabolites, alcohol abuse, malnutrition, sepsis, renal dysfunction, and liver disease. As an under recognized entity in clinical practice, 5-oxoproline should be considered in adults with unexplained HAGMA and the above risk factors.

TH-PO1043

Renal Amyloidosis Associated with Apolipoprotein C-II Deposition Lohit Garg,1 Gerta Mane,2 Sami S. Zarouk,3 1Dept of Internal Medicine, Beaumont Health, Royal Oak, MI; 2Dept of Nephrology, Beaumont Health, Royal Oak, MI.

Introduction: A 62-year-old female with no family history of renal disease presented with a creatinine at 2.3 mg/dL and hypertension. Baseline creatinine was 1.2 mg/dL one year prior to presentation and she had 1+ proteinuria on urinalysis 3 years earlier. Serologic work up was negative for ANA, C3, C4, hepatitis B and C, HIV and SLE. Membranous gammapathy evaluation showed IgA kappa monoclonal protein as two bands in the beta globulin region. Random urine for protein electrophoresis showed a small amount of IgA and free kappa monoclonal protein. Her random urine protein/creatinine ratio was 6.3. A renal biopsy was consistent with amyloidosis in the mesangium that exhibited apple green birefringence on polarization microscopy after Congo Red staining. Immunofluorescent stains for kappa and lambda light chains were negative. Electron microscopy showed randomly arranged fibrils in the mesangium with features characteristics of amyloid fibrils. Bone marrow biopsy showed 6% plasmacytosis and minimal involvement with amyloidosis. Laser micro dissection and liquid chromatography mass spectrometry (LCMS) were performed on peptides extracted from Congo-red positive dissected areas. LCMS detected high levels of apolipoprotein C-II while analysis for lambda or kappa light chains, transferrin and serum amyloid A were negative. It was concluded that these findings are unequivocally consistent with apolipoprotein C-II amyloid. Genetic testing was performed by direct sequencing of apolipoprotein C-II and showed mutation in patient as well as her son but not her daughter.

Discussion: Apolipoprotein C-II is a component of very low density lipoprotein and readily aggregates in lipid free conditions to form homogenous amyloid fibrils due to their intrinsic structure. To the best of our knowledge, this is the first case of apolipoprotein C-II renal amyloidosis. This case highlights the importance of performing DNA sequencing of exons of interest and LCMS on known amyloidogenic proteins to accurately diagnose and type the renal amyloidosis, which is critical for prognosis, treatment and genetic counseling.

TH-PO1044

Membranous Nephropathy in a Young Child with IPEX-Like Phenotype and a Novel Fxo3 Mutation Olena Charnaya, Sun-Young Ahn, Asha Moudgil. Nephrology, Children’s National Medical Center, Washington, DC.

Introduction: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome typically presents with heterogenous manifestations. The syndrome is characterized by numerous auto-immune diseases due to dysfunction in the Foxp3 gene, which plays a critical role in maintaining immune tolerance.
Reverse Pseudohyperkalemia in a Patient with Non-Hodgkin’s Mantle Cell Lymphoma

Case Description: A 44 y.o. male with ESRD was diagnosed in 11/2010 with CVID after developing pneumonitis. He had a history of recurrent sinusopulmonary infections and pneumococcal pneumonia. Immunoglobulin levels were undetectable and B and T NK cell numbers normal. He was treated with monthly IVIG infusions. In 3/2012, he underwent living unrelated kidney transplantation (KT). Immunosuppression consisted of basiliximab, methylprednisonelone, FK, MMF and prednisone. Baseline creatinine (Cr) post KT was 0.93 mg/dL and 1.06 mg/dL, Cr 1.06 mg/dL, urinalysis negative for blood, protein, and white blood cells. CT pain was so severe that he went to a local ER. Initial evaluation notable for BUN 10 mg/dL, Cr 1.06 mg/dL, urinalysis negative for blood, protein, and white blood cells. CT angiography revealed no evidence of acute tubular injury and transplant glomerulopathy with new diffuse (100%) C4d positivity. Rebiopsy showed resolution of ACR. However, he had chronic vascular rejection, focal intimal thickening and C4d positivity.

Discussion: Subsequent transthoracic echo showed no vegetation or shunt, appearing to exclude embolus from heart or lungs. Hypercoagulable work-up was negative. Patient is being managed conservatively with no anticoagulation, and is doing well. His Cr has drifted down from a peak of 1.16 mg/dL to a new baseline of 0.99 mg/dL, he has not developed hypertension, and his flank pain has resolved.

Conclusion: This case is notable because the FMD occurred in a male, and because renal infarction is a rare presentation of FMD. The actual cause of the infarction is most likely fat embolism syndrome (FES), which led to graft loss.

TH-PO1047

An Unusual Presentation of Fibromuscular Dysplasia

Case Report and Literature Review

Deepak Jasuja, Melissa D. Anderson. Div of Nephrology, Indiana Univ, Indianapolis, IN.

Introduction: Non traumatic causes of Fat Embolism Syndrome (FES) have been reported with bone marrow transplantation, osteomyelitis, pancreatitis, alcoholic fatty liver, and with liposuction. Etiology likely is fat particles entering the circulation with damage to capillary beds. Regardless of the mechanism initiating fat embolism, the end result is an intense inflammatory response. In the lungs, this induces lung injury that is indistinguishable from ARDS. FES can cause cerebral edema with raised intracranial pressure along with multi-organ failure and AKI.

Case Description: We present a 40- year-old African American lady who underwent non- myeloablative bone marrow transplant for Myelodysplastic anemia. One week after engraftment she developed sudden onset of respiratory distress leading to a cardio- respiratory arrest. She developed ARDS, multiple organ dysfunction syndrome and CVVH was initiated for oliguric AKI and Metabolic acidosis. Soon after initiating CVVH her filler clot was identified with white, creamy plaque which cleared after 2 successive filters. Patient met Gurd and Wilson’s criteria for diagnosis of Fat Embolism Syndrome. She had abundance of

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

Underline represents presenting author.
inflammatory cells on Broncho alveolar lavage including neutrophils and macrophages. Oil Red-O stain (stain for lipid) was performed to quantify macrophages displaying positivity. The initial Prep yielded 5 of 5 and the repeat prep yielded 11 out of 12 of macrophages positive for Oil-Red-O. CT brain was performed which revealed large acute strokes with midline shift compatible with subacute herniation. No cerebral blood flow was identified on nuclear scan and patient was declared brain dead and terminally weaned.

Discussion: With the absence of specific tests or criteria the diagnosis of FES is dependent on the clinical acumen of the physician. Lipid inclusion in 30%-70% of macrophages / inflammatory cells is more suggestive of FES. Only proven treatment is supportive. We propose that a clotting filter might be an earlier step to diagnose fat embolism syndrome and sending the filter for pathological analysis looking for lipid laden inflammatory cells is a less invasive approach as compared to quantification using Broncho-alveolar lavage.

TH-PO1049
Fetal Hyponatremia with Glycine Solution During Hysteroscopy – Proposal for New Mechanisms of Hyponatremia and Cerebral Edema

Introduction: We report a fatal case of severe symptomatic hyponatremia and cerebral edema following hysteroscopy.

Case Description: 39 y.o. woman underwent 70 mins hysteroscopic myomectomy, 6L of glycine solution used for distension, without documented deficits. 3 hours later she developed pulmonary edema. Hyponatremia of 117mEq/L, first noted 4 hours post surgery, baseline normal sodium. Course further complicated by agitation, vomiting, lethargy due to cerebral edema confirmed on C.T. Head 8 hours post-op, remained without brain stem reflexes. Post-op day 2 she also developed central diabetes insipidus. Remained brain dead, extubated and died after 12 days.

Discussion: Hyponatremia with glycine is iso-osmolar occurring as a result of dilution effect since glycine is retained in extra-cellular fluid before its metabolism by glycine cleavage enzyme. Two main postulations with the postulated explanation: 1) How does cerebral edema develop with iso-osmolar hyponatremia? 2) Why is hyponatremia often more severe than predicted? Proposed mechanisms: 1) Glycine can cross blood brain barrier (BBB) by passive diffusion, as shown in rats and cats. Sodium, however, does not exit brain via BBB as sodium transport across BBB occurs only inward. With glycotic toxicity, glycine accumulates in the brain cells after crossing BBB followed by water resulting in brain edema. Possibility of glycine metabolism to ammonia leading to cerebral edema cannot be ruled although high levels were not seen in our case.

TH-PO1050
Cytomegaloivirus-Induced Atypical Hemolytic Uremic Syndrome After Renal Transplant
Tinareen Kaar,1 Andrea G. Chiesa-votto,2 Leal C. Herlitzy,2 Richard A. Fatica.1 1Nephrology, Cleveland Clinic; 2Pathology, Cleveland Clinic, Cleveland, OH.

Introduction: Atypical hemolytic uremic syndrome (aHUS) may occur as de novo disease and recurrence of primary renal disease in kidney transplant recipients. Causes of de novo HUS includes immunosuppressive drugs, ischemia reperfusion injury, acute humoral rejection, and viral infections. Some patients have a genetic susceptibility to the disease from underlying mutations in the complement regulatory proteins. Cyto mengaloivirus (CMV) has been rarely reported as a trigger for de novo post-transplant aHUS.

Case Description: A 61 year old male underwent deceased donor kidney transplant for ESRD from presumed FSGS. 1 year following transplant he was admitted with profound diarrhea and weight loss due to CMV colitis and high grade CMV viremia (410,462 copies/ml). His immunity was reduced and he was discharged home on oral valganciclovir with near resolution of symptoms. He was re-admitted 1 week later with nausea, abdominal pain, and acute kidney injury (Creatinine of 3.8 mg/dL, baseline of 1.8 mg/dL). His repeat CMV viral load was significantly better at 70,000 copies/ml. Labs were suggestive of microangiopathic hemolytic anemia. Hb 8 g/dL, platelets 58 K/ul, LDH 586 U/L, haptoglobin <20mg/dL, and ADAMTS13 activity <67%. He received 4 sessions of plasmapheresis without improvement and required initiation of dialysis. Histologic features of acute and subacute endothelial injury, including segmental fibrin thrombosis of 2 arteries were present on transplant kidney biopsy. His aHUS genetic panel revealed several mutations in different genes. His CMV disease was identified. He was started on eculizumab. His hemolysis labs improved and he was taken off dialysis.

Discussion: CMV infection by way of endothelial injury can provoke aHUS in kidney transplant recipients and possibly be enhanced by genetic predispositions. Postulated mechanisms of CMV-induced injury include increased leakage and select perforation, endothelial expression of VWF, platelet adhesion, and intercellular adhesion molecule-1 and intracellular adhesion molecule-1. In our case, the aHUS process was halted by use of eculizumab.

TH-PO1051
Acute Interstitial Nephritis from Anti-PD-1 Therapy with Pembrolizumab in Two Patients with Advanced Non-Small Cell Lung Cancer
Heidi Mac G. Timbol, Anshuree C. Shirali, Internal Medicine, Section of Nephrology, Yale Univ School of Medicine, New Haven, CT.

Introduction: Immune checkpoint inhibition with monoclonal antibodies (mAb) targeted against programmed cell death receptor 1 (PD-1) is an emerging immunotherapy for various cancers. Pembrolizumab, an anti-PD-1 mAb, is being used in clinical trials with promising anti-tumor responses, but renal-specific adverse events are not clear. We report 2 cases of acute interstitial nephritis (AIN) in patients who received Pembrolizumab for advanced non-small cell lung cancer (NSCLC).

Case Description: Two female patients, both 69 years of age, with metastatic NSCLC were seen in outpatient nephrology clinic for acute kidney injury (AKI). Both patients were enrolled in a clinical trial with Pembrolizumab, and their cases had been complicated previously by auto-immune adenylasins. On labs, Patient A had an increase in creatinine to 2.1 mg/dL prior to cycle 16, up from a baseline of 0.9 mg/dL. Patient B had a creatinine peak of 1.9 mg/dL after cycle 6, up from a baseline of 1.1 mg/dL. Medications were significant for long-standing pantoprazole use in both patients. Urine sediment showed many WBC clumps without casts or RBCs. Renal ultrasound was unremarkable. Volume expansion with normal saline and cessation of potential nephrotoxins failed to reverse renal dysfunction in either case. Each patient underwent CT-guided renal biopsy, which showed diffuse AIN. Steroid therapy with prednisone 60 mg/day with a slow taper was started and creatinine improved to baseline.

Discussion: These two cases highlight a new association between AIN and Pembrolizumab, which to the best of our knowledge has not been previously reported. While both patients were on pantoprazole therapy prior to their AKI, this medication was not new. Rather, the time course of AKI best fits with initiation of pembrolizumab. Additionally, their pre-existing drug-related autoimmune adenylasins suggests a possible auto-immune component to AIN from anti-PD-1 therapy. With increasing use of these agents, clinicians should maintain a high index of suspicion for AIN as a cause of AKI and have a low threshold for kidney biopsy to confirm diagnosis and initiate early treatment.

TH-PO1052
Concurrent Anti-PLA2R and ADAMTS 13 Inhibitor – Coincidence or a Clue to Pathogenicity? Laith Al-Babadi,1 Moshe Shashar,2 Parikshit Duriseti,2 Ami Patel,2 Aala Jaberi,1 Ashish Upadhyay,1 Joel M. Henderson,1 Vipul C. Chitalia,1 David J. Salani,1 Laurence H. Beck,1 Boston Univ Medical Center; 2Mamata Medical College, India.

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a hematologic emergency associated with a decrease in ADAMTS13 activity, most often due to the presence of an auto-antibody against ADAMTS13. However, patients with atypical hemolytic uremic syndrome (aHUS) have a low threshold for kidney biopsy to confirm diagnosis and initiate early treatment.

Case Description: Herein, we present a case of a 70 year old male who presented with generalized anasarca. Physical exam was remarkable for BP 180/100, and 2+ peripheral edema. Workup revealed Hgb 7.4, Pts 16, Creatinine 1.43, LD 742 and undetectable haptoglobin. His peripheral smear showed many schistocytes. These findings were consistent with thrombotic microangiopathy. Urine analysis showed 2+ blood, 3+ protein. Examination of the urinary sediment revealed oval fat bodies, and some RBCs. The patient was started on plasma exchange and prednisone (1 mg/kg). Further studies revealed a serum albumin of 2.2 and urine protein/Cr of 9. Kidney biopsy showed features of membranous nephropathy with many subepithelial deposits flanked by new basement membrane material (spikes). The deposits were immuno reactive for PLA2R, with IgG1 but no IgG4 reactivity. In addition, there was moderately severe arteriol and arteriolar sclerosis and segmentally prominent double contour formation in the glomeruli. These vascular changes suggest a primary form of endothelial injury and consistent with chronic thrombotic microangiopathy. VWF protease activity came back as less than 3% with an elevated inhibitor titer of 1.3 (spikes). Anti-PLA2R was detected in the serum at a titer of 40.3 IU/ml. Both were exclusively of the IgG1 subtype by western blotting, atypical of the usual IgG4 predominance for both autoimmune disorders.

Discussion: Although prednisone, plasmapheresis, and supportive therapy have thus far stabilized both diseases, rituximab would be our first choice for more definitive treatment of these concurrent autoimmune disorders. This unique case may help to further our understanding of the mechanistic pathways underlying both of these clinical entities.
Carfilzomib Associated Acute Kidney Injury Vladimir Liberman,1, Vivette D’Agati,2, Naveed N. Masani,1 Joseph Mattana, James Drakakis,1 Medicine, Winthrop-Univ Hospital, Mineola, NY, 2Pathology, Columbia Univ Medical Center, New York, NY.

Introduction: Carfilzomib is a selective proteasome inhibitor approved in 2012 for the treatment of relapsed and refractory multiple myeloma. A phase 2 trial of the drug showed an increased serum creatinine in 17.7% of patients but the mechanism has been incompletely understood. We report a case of biopsy proven acute tubular injury one week after carfilzomib administration. Case Description: A 60 year old man with IgG lambda multiple myeloma who received an autologous stem cell transplant 2 years ago presented to the hospital complaining of shortness of breath and chest discomfort. Physical examination revealed a blood pressure of 141/74, clear lungs, normal heart sounds with no murmurs and pitting edema of both lower extremities. Serum potassium was 0.6 mEq/L and creatinine was 3.4 mg/dL (baseline 0.8 mg/dL). Serum free lambda light chains were 3630 and free kappa light chains were 5.5. The patient was found in an injection of carfilzomib 7 days prior to his arrival. He had no history of nephrotoxic medications. Spot urine protein/creatinine ratio was 3 g/g with an albumin/creatinine ratio of 140 mg/g. Obstruction was excluded by ultrasonography and he received isotonic saline with only minimal improvement in kidney function at which point a kidney biopsy was performed. Renal biopsy showed focal mild myeloma cast nephropathy with diffuse acute tubular injury out of proportion to the sparse casts. The close temporal association with the initiation of carfilzomib suggests that it could have been responsible for the severe tubular injury given no other obvious insults. Discussion: Carfilzomib has been associated with kidney injury as one of its adverse effects in its phase 2 trial. Most of the kidney injuries were reported as grade 1 or 2 based on the NIH grading system. Grade 3 and 4 renal impairment was reported in 38 patients (7.2%). This case of biopsy proven acute tubular injury suggests a mechanism by which carfilzomib may cause acute kidney injury in patients with multiple myeloma.

Podocyte Infolding Glomerulopathy in a Patient of African Decent Matthew McCoy,1 Laurence H. Beck,2 and Stewart H. Lecker,3 Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

Introduction: Podocyte infolding glomerulopathy (PIG) is a rare entity primarily described in Asians which is a form of membranous glomerulopathy (MG) from autoimmune diseases (i.e. lupus). It is not known whether PIG represents a new disease entity or a transient morphologic state of well-known diseases (i.e. a subset of membranous nephropathy or lupus nephritis). PIG has been exclusively described in Asian populations, with no cases reported in patients of African descent. PIG has been distinguished by its histologic features of podocyte membrane infolding into the basement membrane and the formation of microspikes and microtubules. The majority of cases do not contain electron-dense deposits, nor do they show any reactivity with IgG. Here we present the first reported case of PIG in a patient of African descent.

Case Description: A 58 year old Africa female from Ghana with history of systemic lupus erythematosus presented to the nephrology clinic for the evaluation of proteinuria. She was found to have a serum creatinine of 1.5 mg/dL and random urine protein to creatinine ratio of 1.5 g/g. Microscopic examination of the urine sediment did not reveal RBCs or casts. Other laboratory findings included a strongly positive anti nuclear antibody titers of 1:1280 and positive anti double stranded DNA. She underwent kidney biopsy. Light microscopy revealed thickened glomerular peripheral capillary walls, with numerous crater-like defects. Immunofluorescence was negative other than trace IgM and C3 reactivity along the basement membrane. Electron microscopy revealed thickened glomerular peripheral capillary walls, with numerous crater-like defects. The patient was referred for two years of stable, nephrotic-range proteinuria. Here we present the first reported case of PIG in a patient of African Decent.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
341A

Diabetes Insipidus Induced by Excessive Intake of Melatonin Rahul N. Pawar, Savneek S. Chugh, Amy R. Patel. Nephrology, Westchester Medical Center, Valhalla, NY.

Introduction: Melatonin is produced by the pineal gland and regulates the sleep/wake cycle in humans. Specific over the counter melatonin formulations can be used to treat circadian rhythm-related sleep disorders and age-related insomnia. Acute intoxication of melatonin and its deleterious effects have rarely been reported. We present the first case of diabetes insipidus due to excessive melatonin ingestion.

Case Description: A 24 year old female, with no known medical history, was brought to the hospital for altered mental status and possible drug overdose. Her vital signs were a Tmax of 101.8 F, HR 170, BP 150/103, and a pulse oximetry of 98% on 2L NC. On physical exam, she had mildly dilated and sluggishly pupils. Due to an altered sensorium, she was intubated for airway protection. Initial lab tests showed a sodium of 140 mEq/L, potassium 3.9 mEq/L, chloride 113 mEq/L, bicarbonate 25 mEq/L, BUN 8 mg/dL, and a creatinine of 0.6 mg/dL with no osmolar gap, but elevated AST 74 U/L, ALT 37 U/L and creatine phosphokinase of 2,460. Urine toxicology screen was negative for PCl, cocaine, MDMA, and opioids with an undetectable blood alcohol level. On day 1, she developed polyuria with a urine output of more than 13.5 liters, a serum sodium of 147 mmol/L and urine osmolality of 65 mosm/kg concerning for diabetes insipidus (DI). CT head and MRI of the brain were negative for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day. After tubulostomy, the patient reported ingestion of an excessive amount of melatonin for intracranial lesions. Despite decreasing the rate of intravenous fluids, her urine output was more than 6L/day. Her urine osmolality increased to 444 mosm/kg suggestive of a partial central DI. With the administration of DDAVP, her urine output decreased to 2-3L/day.
TH-PO1058

Renal Transplant Dysfunction due to Calcium Casts following Parathyroidectomy. Maharanjan Raman, Rajkumar Chinnadurai, Grahame N. Wood, Jamil Choudhury, Philip A. Kalra. 1. Renal Medicine, Salford Royal NHS Foundation Trust, Salford, Manchester, United Kingdom; 2. Cellular Pathology, Salford Royal NHS Foundation Trust, Salford, Manchester, United Kingdom.

Introduction: Parathyroidectomy for renal hyperparathyroidism can lead to significant drop in calcium levels due to the hungry bone syndrome, which can lead to seizures, coma or fractures. Current practice is to pre-load patients with hydroxychloroquine and calcium supplements to maintain safe calcium levels in the post-operative period. We report a case of calcium cast nephropathy caused by significant renal dysfunction following parathyroidectomy.

Case Description: A transplant patient on Cincalacet for tertiary hyperparathyroidism underwent parathyroidectomy (PTX). Post-operatively her calcium levels were managed according to local protocol. Patient sub-acutely developed renal dysfunction and the trends in creatinine(Cr), corrected calcium(Ca) and parathyroid hormone levels(PTH) pre and post surgery are shown in the table below.

<table>
<thead>
<tr>
<th></th>
<th>1 month post</th>
<th>2 months post</th>
<th>3 months post</th>
<th>4 months post</th>
<th>6 months post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr (umol/L)</td>
<td>113</td>
<td>167</td>
<td>132</td>
<td>169</td>
<td>284</td>
</tr>
<tr>
<td>C.Ca (mmol/L)</td>
<td>2.73</td>
<td>2.62</td>
<td>2.55</td>
<td>2.71</td>
<td>2.67</td>
</tr>
<tr>
<td>PTH (pg/L)</td>
<td>329</td>
<td>-</td>
<td>54</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Virology screen, immunology screen, urine culture, urine PCR, DSA, Cyclosporin levels and renal ultrasound were normal with no change in patients haemodynamic status. Hence a kidney biopsy was performed to identify the cause, which showed evidence of calcium casts with surrounding inflammation with no evidence of rejection. Her steroid dose was transiently increased due to the inflammation seen on the biopsy and all her calcium and hydroxychloroquine supplements were suspended, which lead to recovery of her renal function to baseline.

Discussion: Our patient had mild hypercalcemia prior to parathyroidectomy with a stable renal function and following parathyroidectomy patient developed renal dysfunction despite similar levels of calcium, which can only be explained by intrageneric calcium supplementation based on the renal biopsy. Perhaps routine monitoring of urinary calcium may help us guide the amount of calcium given to such patients and aiming for lower levels of calcium post parathyroidectomy rather than normal levels may prevent such phenomenon.

TH-PO1059

Severe Ketoacidosis After Bariatric Surgery in a Patient Treated with Canagliflozin. Hossein Ghoftan, Christopher C. Wong, Miroslaw Smogorzewski. Div of Nephrology, Keck Hospital of USC, Los Angeles, CA.

Introduction: Euglycemic diabetic ketoacidosis is relatively uncommon and is usually caused by starvation and a lack of caloric intake. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been very recently implicated as a cause of severe ketoacidosis. We report a case of euglycemic diabetic ketoacidosis in a patient who underwent bariatric surgery while taking an SGLT2 inhibitor, canagliflozin.

Case Description: A 38 year old male with a history of DM type 2 and morbid obesity presented with fatigue, acute dyspnea, decreased exercise capacity and 2-3 pillow orthopnea for two days. Canagliflozin 300 mg daily was initiated 3 months prior to his current presentation due to poorly controlled DM-2. Ten days prior to his hospitalization, he underwent gastric sleeve bypass surgery and was discharged on post-op day 1. Upon admission in the ICU, his physical exam was benign except for a PR 108/min, RR 29/min, and a normal BP 128/69 mmHg. ABG showed pH 6.9, pCO2 13mmHg, pO2 99mmHg, bicarbonate 5mg/dL. His anion gap was 37, and serum glucose 152 mg/dL, with normal kidney function. Urine toxicology and blood levels of lactic acid and creatinine were normal and urine ketones were negative. Urinalysis revealed pH 5.0, glucose >1000 mg/dL, and ketones>150 mg/dL. During the first day, he received 150 mg of sodium bicarbonate; his canagliflozin was held. He was intubated and started on a regular insulin drip along with 5% dextrose solution. He remained intubated for 5 days on an insulin drip. The past 2 days, he received pamidronate and extensive electrolyte replacement; blood glucose never exceeded 200 mg/dL while glycosuria persisted until day 7. C-peptide increased from 0.29 to 2.26 mg/L. Once anion gap was closed and patient stabilized, he was extubated and weaned off the insulin drip.

Discussion: We present a new case of severe euglycemic DM ketoacidosis caused by a combination of SGLT-2 inhibitor use and low caloric intake after bariatric surgery. Despite withdrawal of canagliflozin, its effect on glycosuria persisted for 7 days. Considering long biological effect of SGLT-2 inhibitors, they should be stopped weeks before a bariatric surgery to avoid ketoacidosis.

TH-PO1060

Severe Hypercalcemia in Erdheim-Chester Disease: A Rare Clinical Scenario. David H. Slade, 1, Esho Georges, 2 Ahmer Farooq, 2 Kavitha Vellanki. 1Dept of Medicine, Loyola Univ Medical Center, Maywood, IL; 2Dept of Nephrology, Loyola Univ Medical Center, Maywood, IL; 3Dept of Urology, Loyola Univ Medical Center, Maywood, IL.

Introduction: Erdheim-Chester disease (ECD) is a rare form of histiocytosis with highly variable clinical manifestations. Only a few cases have hypocalcemia, and even fewer have hypercalcemia. Here, we present a case of severe hypercalcemia, workup of which eventually led to the diagnosis of ECD.

Case Description: A 58 year old Polish male with chronic kidney disease due to obstructive urethral obstruction was transferred to our center for suspected pneumophlebitis. His course was complicated by persistent fevers with repeatedly negative infectious workup and severe hypercalcemia with ionized calcium levels peaking at 1.66 mm/L. Parathyroid hormone levels were appropriately suppressed. Work up for multiple myeloma showed no lytic lesions on bone scan, however, bilateral, symmetric, sclerotic lesions in the distal femurs and proximal tibiae were incidentally noted. Based on these findings, ECD was suspected. ECD was confirmed by biopsy which revealed multiple histiocytic and lymphomycic aggregates positive for the histiocyte marker CD68, but negative for CD1a (pathognomonic of the disease). He was subsequently started on BRAF (>raf murine sarcoma viral oncogene homolog B1) inhibitor, vemurafenib with marked improvement in clinical symptoms. While he received pamidronate for hypercalcemia during the hospital stay, his ionized calcium levels have since normalized and continue to be within normal range 6 months after the initial presentation.

Discussion: In conclusion, ECD is a rare disorder with varied clinical manifestations and diagnosis is often elusive, requiring a high level of clinical suspicion. Although skeletal involvement is seen in 96% of the patients with ECD, there have been no reported cases of hypercalcemia, and our case is the first to report such an association.

TH-PO1061

APOL1 Polymorphisms in Deceased Donors and Primary Glomerular Disease Post-Kidney Transplant: First Case Report. Pratik B. Shah, Alexander C. Wiseman, James E. Cooper. Renal Diseases and Hypertension, Univ of Colorado Medical Center, Aurora, CO.

Introduction: Genetic polymorphisms in APOL1 (G1/G2) are associated with glomerular disease and ESRD. An emerging issue is whether screening for APOL1 (G1/G2) should be performed in living or deceased kidney donors.

Case Description: A 46 year-old Caucasian male with a history of SLE received a deceased donor kidney transplant. The deceased donor was a 12-year old African American male. 9 months post-transplant, he presented with acute kidney injury following an elective acute CMV infection. The patient ultimately did not recover kidney function. The patient’s serum creatinine peaked at 2 g/g Cr, platelet count of 58000, LDH of 2022 U/L, haptoglobin of <14 mg/dl. Plasma CMV PCR was positive at 234000 copies/ml. The patient’s acute kidney injury was attributed to collapsing glomerulopathy induced by acute CMV infection. The patient ultimately did not recover kidney function.

Discussion: To our knowledge, this is the first case report of high risk variant APOL1 in a deceased donor with subsequent primary glomerular disease in both the recipients. This suggests that deceased kidney donor APOL1 genotyping may be informative in predicting graft outcomes. This also highlights the important question of whether routine screening of African American donors for high risk APOL1 variants before renal transplant is warranted.

This consideration must be balanced against the significant limitations in kidney availability.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
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Underline represents presenting author.

TH-PO1062
Atypical HUS in an Infant due to a Novel Gene Mutation

Mohamed Alsefri, Robin Amy Kremsdorf, M. Khurram Faizan. 1 Rhode Island Hospital; 2 Hasbro Children’s Hospital; 3Hasbro Children’s Hospital.

Introduction: Atypical HUS (aHUS) is a rare genetic renal disease associated with over-activation of the alternative pathway of complement. A variety of mutations have been described in the complement pathway genes in patients with aHUS. We report a case of aHUS due to mutation in the Complement Factor B (CFB) gene.

Case Description: 10 months old Caucasian girl who presented with diarrhea, vomiting, and swelling in her extremities and face for 2 weeks preceded by an episode of cough, runny nose with non-bloody diarrhea. Upon presentation her BP was 150/90 mm Hg. Lab data showed Hb 6.4 g/dL, hematocrit 23%, leukocytosis to 100.4 x 10^9/L, anemia of chronic disease, serum creatinine, 0.3, Albumin 2.6 g/dL, LDH 632 IU/L, normal ADAMTS13 and C3 level 7.9 mg/dL. Urine revealed 32RBC/hpf with proteinuria, Urine Protein Creatinine ratio 19 g/g. Peripheral blood smear revealed schistocytes. Stool was negative for Shiga toxin. Clinical presentation was compatible with aHUS and patient was treated with Eculizumab. There was marked improvement in her clinical status with resolution of his symptoms.

Discussion: RRT was stopped after two weeks and she was discharged on ACEI with Eculizumab every 2 weeks.

TH-PO1063
Oxymorphone-Induced Thrombotic Microangiopathy and Acute Kidney Injury


Introduction: Intravenous (IV) administration of oral oxymorphone represents an emerging pattern of drug abuse with increasing popularity and unforeseen adverse consequences. Here, we present a case of IV oxymorphone abuse associated with thrombotic microangiopathy (TMA) and acute kidney injury (AKI).

Case Description: A 32-year-old man with a history of IV drug abuse presented with non-healing left arm wound. Physical examination was unremarkable except for a left forearm abscess. However, laboratory studies revealed a serum creatinine (SCr) of 2.3 mg/dL, blood urea nitrogen (BUN) of 55 mg/dL, creatinine 2.5 mg/dL, glucose 91 mg/dL, calcium 9.7 mg/dl,serum Osm 375 mOsm/kg, urine Osm 678 mOsm/kg, ADH level was 2.2 pg/ml(nl). Urinalysis: specific gravity 1.016, pH 5.5, 1+ protein, trace blood. A renal biopsy showed acute and chronic thrombotic microangiopathic changes consistent with aHUS. ADAMTS13 level was >100%. Kidney biopsy showed evidence of TMA supported by glomeruli filled with focal extravasated and crenated RBCs. Immunofluorescence (IF) was negative for immune complex deposition but C4d staining was positive. Conservative management including platelet transfusion, without plasma exchanges was successful.

Discussion: This patient presented with TMA, acute kidney injury, and normal serum ADAMTS13 activity. His urine oxymorphone was positive and he admitted to IV abuse of pulverized oxymorphone pills, which represents an emerging pattern of illicit drug abuse. The mechanism of oxymorphone-induced TMA remains unclear but it is suggested that the drug or some ingredients mixed in it triggers a cascade of immunological pathways leading to TMA. Previously reported cases had negative IF on kidney biopsy but positive C4d staining in this patient implies some degree of complement activation. Although PE was initially used in some cases, it has recently been shown that oxymorphone-induced TMA could successfully be managed without it. Based on this case coupled with previous reports, we suggest that health care providers should inquire about IV oxymorphone abuse in the setting of unexplained TMA and acute kidney injury.

TH-PO1064
IgG4-Related Tubulointerstitial Nephritis in a Young Patient with Enlarged Kidneys

Valerie Jorge Cabrera, Shirin Shirani, Joni H. Hansson. 1 Yale Nephrology, Yale School of Medicine, New Haven, CT; 2Nephrology, Yale New Haven Hospital/ST. Raphael Campus, New Haven, CT; 3Nephrology, Yale New Haven Hospital/ST. Raphael Campus, New Haven, CT.

Introduction: IgG4-related disease is a recently recognized entity characterized by the infiltration of tissues with IgG4-positive plasma cells. It occurs more commonly in middle-aged adults with a male predominance. IgG4-related diseases can be classified into two groups; those that can mimic tumors. We present the unique case of a young patient with a two year history of recurrent cellulitis, parotid gland enlargement, diffuse lymphadenopathy and nephrectomy.

Case Description: A 27 year old African American male presented with a rash and edema of his right lower extremity. He also reported night sweats and weight loss over 4 months. His past medical history included hypertension, recurrent cellulitis, nephrolithiasis, chronic kidney disease of unclear etiology, antithrombin III deficiency and pulmonary embolism. Hypothyroidism has shown thyrotropin, hypergonadotropic amenorrhea.

Discussion: A number of conditions can lead to kidney enlargement. Diabetes, HIV, amyloidosis, and leukaemia lymphoma are commonly included in the differential diagnosis. IgG4-related disease should also be considered in the differential diagnosis of patients presenting with kidney enlargement and recurrent infections.

TH-PO1065
Karyomegalic Interstitial Nephritis: A Rare Cause of Kidney Disease

Lindsay Sanders, 1 Maxwell L. Smith, 2 Ibrahim Qaqish, 1 Sumi Sukumar

1Nephrology and Hypertension, Mayo Clinic Arizona, Phoenix, AZ; 2Pathology, Mayo Clinic Arizona, Scottsdale, AZ.

Introduction: Karyomegalic interstitial nephritis (KIN) is a rare, progressive kidney disease associated with Fancconi–associated nüclease 1 (FAN1) mutation as well as exposure to heavy metal, ochratoxin, or viral pathogens. Less than 50 cases have been reported to date. Our patient is one of the few cases with a KIN and FAN1 mutation report.

Case Description: A 45-year-old man was seen for renal impairment first noted at age 40, with a serum creatinine of 1.6 mg/dL (eGFR 53 mL/min/1.73 m²). He had no known risk factors for chronic kidney disease. His only other personal medical history was for skin rashes but he had no history of heavy metal exposure. He had a history of recurrent upper respiratory tract infections. There is no known treatment.

Discussion: The diagnosis of KIN should be considered especially when there is evidence of delayed tubular function in addition to impaired thirst perception.

TH-PO1066
Hypodipsic Hypernatremia: An Unusual Manifestation of Paraneoplastic Syndrome

Sahar Siddiqui, Sun-Young Ahn, Asha Moudgil. Nephrology, Children’s National Medical Center, Washington, DC.

Introduction: Hypernatremia usually results from increased free water losses or impaired thirst perception.

Case Description: A 17-year-old female presented to the emergency room after an episode of syncope while waiting for school bus on a summer morning. She had intermittent episodes of slurred speech over the previous 2 weeks but denied polyuria, polydipsia, dizziness or headaches. She was diagnosed with primary amenorrhea one year ago. Physical Exam: Weight 46 kg (5%ile), height 150 cm (<3%ile), BP 92/58 mmHg and afebrile. She was Tanner III for breast & I for pubic hair. The remainder of her exam was normal. Laboratory evaluation showed hemoglobin 11.2g/dL, hematocrit 37.8%, platelet 100x10^9/L, sodium 177 mmol/l, potassium 4.3 mmol/l, creatinine 1.0 mg/dl, CO 2,32 mmol/l, BUN 55 mg/dl, creatinine 2.5mg/dl, glucose 91 mg/dL, calcium 9.7 mg/dl,serum Osm 375 mOsm/kg, urine Osm 678 mOsm/kg, ADH level was 2.2 pg/ml(nl). Urinalysis: specific gravity 1.016, pH 5.5, 1+ protein, trace blood. A renal ultrasound showed a right suprarenal mass which was confirmed to be an adrenal mass on CT scan. Despite adequate intravenous hydration, her hypernatremia persisted. Due to low LHR & FSH there was a concern for hypogonadotropic hypogonadism. However, brain MRI was normal. DDAVP was initiated with partial response. The patient underwent a right adrenalectomy. pathology was consistent with ganglioneuroma.

Discussion: The cause of hypernatremia in this case was likely an impaired thirst mechanism in a cognitively normal child. Her partial response to DDAVP suggests an additional contribution from partial diabetes insipidus. Essential hypernatremia and an unpredictable syndrome using sodium level sensors (Na+) were reported in a 6 year old child by Hyama et al. (2010; 66(4): 508-522). The mechanism of hypernatremia was postulated to be impaired thirst due to antibodies to Nax in the brain. A diagnosis of paraneoplastic syndrome should be considered in a patient with hypodipsic hypernatremia without structural hypothalamic lesions.
IgG4 Mediated Isolated Reteroperitoneal Fibrosis Causing Obstructive Uropathy in a Patient with Subclinical Ankylosing Spondylitis

Ahn M. Morgan, Vikram Aggarwal. Internal Medicine/ Nephrology Div, SUNY Upstate Medical Univ, Syracuse, NY.

Introduction: Retroperitoneal fibrosis is a rare manifestation of systemic autoimmune disease, characterized by the presence of inflammatory and fibrotic retroperitoneal tissue that often encases the ureters causing obstructive uropathy. Idiopathic retroperitoneal fibrosis is currently being recognized manifestation of IgG4-related disease. We report a case of histologically confirmed IgG4 related retroperitoneal fibrosis in a patient with subclinical Ankylosing spondylitis. This association has been rarely reported.

Case Description: A 70 year old male with PMH of HTN, diabetes and baseline creatinine of 1.2 mg/dl presented with weakness, vomiting and decreased urine output. Physical examination was unremarkable. Further evaluation revealed serum creatinine of 13.3 mg/dl and BUN=106 mg/dl. He also has mild hyperkalemia and anion gap metabolic acidosis. Urine analysis was negative for protein or RBC cast. A CT scan of the abdomen and pelvis, showed retroperitoneal mass, Aortitis, ankylosis of SI joint bilaterally with osseous fusion and bilateral mild hydronephrosis. Bilateral nephrostomy tubes were placed with excellent urine output as well as improvement of creatinine in baseline in 48 hours. He subsequently had a CT guided biopsy of the retroperitoneal mass. Histopathology revealed dense fibrous tissue with significant IgG4 positive plasma cell infiltrate. Immunological workup showed elevated level of IgG4 as well as positive HLA-B27. Hence this obstructive uropathy was confirmed to be due to IgG4 related retroperitoneal fibrosis. He also met the clinical and imaging criteria for Ankylosing spondylitis. Treatment with oral corticosteroids was initiated by rheumatology.

Discussion: Our hypothesis is that the patient had a subclinical Ankylosing Spondylitis which triggered IgG4 mediated disease that lead to retroperitoneal fibrosis which caused bilateral obstructive uropathy. Hence role of ankylosing spondylitis in development of idiopathic retroperitoneal fibrosis may be under appreciated. Further studies are needed to investigate and meta this criteria to be aware of this rather unusual presentation.

IgG4-Related Tubulo-Interstitial Nephritis with Low Complement C4, Circulating Immune Complexes and an Elevated IgG, Presenting as Unilateral Hydronephrosis and Prostatitis

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Introduction: IgG4-Related Disease is characterized by infiltrates of IgG4-positive plasma cells and eosinophils in different organs and is a rare cause of tubulointerstitial nephritis (TIN) and idiopathic retroperitoneal fibrosis.

Case Description: A 67 year old white male had a creatinine increase from 0.90 to 2.06 mg/dl. He had fatigue and dyspepsia. Complement C3 was normal, C4 low 0.06 g/l, C1Q-BA 28% (N<8%), but ANA/ENA, DDNS, AST, ANCA, HBV, HCV and M-protein were negative. IgG4 3.0 g/l (N 0.08-1.40 g/l) Urine showed 3 RBC/HPF, protein 0.36 g, albumin 61 mg per 24h. On ultrasound both kidneys were 13 cm with right sided hydronephrosis and 300 ml urinary retention. CT-Urography showed obstruction of the right ureter at the iliac artery. A bladder catheter and ureteral stent did not improve renal function. A MAG-3I-I inferior vena cava showed a non-functioning right kidney without hydronephrosis. On autopsy, the CT showed soft tissue surrounding the aorta and the right iliac artery. A kidney biopsy showed TIN with a dense infiltrate of IgG4-positive plasma cells and eosinophils with impressive fibrosis, a vein showed obliterator phlebitis, consistent with IgG4-related TIN. TIN was treated with prednisone 40 mg daily and after 1 week he reported a dramatic clinical improvement, his creatinine decreased to 1.7 mg/dl.

Discussion: Hydronephrosis first dominated the clinical picture, delaying diagnosis, but the low C4, positive C1Q-BA and large kidneys suggested IgG4-related TIN. We found only one report of IgG4-related TIN with hydronephrosis, but that was after uraemic tract tuberculosis. Rare cases were reported of IgG4-related segmental ureteritis or prostatitis without TIN and the cases of IgG4-related TIN had no hydrenephrosis. The present case is the first with coincident biopsy-proven IgG4-related TIN, ureteral obstruction and prostatitis. Hydronephrosis does not exclude, but may be part of IgG4-related disease.

Monocolonal Light Chain Proximal Tubulopathy with Unique Ultrastructural Microtubular Inclusions


Introduction: Renal disease related to monocolonal gammopathies is common and varied. An uncommon lesion is proximal light chain tubulopathy (PLCT), which may present with Fanconi chain syndrome (FS) and variable degrees of renal failure. Most have ultrasonographic (US) findings of proximal tubule damage with crystalline inclusions of k LC’s within proximal tubular cells (PTC). A minority of PLCT do not have crystals; these may have LC restrictions. We describe a patient with a rare finding: PLCT with light chain (LC)-related microtubular inclusions.
Discussion: This is the second reported case of necrotizing and crescentic glomerulonephritis associated with IgG1-κ anti-GBM antibody. It is unknown if this disease is driven by an underlying autoimmune process or monochlonal gammopathy. Both cases are atypical for classic anti-GBM disease due to their relapsing nature.

TH-PO1072
First Reported Case of Collagenofibrotic Glomerulopathy in a Patient with Multiple Myeloma
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Introduction: Collagenofibrotic glomerulopathy is an extremely rare idiopathic glomerular disease characterized by abnormal accumulation of atypical spiralized and frayed type III collagen fibrils in mesangial and subendothelial areas, and elevated serum procollagen III and hyaluronan levels. Proteinuria (commonest feature), edema, hypertension, and occasional progression to ESRD are commonly seen. We report the first published case of Collagenofibrotic glomerulopathy in Multiple Myeloma.

Case Description: A 54 year old male with recent history of IgG kappa Multiple Myeloma (May 2011); with underlying CKD stage 3 and baseline Creatinine at 2 mg/dl, in remission status-post autologous stem cell transplant (January 2012) and on Lenalidomide maintenance therapy, presented with proteinuria of 4g. Kidney biopsy revealed Nodular and Focal glomerulosclerosis with IF weakly (+) for IgG, IgA, IgM, C3, C4, c1q, Kappa and Lambda light chains with +3 staining for IgM and c1q. EM showed patchy foot process effacement with massive deposition of collagen-III fibers. The weak and non-specific staining, along with massive collagen-III fiber deposition fitted with the description of Collagenofibrotic glomerulopathy, and made an immune mediated kidney injury less likely.

Discussion: Discussion: Collagenofibrotic glomerulopathy is an extremely rare disease characterized by massive intraglomerular atypical type III collagen fiber deposition. Proteinuria is the cardinal manifestation of this disease. Clinically, patients present with edema, hypertension and often progress to ESRD. Etiology and pathogenesis remains elusive. Most cases are seen in Japan and an autosomal-recessive mode of inheritance has been described. Definitive diagnosis is established by identifying collagen-III fibrils by IF and EM with special staining. No specific treatment is available unfortunately.

TH-PO1073
Severe Acute Kidney Injury (AKI) with Organomegaly in a 17 Days Old Newborn: When Pathology Makes the Difference
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Introduction: Acute tubulointerstitial nephritis (ATIN) is a significant cause of AKI in children and is often due to allergic drug reactions or infections. Diagnosis of ATIN is usually clinical and renal biopsy not routinely performed.

Case Description: A previously healthy 17 days old baby presented with decreased oral intake, vomiting and oligoanuria. His first laboratory results showed an elevated creatinine (1.7mg/dL) with metabolic acidosis, hypernatremia (Na 160mmHg), hyperkalemia (K 8.8 mEq/L) and thrombocytopenia (platelets 16x10^9/L). His urine analysis was abnormal (proteins 3gr/L, WBC 50000/hpf, RBC 20000/hpf, red blood casts). An ultrasound revealed bilateral hydronephrosis. Renal biopsy findings were consistent with severe ATIN. The most likely etiology for ATIN was drug reaction. The initial potential drug reaction was penicillin, which was stopped and the baby was put on ceftriaxone. The baby improved and was discharged home for a Foley catheter associated Escherichia coli urinary tract infection & E. coli confirmed on urine culture.

Discussion: This interesting case showed AL lambda amyloidosis in kidney transplant allograft as a cause of Massive Nephritie Syndrome with AKI that responded to chemotherapy. 51 year old African American female with history of ESRD secondary to APOD s/p DDKT in Oct 2010 with Thymoglobulin induction, maintained on 3 drug immunosuppression including tacrolimus, mycophenolate and prednison with baseline creatinine of 1.5, presented with anasarca and orthostatic hypotension. Her serum albumin was 1.2mg/dL. She underwent extensive investigations including Echo, transplant allograft ultrasound all of which came back unremarkable. She has sudden onset sub nephritic range proteinuria in Aug 2013 which progressed to nephritic range in Feb 2014. She has 34g of protein on a 24h urine collection 90% of which was albumin. Her UPCR gradually got worse from 10 to 32 with worsening in serum Cr from 1.5 to 5.5. She has poor response to IV Lasix with albumin infusion and has severe orthostatic symptoms. Her SPEP and UPAP were negative. Urine IFE showed lambda light chain. Serum free light chain showed elevated lambda levels. Due to worsening and explosive proteinuria with worsening anasarca renal allograft biopsy was done that showed lambda AL amyloidosis involving glomeruli, arterioles and arteries along with light chain proximal tubulopathy. Congophilic casts consistent with light chain cast nephropathy. Pt underwent bone marrow biopsy that did not show MM. She was treated with bortezomib combined with cyclophosphamide and dexamethasone and has good response with improvement in orthostatic hypotension, serum albumin level and lambda light chain got normal.

TH-PO1076
Pauci-Immunoglobulin Glomerulonephritis and Escherichia Coli Bacteremia: A Rare Coincidence or a True Causal Association?
345A

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

Discussion: ATIN is rare in neonates and usually drug-induced. This is the first report of a renal biopsy-proven ATIN in a neonate. Even if procedural risks of a renal biopsy are not negligible, it can make the difference in certain cases by dictating appropriate management.
She promptly responded to standard treatment of septic shock and her serum Cr improved to 1.6 mg/dL on discharge. Ten days later, she was readmitted to the hospital after a follow up visit to her primary physician where a routine blood work showed her serum Cr to be elevated to 6.8 mg/dL. Urine sediment revealed several RBCs and few granular casts. Anti-myeloperoxidase antibody was positive with a titer of 1:640. Other serological tests were negative. Her renal function declined further and she was initiated on hemodialysis. A renal biopsy was consistent with pauci-immune necrotizing and crescentic GN. She was treated with steroids, intravenous cyclophosphamide and plasmapheresis following which she came off dialysis & her serum Cr stabilized around 1.8 mg/dL. ANCA was checked and was positive for anti-MPO antibodies. Renal biopsy showed membranoproliferative glomerulonephritis with deposition of IgG kappa light chain cryoglobulins as well as immune complexes and/or paraproteins. Review of the literature reveals a small number of cases of PGNMID associated with CLL and cryoglobulinemia. The pathophysiology of GN in CLL is possibly due to glomerular deposition of immune complexes and/or paraproteins. Review of the literature reveals a small number of cases of PGNMID associated with CLL and cryoglobulinemia. We report a case of ANCA necrotizing vasculitis in a patient with CLL and cutaneous, renal and cerebral involvement due to monoclonal cryoglobulinemia. Despite leukemia treatment and regular hematocrit monitoring her clinical condition deteriorated and patient expired.

TH-PO1077
Cryoglobulinemic Vasculitis and Glomerulopathy Associated with Chronic Lymphocytic Leukemia
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Introduction: Cryoglobulinemia manifests as ischemic or occlusive vasculopathy with or without renal involvement. Early stage Chronic lymphocytic leukemia (CLL) has not been reported with vasculitic lesions as its first manifestation. We report a rare case of Stage I CLL with cutaneous, renal and cerebral lesions due to monoclonal Type I cryoglobulinemia.

Case Description: A 60-year-old woman presented with abdominal pain due to retroperitoneal hematoma from a ruptured right gonadal artery, which was embolized. Labs included eucocytosis, anemia with mild azotemia. Flow cytometry was consistent with CLL. The patient was readmitted with a serum creatinine of 11.2 mg/dL and proteinuria and required hemodialysis. There were extensive lesions on her lower extremities and a necrotic left forearm ulcer. Renal biopsy revealed membranoproliferative glomerulonephritis with deposition of IgG kappa light chain cryoglobulins as well as intraluminal hyaline deposits (Figure 1), infiltrates consistent with CLL and thrombi in intrarenal arteries. Biopsy was complicated by hematoma leading to left nephrectomy. Plasmapheresis was initiated for cerebral infarcts related to cryoglobulinemia. Despite leukemia treatment and regular hemodialysis her clinical condition deteriorated and patient expired.

TH-PO1080
PGNMID in a Patient with Hepatitis C
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Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is infrequently associated with hematological disease but more commonly presents like an immune-complex glomerulonephritis. Few have reported cases associated viral infections such as hepatitis C. We report a case of PGNMID in a patient with active HCV infection.

Case Description: A 56 year-old male with refractory hepatitis C (post treatment with interferon and Ribavirin), HTN and coronary artery disease presented with rising creatinine (peak 5.3 mg/dL) from baseline (0.9 mg/dL a year ago) and no kidney disease in family. He reported months of progressive fatigue, dyspnea on exertion, nausea, vomiting, and dark urine. He endorsed chronic Hepatoren use for leg pain. On examination BP was normal with clear lungs and no edema. Urinalysis revealed blood but minimal proteinuria with urine protein to creatinine ratio of 0.5 g/g and albumin 4.2 g/dL. Complements were low (C3 83 mg/dL, CH50 <10 U/mL). HCV-RNA quantification was 1.7 million copies. SPEP, plasma light-chains, ANA, ANCA, Anti GBM, HIV, Hep B serologies were normal. Bone survey was negative. Renal biopsy revealed diffuse linear staining of glomerular basement with monoclonal IgG/kappa immunoglobulin and endocapillary focal glomerulonephritis, chronic interstitial nephritis with ATN. Renal function did not improve until Prednisone was initiated, down to 3.3 mg/dL. Cyclophosphamide was started after discussion with his gastroenterologist. Antiviral therapy has been delayed until further improvement of renal function.

Discussion: We report a case of PGNMID associated with HCV. There are 2 other reports of HCV associated PGNMID however with membranous glomerulonephritis pathology. 30% of PGNMID patients have some heavy- and light-chain isoforms as the glomerular deposits. Membranoproliferative (57%) or endocapillary proliferative (35%) are the most two common histological variants. Nas et al in a series of 32 patients reported after an average of 30.3 months of follow-up, 38% had complete or partial recovery, 38% had persistent renal dysfunction, and 22% progressed to ESRD. Viral infection such as HCV associated immune disorders could be implicated in the pathogenesis. Currently, there is no consensus regarding the management of this entity.

TH-PO1079
Myeloma Cast Nephropathy with Acute Renal Failure, Skin Rash, Eosinophilia, and Low Complement C4 Level
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Introduction: We here report myeloma cast nephropathy with skin rash, eosinophilia and low complements which is a very atypical presentation of this renal condition.

Case Description: A 53y Caucasian female was admitted with 3 day confluent erythematous skin rash, acute renal failure with sCr 17.6 mg/dL. Five days prior, she was prescribed cephalexin for root canal infection. Initial diagnosis of acute interstitial nephritis was made but patient didn’t respond after stopping antibiotics and steroid course trial. urine exam showed WBC clumps and no casts. Serological biomarkers were done and reported Negative ANA, ANCA, cryoglobulins, Hepatitis B, Hepatitis C and HIV. Complement C4 was low with normal C3. Patient’s laboratory workup showed normocytic normochromic anemia and pseudohyponatremia per osmolality check, SPEP and SFLC ordered and was positive for M-spike with free light chain analysis showing predominant Lambda more than 4 g/L. Renal biopsy showed myeloma cast nephropathy.

Bone marrow biopsy confirmed MM with 80% plasma cell. Patient received bortezomib +dexamethasone + cyclophosphamide chemotherapy and her renal function completely improved after being dialysis dependent for about 12 weeks. Patient is being evaluated for BDM transplant after chemotherapy response.

Discussion: Multiple Myeloma can cause renal damage in many ways which sometimes can be misleading and very uncharacteristic. Up to our knowledge, this presentation is quite uncommon in literature and hence we suggest including myeloma related kidney injury in such clinical presentation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR- Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Cases of Nephrotic Syndrome During Pregnancy

A Case of Thyroiditis and Nephrotic Syndrome During Pregnancy

Case Description: A 35-year-old pregnant woman presented with proteinuria and edema. Pregnancy-induced nephrotic syndrome (PINS) was diagnosed at 30 weeks gestation. She had a history of Graves' disease. The patient was treated with high-dose corticosteroids and plasma exchange. After treatment, proteinuria resolved, and she had a healthy delivery at 39 weeks gestation.

Discussion: PINS is a rare complication of pregnancy, affecting 1-2% of pregnant women. The pathogenesis involves the activation of the immune system, leading to glomerular injury. Treatment with corticosteroids and plasma exchange is effective in resolving proteinuria and improving maternal and fetal outcomes.

TH-PO1083
A Case of Cryoglobulinemic Nephropathy with Successful Childbirth After Recurrent Episodes of Nephrotic Syndrome During Pregnancy

Case Description: A 35-year-old woman was admitted due to recurrent albuminuria and nephrotic-range proteinuria during pregnancy. Renal biopsy revealed membranoproliferative glomerulonephritis (MPGN). She underwent plasmapheresis and immunosuppressive therapy with good efficacy. She delivered a healthy baby at term with a normal Apgar score.

Discussion: Cryoglobulinemic nephropathy is a rare cause of nephrotic syndrome in pregnancy. Cases often respond to aggressive immunosuppressive therapy. Early diagnosis and prompt treatment can lead to successful pregnancy outcomes.

TH-PO1084
A Case of Glomerular Lipidosis with Type III Hyperlipoproteinemia

Case Description: A 35-year-old woman was admitted with nephrotic-range proteinuria. Renal biopsy revealed lipid deposition in glomeruli. Genetic testing revealed a mutation in the APOE gene. She responded well to statin therapy and lifestyle modification.

Discussion: Glomerular lipidosis is a rare cause of nephrotic syndrome. It is associated with type III hyperlipoproteinemia. Early recognition and management can prevent progression to end-stage renal disease.
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factors might be involved in causing nephrotic syndrome.

A Case of Autosomal Dominant Polycystic Kidney Disease and C3
TH-PO1087

Successful Treatment of Crescentic Glomerulonephritis (GN) in
Hycompomplectem Uticaria Vasculitis Syndrome (HYUV)
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Introduction: HYUV is a rare autoimmune systemic disorder characterized by chronic urticaria, low complements and extracutaneous organ involvement. Kidney involvement is not uncommon (50% of cases), usually of benign nature. The glomerular injury pattern varies from mesangial proliferation to membranoproliferative glomerulonephritis (MPGN). Crescentic MPGN in HYUV is rare; only six cases have been reported in world literature, many with poor outcomes. We present a case of crescentic GN successfully treated with substantial remission.

Case Description: A 55-year-old Caucasian female with a previous episode of hives was admitted to hospital with features of both acute nephritic and severe nephrotic syndrome. She had 6 months history of persistent hives, fatigue, fevers, arthralgia, self-limited recurrent angioedema episodes, and generalized lymphadenopathy. Lymph node biopsy displayed reactive hyperplasia. Her serum creatinine was 4 mg/dl. Her protein to creatinine ratio was 23, serum bilirubin 1.4 mg/dl and total proteins 7.1 g/dl. Serum IgA was 1000 mg/dl, all other serum immunoglobulins were normal. ESR was 70 mm/hr. 12 urine casts/100 HPF. Serologic workup was positive for low C3 and C4 and ANA titer of 1:80. Anti-dsDNA, cryoglobulins, anti-SSA, anti-SSB, chronic hepatitis panel, and pupules for parvovirus, were all negative. C3 and C4 levels were normal. Anti C3d antibody was not performed. Renal biopsy revealed immune complex crescentic MPGN with IgG, IgA, IgM, C3 and C4 deposits on immunofluorescence. Treatment was started initially with high dose glucocorticoids followed by addition of mycophenolic acid and losartan. Her systemic symptoms and acute kidney injury resolved completely. Nephrotic syndrome improved slowly. After 6 months of therapy her proteinuria decreased to 4.5 g/dl and serum albumin increased to 3.8 g/dl.

Discussion: Crescentic GN associated with HYUV appears to convey a poor renal prognosis. Based on available information in five of six reported cases, three progressed to end stage renal disease; one had near complete renal recovery and another had partial recovery with persistent nephrotic range proteinuria. Relatively good outcome in our case may aid to our understanding of this uncommon and newly recognized disease process.

TH-PO1086

An Unusually Early Presentation of Pre-eclampsia
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Introduction: Pre-eclampsia affects approximately 3-6% of pregnancies in the United States. It is defined as new onset hypertension and proteinuria in pregnancy. By definition, it occurs after 20 weeks gestation. However, earlier cases have been reported in the literature.

Case Description: The patient is a 45 y/o woman, 16 weeks + 4 days pregnant with twins (IVF with donor embryo), with a PMHx significant for obesity and borderline HTN under control with anti-hypertensives. Termination of pregnancy was advised and performed. On post-discharge follow-up, her exam was notable for BP 193/122, 1+ upper extremity edema, 2+ lower extremity edema, and bibasilar crackles on lung exam. On labs, Cr 0.85, 3+ protein on UA (previously 1+), hemoglobin 10.5, WBC 13.4, platelets 254K, alanine transaminase 87 U/L, aspartate transaminase 112 U/L, alkaline phosphatase 251 U/L, total cholesterol 249 mg/dl, low density lipoprotein 116 mg/dl, high density lipoprotein 43 mg/dl, triglycerides 151 mg/dl, albumin 2.3. Serologic work-up including ANA, C3, C4, HIV, Hepatitis B, Hepatitis C, anti-dsDNA, cryoglobulins, anti-SSA, anti-SSB, chronic hepatitis panel, and workup for parvovirus, were all negative. Anti C3d antibody was not performed. Renal biopsy revealed immune complex crescentic MPGN with IgG, IgA, IgM, C3 and C4 deposits on immunofluorescence. Treatment was started initially with high dose glucocorticoids followed by addition of mycophenolic acid and losartan. Her systemic symptoms and acute kidney injury resolved completely. Nephrotic syndrome improved slowly. After 6 months of therapy her proteinuria decreased to 4.5 g/dl and serum albumin increased to 3.8 g/dl.

Discussion: Crescentic GN associated with HYUV appears to convey a poor renal prognosis. Based on available information in five of six reported cases, three progressed to end stage renal disease; one had near complete renal recovery and another had partial recovery with persistent nephrotic range proteinuria. Relatively good outcome in our case may aid to our understanding of this uncommon and newly recognized disease process.

TH-PO1088

To Deliver or Not to Deliver: The Dilemma of a Pregnant Patient with Medullary Cystic Kidney Disease Who Develops Acute Kidney Injury

Introduction: Achieving maternity is quite a challenge for women with chronic kidney disease (CKD). Pregnant patients with CKD of any stage but especially stages 3–5 are at increased risk for fetal loss, prematurity and pre-eclampsia.

Case Description: We present a case of a 31 year old pregnant female with a past medical history of CKD stage 3B secondary to medullary cystic disease (MCD) who presented with acute kidney injury at 31 weeks gestation. Her other co-morbidities include a history of diabetes and idiopathic thrombocytopenia (ITP). On admission, the patient had a creatinine of 2.32 mg/dl and was found to have 7 gm proteinuria. During this pregnancy, her baseline creatinine was 1.6-1.8 mg/dl and prior to pregnancy she had baseline proteinuria of 2 gm. Given her elevated creatinine and degree of proteinuria, there was concern that the patient could have pre-eclampsia. A management dilemma occurred and it was unclear whether the patient should have an emergency C-Section for questionable pre-eclampsia. Ultimately, the usual markers of pre-eclampsia such as proteinuria, increased creatinine, hypertension, low platelets, and elevated uric acid levels were all present in our patient. These markers however could be present in our patient due to her underlying medical conditions of CKD, ITP, and MCD. After a multidisciplinary meeting with the obstetrician, nephrologist, and hematologist occurred, it was felt that the patient truly did not have pre-eclampsia. A key decision was made and she was not induced. Her AKI was attributed to volume depletion and progression of CKD. Her creatinine eventually declined to 1.9-2 mg/dl and her proteinuria decreased to 3-5 grams. The patient is now 34 weeks pregnant and her pre-eclampsia has been maintained. As the weeks progress, there are increased chances of fetal development.

Discussion: Our case highlights that in patients with multiple co-morbidities and CKD, the diagnosis of pre-eclampsia can be challenging. Incorrectly labeling a patient as pre-eclampsic can lead to pre-term delivery and risks to the fetus. A multidisciplinary approach along with fetal monitoring can help differentiate pre-eclampsia from other diagnoses, prolonging delivery.

TH-PO1089

Development of Aggressive De Novo Henoch-Schönlein Purpura, 10 Years Post-Kidney Transplant
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Introduction: Histologic recurrence of IgA deposits in renal allografts is as high as 60% in recipients with primary IgA nephropathy, however significant nephritis presenting as de novo Henoch-Schönlein Purpura (HSP) post-kidney transplant (KT) is rare with only a few cases reported. Our patient had biopsy proven idiopathic nephropathy (DN), yet presented with severe HSP with multi-system involvement 10 years post-KT.

Case Description: A 47 y/o female with DN receiving a living related KT in 2005 and was stably maintained on tacrolimus, prednisone, without mycophenolate mofetil (MMF) due to recurrent infections. 10-yrs post-KT, she developed diarrhea, melena and acute renal failure (Cr of 4.19 from 1.5) after completing a course of antibiotics for pneumonia. She developed diffuse purpuric rash and had hematolysis with severe abdominal pain. Abdominal CT scan showed enteritis of the small bowel. EGD demonstrated necrotic ulcers in the esophagus, stomach, and duodenum ulcerative jejunitis with narrowing, showing leukocytoclastic infiltration of vessels, and submucosa. Skin biopsy showed leukocytoclastic vasculitis. Urine had 4+ protein, leukocytes, red blood cells, but no casts. Extensive infectious and serologic workup was negative. KT biopsy demonstrated membranoproliferative glomerulonephritis changes without crescents, coupled with findings of DN and advanced interstitial fibrosis and tubular atrophy. Immunofluorescence showed +4 deposits for IgA and C3 and the patient was diagnosed with HSP. Due to severe GI involvement the patient was treated with pulse
Thrombotic Microangiopathy Secondary to Smoldering Myeloma: A Form
of MGRS

Case Description: A 64 year old AA female with chronic Hepatitis C, hypertension, diabetes mellitus came to our clinic for evaluation of AKI superimposed on chronic kidney disease. Laboratory data revealed serum creatinine of 2.24 mg/dl (baseline Cr 1.5 mg/dl), hypoaalbuminemia (3.2 gm/dL) with a spot urine protein/creatinine ratio of 3.3 (baseline of 1). Her AKI coincided with peripheral eosinophilia. Home medications included hydralazine, lansoprazole and simvastatin. She had recently completed eight weeks of treatment for Hepatitis C with Harvoni and her most recent viral load was undetectable. She denied using any NSAID, antibiotics, PPI or herbal supplements. Physical exam was normal. AKI workup revealed negative ANCA, normal complement, normal serum free immunoglobulin light chain ratio and negative ANA panel.

Discussion: Harvoni is a new combination pill consisting of ledipasvir with sofosbuvir approved by FDA in October 2014 for the treatment of chronic Hepatitis C genotype 1 virus infection. No cases of Acute Kidney Injury (AKI) have been reported with this agent thus far. We report the first case of Harvoni associated biopsy proven acute interstitial nephritis (AIN).

Harvoni Induced Acute Interstitial Nephritis


TH-PO1092

A Case of Leukocyte Chemotactic Factor 2 Associated Amyloidosis

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Introduction: Leukocyte chemotactic factor 2-associated amyloidosis (ALCT2) is a newly described form of nonhereditary amyloidosis. The disease usually presents with chronic kidney disease and bland urinary sediment with variable degrees of proteinuria. We describe a case of a young Hispanic female who presented with nephrotic syndrome without evident insufficiency.

Case Description: A 40 year old Hispanic female with history significant for uncontrolled type 2 diabetes, hypertension and rheumatoid arthritis, was referred to renal clinic for evaluation of nephrotic syndrome. Physical examination revealed peribulbar and bilateral lower limb edema. Pertinent diagnostic data are shown in figure 1.

Figure 1: Diagnostic Data

- Urinalysis: Protein
- Urine microscopy: Bland
- Serum creatinine (mg/dl): 0.5
- Serum albumin (g/dl): 1.4
- SLEP: No M component
- Renal ultrasound: Normal
- Normal kidney size with mild echogenicity

Renal biopsy showed extensive amyloidosis involving the glomeruli, interstitium and arterioles. Immunofluorescence was negative for immunoglobulins and amyloid associated protein. Proteomic typing of the amyloid revealed ALCT2 associated amyloidosis. The patient was started on linsopolone and splenolactone, but her proteinuria failed to improve and she had progressive deterioration of renal function. Two years later, she developed ascites and elevated liver enzymes. Her presentation was concerning for hepatic amyloidosis; therefore, she was transferred to a liver transplant center for further evaluation.

Discussion: Based on two large renal biopsy series, ALCT2 accounts for 2.5-2.7% of all cases of renal amyloidosis. In a multicenter study involving 72 patients with renal ALCT2, 92% were Hispanic, 2.8% were below the age of 50 and 91.4% had a serum creatinine > 1.2mg/dl. One third had nephrotic range proteinuria, but only 10% of all patients presented with nephrotic syndrome. Pathogenesis is not clear. It is postulated that inflammatory processes lead to excessive production of an amyloidogenic variant of ALCT2. Accurate identification of the amyloid protein is essential as disease modifying treatments are available for certain types of amyloidosis.

Complement Polymorphisms in Patients with Thrombotic Microangiopathy Associated with Intrahepatic Hepatitis: Implications for Nephrology

Joe Ghanem, Lukas Haragism, Satish Kumar. Nephrology, Univ of Oklahoma Health Science Center, Oklahoma City, OK.

Introduction: In 2012, the CDC reported 15 cases of unexplained renal failure and idiopathic microscopic polyangiopathy (TMA) in which all patients reported dissolving and intravenously injecting an oral preparation of oxymorphone (Opana) prior to presentation. Since then, 30 additional cases have been reported in the U.S. The mechanism of IV Opana-associated TMA is unclear. ADAMTS13 levels were normal. We report two patients with genetic polymorphisms of complement system proteins as a possible mechanism for Opana-associated TMA.

Case Description: Two patients, a 26 yo WM (Pt 1) and a 38 yo WM (Pt 2) presented with unexplained renal failure (serum creatinine 8.2 and 4.6 mg/dl respectively) in the setting of IV Opana Abuse. Both displayed a hematological constellation of microangiopathic hemolytic anemia, thrombocytopenia, consumed haptoglobin and elevated LDH. Both patients had normal INR/PT/PTT, ADAMTS13 (> 55%) and fibrinogen levels. ANA, HIV, and hepatitis profiles were negative. Renal biopsy showed intermediate sized vessels with mild thrombotic microangiopathy involving 20% of the glomeruli in both patients. Both received plasmapheresis for 5 days. Hematological microangiopathy resolved in Pt 2 but persisted in Pt 1. Both remained dialysis dependent. Genetic studies for complement-mediated HUS demonstrated both to be positive for a heterozygous polymorphism (IVSP-78 G>A) within an intron of the membrane cofactor protein (MCP/CD46) and for a homozygous polymorphism (p.His402Tyr) in the complement factor H (CFH). In addition, both patients had an additional CFH polymorphism (p.Val626Le; Pt 1 homozygous, Pt 2 heterozygous).

Discussion: Our patients suggest a 2 hit mechanism for IV Opana-associated TMA. Both had polymorphisms in complement system proteins MCP and CFH with a potential predisposition for complement-mediated HUS. The MCP/CD46 polymorphism has been shown to be enriched in patients with complement-mediated HUS. Polymorphisms in complement system proteins could cause hyperactivation and dysregulation of the complement system and provide a genetic predisposition for thrombotic microangiopathy, with IV Opana abuse acting as a trigger.

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

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349A
Acute Kidney Injury due to an Excessive Dose of Rivaroxaban

**Case Description:** A 45 y/o man presented to his physician’s office with abdominal pain. Computed tomography (CT) of the abdomen was done and thrombosis of the portal, splenic, and mesenteric vein was identified. He was admitted to the hospital and discharged on coumadin 10 mg daily the next day. After 6 weeks, he was given a prescription for rivaroxaban 20 mg tab and told to take 1 tablet daily. He mistakenly took 2 tablets daily. After 5 days, he noticed painless gross hematuria for several days. He reported to his physician’s office and his serum creatinine had increased to 2.7 mg/dL from a baseline of 1.5. He had a prior history of warfarin use and he was started on dialysis and remained dialysis-dependent at last follow up.

Malignant Pleural Effusion

**Case Description:** A 56 year old female presented with microscopic hematuria (6-10 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serology revealed mixed type III IgG/IgM cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with mixed membranous MPGN. She was treated with plasma exchange, Rituximab, and methylprednisolone. She was treated with plasma exchange, IgG, and is under evaluation for C3 glomerulopathy with nephrotic range proteinuria.

**Discussion:** Case 1: A 18 year old female presented with proteinuria (1.7 g), hematuria (44 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serology revealed mixed type III IgG/IgM cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with mixed membranous MPGN. She was treated with plasma exchange, Rituximab, and methylprednisolone. She was treated with plasma exchange, IgG, and is under evaluation for C3 glomerulopathy with nephrotic range proteinuria.

**Case 2:** 18 year old female presented with proteinuria (6-10 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serology revealed mixed type III IgG/IgM cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with mixed membranous MPGN. She was treated with plasma exchange, Rituximab, and methylprednisolone. She was treated with plasma exchange, IgG, and is under evaluation for C3 glomerulopathy with nephrotic range proteinuria.

**Discussion:** Patients with AIH should be monitored for proteinuria and active urinary sediment due to the risk of glomerulonephritis, despite treatment with prednisone and azathioprine. MPGN is a rare, but important, complication of AIH. Prompt diagnosis by biopsy and aggressive treatment of AIH associated MPGN is critical.

**TH-PO1097 Membranoproliferative Glomerulonephritis with Mixed Cryoglobulinemia in Patients with Autoimmune Hepatitis**

**Case 1: A 56 year old female presented with microscopic hematuria (6-10 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serology revealed mixed type III IgG/IgM cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with mixed membranous MPGN. She was treated with plasma exchange, Rituximab, and methylprednisolone. She was treated with plasma exchange, IgG, and is under evaluation for C3 glomerulopathy with nephrotic range proteinuria.

**Case 2:** 18 year old female presented with proteinuria (1.7 g), hematuria (44 RBC), proteinuria (6.9 g) and acute kidney injury (creatinine 1.5 mg/dL). Her renal function deteriorated requiring hemodialysis treatment. Serology revealed mixed type III IgG/IgM cryoglobulins. Kidney biopsy showed mesangial proliferation, protein thrombi within capillary loops, reduplication of GBM and mesangial interpositioning, consistent with mixed membranous MPGN. She was treated with plasma exchange, Rituximab, and methylprednisolone. She was treated with plasma exchange, IgG, and is under evaluation for C3 glomerulopathy with nephrotic range proteinuria.

**Discussion:** Patients with AIH should be monitored for proteinuria and active urinary sediment due to the risk of glomerulonephritis, despite treatment with prednisone and azathioprine. MPGN is a rare, but important, complication of AIH. Prompt diagnosis by biopsy and aggressive treatment of AIH associated MPGN is critical.

**TH-PO1098 A Case of Chinese Herb (Aristolochic Acid) Nephropathy Leading to ESRD Complicated by Bladder Cancer**

**Case Description:** We report a 59 year old white female who had received Chinese herbs for one and half years before she developed progressive renal insufficiency that over a six month period led to ESRD requiring hemodialysis. A renal biopsy showed extensive tubular loss and collapse with interstitial edema and interstitial fibrosis consistent with the effects of tubular toxic damage caused by aristolochic acid. After one week of hemodialysis, the patient underwent a living unrelated kidney transplant from a friend. Alemtuzumab induction, steroid free maintenance on tacrolimus and mycophenolate (MMF) were started. She had no history of diabetes, hypertension or use of NSAIDS. She underwent monthly urinalysis and screening cystoscopy every six months to rule out urothelial malignancies. Twenty months post transplant she underwent right breast lumpectomy and radiation for intraductal carcinoma. Two and a half years after kidney transplantation, a cystoscopy revealed a bladder mass, a biopsy of which showed high grade urothelial carcinoma with squamous differentiation invading into submucosal connective tissue for which she underwent bilateral native nephrectomy, ureterectomy, cystectomy and transplant kidney ileal loop urinary diversion. One year later the patient was admitted with increased blood pressure and was found to have a malignant pleural effusion of undifferentiated primary which led to her demise. A sample of the Chinese herb that she had used was found to contain aristolochic acid.
Discussion: There has been a high risk of urethral malignancies associated with Chlamydia/aristolochic acid exposure with 40 – 45% of these patients developing multifocal high grade transitional cell carcinoma leading to a suggestions for either prophylactic bilateral native nephrectomy and ureterectomy at the time of renal transplantation or screening cystoscopies every 6 months to identify early stage urethral carcinoma. Our patient is a classic example of aristolochic acid associated nephropathy complicated with urethral cancer.

TH-PO1099

Anti-Tumor Necrosis Factor Therapy – A Trigger for Anti-Glomerular Basement Membrane Disease Carlos Antonio Cortes Sanchez, Hector R. Cordova, Krystahl Z. Andujar. Medical Service, VA Caribbean Healthcare System, San Juan, PR.

Introduction: Tumor necrosis factor (TNF) has a key pathological role in diseases such as rheumatoid arthritis (RA). Vasculitis and other autoimmune diseases have been associated with the use of anti-TNF agents such as Adalimumab.

Case Description: A 73-year-old man with of RA, Hypertension, Diabetes Mellitus type 2 and Non-Hodgkin’s Lymphoma in remission for 3 years complained of decreased urine output, dark urine, poor appetite, weight loss and peripheral edema for three weeks. He was on chronic low dose Prednisone and Adalimumab intermittently during the previous 21 months. Physical exam revealed bilateral lower extremity pitting edema but no skin lesions. Laboratories showed a serum creatinine of 9.5 mg/dl (baseline of 1.3 mg/dl). Urinalysis exhibited many RBC’s, proteinuria (2+) and pyuria without casts. The clinical picture suggested acute glomerulonephritis. Hemodialysis (HD) was started.

Throat swabs were compatible with Anti-Glomerular Basement Membrane Disease. Alveolar hemorrhage was not present. Plasmapheresis therapy decreased anti-GBM titers but there was no recovery of renal function. The patient continued using Adalimumab after discharge. He later returned with hemoptysis due to alveolar hemorrhage, which was resolved after the discontinuation of Adalimumab. The patient remained HD-dependent.

Discussion: The temporal association of the illness with anti-TNF therapy and worsening of symptoms upon reexposure suggest an etiologic role of Adalimumab in the development of Anti-GBM Disease in our patient. Patients receiving anti-TNF therapy should have renal function closely monitored to allow early detection of this infrequent but life-threatening side effect.

TH-PO1100

Severe Pauci Immune Crescent Glomerulonephritis Mimicking ANCA Related Vasculitis Caused by Clinically Silent Dental Abscess Leading to Bacterial Endocarditis Anil K. Chunduri, Maria Saleem Khan, Anthony Alvarado, Tibor Nadassy, Lee A. Hebert. Nephrology, OSUMC, Columbus, OH.

Introduction: Severe crescentic GN is usually categorized based on the cause if it is Anti GBM or IC mediated disease. However, it is not widely appreciated that some instances of pauci immune GN are actually the result of severe occult systemic infections. We present a case of severe pauci immune crescentic GN whose initial assessment for infection was negative. The patient was assumed to have idiopathic AAV and was treated with high dose steroids. Despite no obvious signs of infection, bacteremia was on our differential due to pancytopenia. These findings are rarely common, if ever, associated with AAV.

Case Description: 55 year old male with PMH of CAD presented to an outside hospital with fatigue. Initial labs revealed Hb: 7.6g/dL, WBC: 2.8 K/µL, Pt: 44 K/µL, Creat: 2.26 mg/dL. Infectious work up was negative. Autosome workup revealed: ANA positive (1:40), Anti GBM (<20), Anti PR3 (0.6), ANCA and Anti MPO: negative. C3: 77mg/dL, C4: 16.9 mg/dL (wmp). Cryoglobulin (<5), Urine PCR ratio was 1.2. Further workup included a bone marrow biopsy and kidney biopsy, which was suggestive of pauci-immune crescentic and necrotizing GN. He received treatment with steroids and was discharged on steroid taper. His creatinine upon discharge was 1.5 mg/dL. On follow up his creatinine was elevated to 3.5 mg/dL. He was transferred to our institution. Repeat Infectious work up revealed streptococcus viridians bacteremia, tricuspid and aortic valve endocarditis. A panoramic radiograph of his teeth showed periapical abscess. He was subsequently diagnosed with infection related acute pauci-immune crescentic necrotizing GN. Unfortunately this patient remained dialysis dependent at the time of discharge.

Discussion: It is well established but not widely appreciated that severe pauci-immune crescentic GN can be the direct result of infection. Thorough investigation is warranted even if the initial infectious workup is negative, if the patient does not have a positive response to conventional therapy to improve morbidity and mortality.

TH-PO1101

POEMS syndrome with Cast Nephropathy Amanda K. Hall, Josephine Abraham, Monica Patricia Revelo Penafiel, Frederic Clayton. ’Div of Nephrology and Hypertension, Univ of Utah, Salt Lake City, UT; ’Div of Pathology, Univ of Utah, Salt Lake City, UT.

Introduction: POEMS syndrome(Polynuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is a plasma cell disorder with peripheral neuropathy and any of the following features osteosclerotic bone, Castelmann’s disease, increased levels of serum vascular endothelial growth factor(VEGF), organomegaly, endocrinopathy, edema or skin changes. We report a case of POEMS presenting with acute renal failure due to cast nephropathy.

Case Description: A 63-year-old Caucasian female presented with a 3 month history of increasing weakness and was diagnosed with chronic inflammatory demyelinating polyneuropathy. She was also noted to have new onset diabetes mellitus and hypothyroidism. She was treated with intravenous immunoglobulin(IVIG) with minimal response. She was admitted with acute renal failure initially thought to be secondary to IVIG, progressive weakness, and shortness of breath. Serum beta 2 microglobulin was elevated and kappa/lambda ratio was abnormal with Bence-Jones proteinuria. Renal biopsy was deferred as the patient developed respiratory failure, subarachnoid hemorrhage, and a left middle cerebral artery stroke. Comfort measures were initiated. Bone marrow biopsy confirmed multiple myeloma. With 20% clonal plasma cells, azathioprine was stopped and an uneventful hepatomegaly, splenomegaly, and peripheral nerve demyelination with active axonal loss. Renal examination showed cast nephropathy with monoclonal kappa light chains.

These features are characteristic of POEMS given the multiple myeloma with neuropathy, organomegaly, rash and new onset diabetes mellitus and hypothyroidism.

Discussion: POEMS is a paraneoplastic syndrome associated with plasma cell dyscrasia. Polyneuropathy with plasma cell disorder should prompt evaluation for POEMS as outcomes have been excellent with diagnosis and treatment.

TH-PO1102

Acute Interstitial Nephritis Associated with a New Breast Cancer Chemotherapy Regimen Cory Handelsman, Michael T. Tanoue, Amy Kwon, Steven Salvatore, Jeffrey I. Silberzweig. ’Div of Nephrology, Weill Cornell Medical College; ’Dept of Medicine, Weill Cornell Medical College; ’Dept of Pathology, Weill Cornell Medical College, New York, NY; ’The Rogosin Inst, New York, NY.

Introduction: Acute interstitial nephritis (AIN) as a direct consequence of chemotherapy is infrequently described. A recent review implicated ifosfamide, tyrosine kinase inhibitors, and pemetrexed as culprits in this process. We describe a case of AIN related to the recently approved chemotherapy regimen of pertuzumab, trastuzumab, and docetaxel for HER-2 positive metastatic breast cancer. While diarrhea, rash, and pruritis are well-known side effects, this report is the first to show AIN as a consequence of this chemotherapy regimen.

Case Description: A 69-year-old woman recently diagnosed with HER-2 positive breast cancer and treated with six cycles of neoadjuvant pertuzumab, trastuzumab, and docetaxel was hospitalized for acute kidney injury after two days of diarrhea and vomiting. Admission labs demonstrated leukocytosis to 26,000/µL, serum creatinine of 5.9 mg/dL (baseline of 1.55 mg/dL), and elevated urinary “p” gap metabolic acidosis with a lactic acid of 4.5 mmol/L. Urinalysis showed pyuria with occasional granular casts. Fractional excretion of sodium was 1.88%. Renal sonogram showed normal resistive indices with no evidence of hydronephrosis or calculi. Infectious workup, including blood, urine, and stool studies, was unrevealing. Despite aggressive hydration and resolution of diarrhea and vomiting within 48 hours, her renal function worsened; her creatinine peaked at 9.0 mg/dL on hospital day 3. She was non-oliguric throughout the admission. A renal biopsy revealed moderate diffuse and subacute, interstitial inflammation characterized by lymphocytic infiltration with moderate eosinophilia and diffuse tubular injury. Some endothelial injury

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was present as well. The patient was diagnosed with AIN secondary to chemotherapy and treated with prednisone. Two weeks later, her symptoms had fully resolved and her serum creatinine had returned to baseline.

**Discussion:** This is the first documented case of AIN related to combination chemotherapy with docetaxel, pertuzumab, and trastuzumab.

**TH-PO1103**

Sarcoidosis-Lymphoma Syndrome Presenting with Severe Refractory Hyercalcemia

Otsita W. Okechukwu,1 Barry M. Wall,2 Elvira Gomovanova,1 Deepak Nandikanti,1 *Nephrology Div, UTHSC, Memphis, TN; †Nephrology Section, VAMC, Memphis, TN.

**Introduction:** Sarcoidosis-lymphoma syndrome (SLS) is rare. Sarcoidosis (S) usually precedes lymphoma (L) by many months. Constitutional symptoms and hilar lymphadenopathy are key findings. We report a SLS case presenting with severe acute hyercalcemia and acute kidney injury (AKI).

**Case Description:** Case Report: A 70 yr-old Caucasian male was hospitalized with symptoms of generalized weakness, poor oral intake, and altered mental status. Examination was significant for dry mucous membranes, depressed mentation, evidence of bilateral pleural effusions, mild ascites, and 2cm well-delineated hyperpigmented erythematous plaques on anterior chest wall. Laboratory findings included a corrected serum Ca 19.4mg/dL (2 months prior: 9.3mg/dL), ionized Ca 2.3 mmol/L, BUN 35mg/dL, serum creatinine 2.5mg/dL (baseline 1.4 mg/dL), and mild anemia. Further work up revealed suppressed PTHrP (0.2pg/mL), normal 25D, TT3, TT4, serum urine electrolyte, calcium, calciotril, ACE, CEAl, PSA, and TSH. A working diagnosis of hypercalcemia of malignancy was made. Intravenous fluids, calcitomin, prednisone, and low dose pamidronate were initiated; however, his calcium continued to remain poorly responsive to conservative management. Calcium hemodialysis was required. Skin biopsy of chest wall lesion demonstrated non-caseating granulomatous dermatitis consistent with sarcoidosis. Thoracentesis was performed and pleural fluid cytology showed occasional plasmacytoid lymphoid cell and polyclonal T-cells on flow cytometry. However, flow cytometry of ascitic fluid was positive for monoclonal B cells. Computed tomography (CT) demonstrated diffuse soft tissue lung masses and abdominal carcinomatosis. Oesophageal survey was normal. CT-guided omental mass biopsy showed dense fibrous tissue with lymphoplasmacytic infiltrate. The diagnosis of SLS with associated B-cell lymphoma was made. Given poor functional status and widespread disease, the patient and his family opted for hospice care.

**Discussion:** Severe refractory hypercalcemia leading to AKI is unusual for sarcoidosis and should prompt investigation for concomitant lymphoma.

**TH-PO1104**

End Stage Renal Disease Secondary to Oxalate Nephropathy in a Patient with Undiagnosed Chronic Pancreatitis

Kalvany Chandras, Buri R. Don. *Div of Nephrology, UC Davis Medical Center, Sacramento, CA.

**Introduction:** Oxalate nephropathy is a rare, underdiagnosed, devastating disease characterized by extensive oxalate deposition, acute kidney injury and rapid progression to end stage renal disease (ESRD). Secondary hyperoxaluria occurs in enteric disorders associated with increased intestinal oxalate absorption and renal tubular injury. Chronic pancreatitis is a rare cause of oxalate nephropathy.

**Case Description:** A 66-year-old white man with history of diabetes mellitus, hypertension and recurrent kidney stones, was noted on routine labs to have an elevated serum calcium level (11.7 mg/dL, baseline 1.17 mg/dL, 6 months prior). He reported having chronic diarrhea, fatigue, loss of appetite and weight loss over the past 6 months. Workup revealed pancreatic calcifications consistent with chronic pancreatitis. Urinalysis and renal ultrasound were normal. Renal biopsy revealed acute tubular necrosis with extensive oxalate deposition. A 24 hr urine collection noted increased oxalate and reduced citrate excretion. Despite a 6 month course of a low oxalate diet, pancreatic enzymes, calcium supplementation, and sodium citrate to alkalize the urine, the patient’s renal function failed to improve, and he is preparing for home hemodialysis.

**Discussion:** Enteric hyperoxaluria can lead to acute oxalate nephropathy. It has been described in patients with post-gastric bypass surgery and inflammatory bowel disease. There are rare reports noting the association between chronic pancreatitis and oxalate nephropathy leading to chronic kidney disease (CKD) and rarely ESRD. The pathogenesis of hyperoxaluria in chronic pancreatitis remains uncertain, but it is postulated that fat malabsorption may increase the formation of fatty acids that inhibit the formation of calcium oxalate in the GI tract, combined with increased colonic mucosal permeability, leading to hyperoxaloremia, hyperoxaluria and oxalate crystalization in the kidney. Treatment remains largely empirical, aiming at decreasing oxalate burden to the kidney as was done in this patient. Oxalate removal with dialysis has not been shown to be beneficial. Oxalate nephropathy can be a late complication of chronic pancreatitis leading to CKD and ESRD.

**TH-PO1105**

mRNA Expression of Proinflammatory Mediators in Common Variable Immunodeficiency with Granulomatous Interstitial Nephritis: Case Report

Giacoamo Mori, Giulia Ligabue, Sara De biass, Milena Nasi, Andrea Cossarizza, Gianni Cappelli. *Univ Hospital - Modena.*

**Introduction:** Common Variable ImmuneDeficiency (CVID) impact on kidney function is poorly understood. We present a case of a woman, 39 years old, affected by CVID, expressing as hypogammaglobulinemia, anemia and chronic kidney failure secondary to granulomatous interstitial nephritis(IN).

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**TH-PO1106**

Nephrotic Range Proteinuria without a History of Penicillamine Therapy in a Patient with Wilson’s Disease

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**Introduction:** Wilson’s disease (WD) is a rare autosomal recessive genetic disorder of copper metabolism, characterized by hepatic and neurological abnormality. Although penicillamine is one of the key drugs for treatment of WD, in rare cases it may have a toxicogenic effect leading to nephrotic syndrome due to membranoproliferative glomerulopathy. Here, we report a case of WD in a patient who showed nephrotic range proteinuria clinically and focal segmental glomerulosclerosis (FSGS) histologically, without a history of treatment with penicillamine.

**Case Description:** We treated an 18-year-old girl who had been diagnosed as having WD at the age of 6 years and treated with trientine. She had normal liver function and normal urinalysis parameters. At the age of 16 years, she had developed acute liver failure due to poor drug compliance. Although her liver function subsequently recovered after plasma exchange and medications including zinc and trientine, slight proteinuria began to appear. As the proteinuria increased gradually to within the nephrotic range, we performed a kidney biopsy one year later. The patient had normal blood pressure, no edema, and her body mass index was 26.9. Blood examinations demonstrated no hypoproteinemia, no immunological abnormalities and normal kidney function. Although urinalysis revealed no hematuria, the urine protein/creatinine ratio was increased to 2.98. A kidney biopsy demonstrated perihilar FSGS and arteriolar intimal thickening, without tubular-interstitial or glomerular basement membrane changes. We diagnosed the patient as having secondary FSGS after successful treatment in response to WD medication.

**Discussion:** Although the kidney manifestations in WD include aminoacidurias and nephrocalcinosis, these were not observed in our patient. As her symptoms were relatively milder than those of typical FSGS and she had several known causes of secondary FSGS including arteriolar intimal thickening, our histological diagnosis was secondary FSGS. To our knowledge, this is the first report of histologically confirmed FSGS in a patient with WD.

**TH-PO1107**

Denosumab for the Treatment of Bishophosphate Refractory Hypercalcemia of Malignancy

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**Introduction:** Hypercalcemia is common in malignancy, occurring in 20-30% of patients. Volume expansion with normal saline is the mainstay of therapy, with the addition of bisphosphonates in cases of severe hypercalcemia. Here we describe a case of bisphosphate resistant hypercalcemia of malignancy and discuss potential treatment options for refractory cases.

**Case Description:** A 62 year-old male with T2 paraplegia following a fall 24 years ago presented to the ER for evaluation of a debucus ulcer. On arrival his vital signs were unremarkable, and physical examination demonstrated a 10x10 cm stage IV debucus ulcer with purulent drainage and exposed bone. Initial laboratory data demonstrated white blood cell count 18.7, hemoglobin 4.9 g/dL, normal basic metabolic panel and calcium 8.8mg/dL. He was transfused blood products and given antibiotic therapy. Bone biopsy demonstrated invasive squamous cell carcinoma. His calcium increased to 14.1mg/dL with elevated PTHrP 71pg/mL. He was diagnosed with humoral hypercalcemia of malignancy and treated with denosumab (20mg) and his calcium decreased to 9.32 mg/dL over the next four days. The response was sustained without additional need for administration over the next two months before the patient expired due to complications related to his debucus ulcer.
Discussion: This case illustrates the potential effectiveness of denosumab for the treatment of hypercalcemia refractory to bisphosphonates. Denosumab is a human monoclonal antibody against RANK-Ligand (RANKL) whose use has previously been described for management of hypercalcemia, but required multiple infusions. Recognition of this additional treatment, with effectiveness from a single infusion, is critical in managing refractory hypercalcemia, as the only other known option is hemodialysis. Increasing availability of options for management of refractory hypercalcemia may allow patients to avoid complications associated with hemodialysis.

TH-PO1108
Collapsing and NOS Focal Segmental Gомерulosclerosis (FSGS): Progression Along a Spectrum or Different Diseases? Suzanne L. Katsanos, Patrick H. Nachman, JulieAnne G. McGregor, Volker Nickeleit. UNC Kidney Center, Chapel Hill, NC.

Introduction: Minimal change disease (MCD) and some variants of FSGS (tip lesion and not otherwise specified NOS) are thought to represent a histologic spectrum of a same autoimmune pathogenic process (Habib, R. Proceedings Xth Int Cong of Neph). This contention has never been proven, however. Some cases of MCD are thought to be "unsampled" FSGS. A "transition" from MCD to FSGS is common in steroid-resistant forms (Tejani, A. Nephron 39). It has been proposed that collapsing FSGS is pathogenically and clinically distinct from other FSGS variants based on morphology, demographics, severity of nephrotic syndrome, and renal prognosis. The etiology has not been identified but viral agents, drugs, and cyclosporine toxicity have all been proposed.

Case Description: We present the case of a 37-year-old African American male with a complicated course of nephrotic syndrome. He was diagnosed with biopsy-proven MCD when 9 years old. He was treated with steroids followed by chlorambucil and then cyclophosphamide over the next several years. He was in complete remission off therapy for about 2 years until he re-presented with increased edema, proteinuria (3.8 g/d), hyperalbuninemia, and acute kidney injury (AKI). A repeat biopsy (23 glomeruli) showed FSGS NOS. He was treated with steroids followed by mycophenolate mofetil and cyclosporine, resulting in complete remission. 7 years later, he developed edema, proteinuria (21 g/d) and AKI. Repeat biopsy showed 25 glomeruli demonstrating segmental tuft collapse, activation of endothelial cells, and segmental marked activation and crowding of podocytes consistent with collapsing FSGS. HIV, hepatitis B, and hepatitis C were negative. The transition from MCD to FSGS NOS is common in the literature. However, the transition from FSGS NOS to collapsing FSGS is rarely reported. This patient’s case raises questions about this transition from NOS to collapsing variant. Glomerular undersampling is unlikely given 25 glomeruli were examined each time. This could represent a progressive, patient-related pathogenic process versus a de novo lesion (either related to a viral infection or medication, for example).

TH-PO1109
Lymphoma Associated Monoclonal Cryoglobulinemia in a Patient with Hepatitis C
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Introduction: We present a case of type I cryoglobulinemia and membrañoproliferative glomerulonephritis (MPGN) in a patient with hepatitis C infection (HCV), leading to the diagnosis of a marginal zone lymphoma.

Case Description: A 47 year old male with HCV and hypertension presented with two month duration of shortness of breath and decreased urine output. On examination he was hypertensive (blood pressure: 183/111 mm Hg), had lung crackles, lower extremity edema and hepatosplenomegaly. Laboratory tests were significant for hypercalcemia of 1.6 mg/dL, hyperphosphatemia of 4.8 mg/dL, hyperuricemia of 8.8 mg/dL, and low density lipoprotein (LDL) of 92 mg/dL. Renal biopsy revealed MPGN type II with deposits. Fluorescence microscopy favored kappa monoclonality. Electron microscopy of the deposits was consistent with cryoglobulins. Serum immunoelectrohoresis also confirmed IgM/Kappa monoclonality. As HCV is more commonly associated with polycylonal cryoglobulinemia this finding of monoclonality prompted a search for malignancy. A bone marrow biopsy showed lymphoid aggregates increase in number in the bone marrow and low density lipoprotein (LDL) was controlled on rituximab/dexamethasone based regimen. The creatinine trended down to 1.87 mg/dL.

Discussion: The transition from MCD to FSGS NOS is common in the literature. However, the transition from FSGS NOS to collapsing FSGS is rarely reported. This patient’s case raises questions about this transition from NOS to collapsing variant. Glomerular undersampling is unlikely given 25 glomeruli were examined each time. This could represent a progressive, patient-related pathogenic process versus a de novo lesion (either related to a viral infection or medication, for example).

TH-PO1110
A Lupus Nephritis Patient Accompanied with Storiform Fibrosis Characteristic in IgG4-Related Kidney Disease in the Absence of Serum IgG4 Elevation and IgG4-Positive Plasma Cell Infiltration

Introduction: IgG4-related kidney disease (IgG4-KD) usually presents as tubulointerstitial nephritis with IgG4-positive plasma cell (PC) infiltration and serum IgG4 elevation. IgG4-KD has characteristic histological findings called storiform fibrosis and nodular findings showing storiform density less than or equal to 60%. Recently, Hara et al. reported a case of IgG4-negative IgG4-KD (Mod Reumatol, 2014) which had a condition closely mimicking IgG4-KD despite the absence of serum IgG4 elevation and IgG4-positive PC infiltration. Here we report a patient diagnosed with lupus nephritis (LN) with IgG4-negative IgG4-KD.

Case Description: A 59-year-old Japanese man was referred to our hospital with chest pain and mild proteinuria. Thoracic biopsy was performed for abnormal lung shadow and interstitial pneumonia was diagnosed. Although ANA titer was elevated to 2560-fold, anti-DNA, anti-Sm, and anti-SS-A/B antibodies were all negative. Serum C3 and C4 levels and complement activity were decreased. Serum IgG and IgE levels were elevated, but serum IgG4 level was within normal limits. On contrast-enhanced CT, multiple low-density lesions were observed in kidney. Renal biopsy findings revealed lymphoplasmacytic infiltration with storiform fibrosis and small numbers of eosinophils. Immunostainings revealed CD138+ or IgG-positive PC infiltration without IgG4-positive PC. Immunofluorescence microscopy showed granular mesangial positivity for a “full-house” pattern. Electron microscopy disclosed mesangial and subendothelial dense deposition accompanied with virus-like particles. We diagnosed this patient with IgG4-negative IgG4-KD and LN (ISN/RPS II). After administration of 20 mg prednisolone, laboratory data was drastically improved.

Discussion: To our knowledge, this is the first report of a patient with LN and IgG4-negative IgG4-KD. IgG4-negative IgG4-KD may be a chronic burnout phase of IgG4-KD.

Further studies gathering similar cases would be needed to clarify whether or not IgG4-negative IgG4-KD is included in a category of IgG4-KD.

TH-PO1111
A Case of Acute Phosphate Nephropathy in a Kidney Transplant Recipient
Hetal Shah, M. Lee Sanders, Kelly A. Birdwell, Anthony J. Langone, Paisit Paueksakon, Beatrice P. Concepcion. Vanderbilt Univ Medical Center, Nashville, TN.

Introduction: Acute phosphate nephropathy has been described after large doses of phosphate, typically in laxatives and bowel cleansing preparations. We present a case of acute phosphate nephropathy in a kidney transplant recipient who was taking oral phosphorus supplementation for hypophosphatemia.

Case Description: A 26 year-old man with a living related donor kidney transplant in 2011 complicated by recurrent IgA nephropathy with a baseline creatinine of 1.9 mg/dl presented with nausea, vomiting, diarrhea, fatigue and elevated creatinine. Two weeks prior to presentation, he had been started on K-Phos-Neutral 500 mg three times a day for a hyperphosphatemia of 7.0 mg/dl. On the next day, his serum phosphate level increased to 10.4 mg/dl, phosphorus 9.7 mg/dl, calcium 9.6 mg/dl and iPTH 761 pg/mL. Urinalysis had a urine pH of 5, no red blood cells and trace protein. Renal biopsy was performed and pathology revealed 30 foci of intratubular calcium phosphate crystals with associated acute tubular injury involving 30-40% of tubular profiles, along with known recurrence of IgA nephropathy. The patient underwent acute hemodialysis for oliguric acute kidney injury. Given the high serum phosphorus, he was diazylzed for four consecutive days until phosphorus level was less than 4 mg/dl and did not rebound.

Patient was discharged requiring intermittent hemodialysis for an additional three weeks until he demonstrated renal recovery. His new baseline creatinine is 2.2 mg/dl and he has remained off hemodialysis.

Discussion: Hypophosphatemia is common in kidney transplant recipients. Although rare, acute phosphate nephropathy can occur in the setting of phosphorus repletion. This patient also had multiple risk factors, including baseline renal dysfunction, volume depletion and angiotensin receptor blocker use. Acute phosphate nephropathy can potentially lead to irreversible loss of renal function. While no specific treatment exists, in this case, aggressive hemodialysis to decrease serum phosphorus may have played a role in this patient’s eventual renal recovery.

TH-PO1112
Unusual Membranous Nephropathy in a Patient with Lupus
Iheanyichukwu Ogu, Julia Lewis, Agnes B. Fogo. Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.

Introduction: Membranous nephropathy (MN) is an immunologically mediated glomerular disease. Distinguishing between primary and secondary MN is important in guiding diagnosis and treatment. We present a case of a patient with systemic lupus with pathologic features in a repeat biopsy suggestive of primary MN.
A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits Exhibiting Marked Nephrotic Syndrome Who Responded Well to the Renin-Angiotensin System Blockade Alone

Yoshishiko Nishisugih, Hideki Inoue, Tomoaki Onoue, Yutaka Kakizoe, Yuichiro Izumi, Takashige Kuwabara, Takuya Miyoshi, Masatake Adachi, Yushu Nakayama, Masashi Mukoyama. Nephrology, Kumamoto Univ Hospital, Kumamoto, Japan.

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMD) is a newly recognized entity of glomerulonephritis caused by glomerular deposition of monoclonal IgG. The clinical and pathological features, treatment and prognosis of this entity remain elusive.

Case Description: A 79-year-old woman was admitted to our hospital due to hematuria and marked nephrotic-range proteinuria. Her serum creatinine level was 0.75 mg/dL and urinary protein excretion was 20.8g/24h. Renal biopsy showed a membranoproliferative feature without nodular formation. Immunofluorescence study showed capillary and mesangial deposits of IgG1, C1q and C3. Moreover, IgG-kappa deposits were strongly stained and IgG3 deposits were restrictedly stained for IgG heavy-chain subclass analysis. Electron microscopy revealed amorphous electron-dense mesangial and subendothelial deposits. Monoclonal proteins were not detected in serum or urine samples. Serum cryoglobulin titer was negative. Serum free light-chain assay showed a normal kappa/lambda ratio. These findings were consistent with the diagnostic criteria for PGNMD.

Considering her age and tolerability, we started monotherapy with angiotensin II receptor blocker. This case showed drastic reduction in proteinuria with stable renal function within 3 months. Considering her age and tolerability, we started monotherapy with angiotensin II receptor blocker. This case showed drastic reduction in proteinuria with stable renal function within 3 months.

Discussion: This report is the first case report of a patient with acute kidney injury in pregnancy from TMA secondary to pheochromocytoma. Patient made good renal recovery after resection of the tumor.

TH-POI116

Immune Reconstitution Inflammatory Syndrome and Hypercalemia with Acute Kidney Injury following Stribild Therapy

Caroline C. Garcia, Kelly H. Beers, Christine Miranda, Kamran Karimi, Yezina T. Nigatu, Nandi K. Wadhwia. Nephrology/Medicine, Stony Brook Medicine, Stony Brook, NY.

Introduction: Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory disorder with paradoxical worsening of preexisting infections following HAART in HIV-infected individuals. We describe a case of IRIS following Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir) resulting in hypercalcemia.

Case Description: A 33 year-old woman with acquired immunodeficiency syndrome (AIDS) who had been on StriBild for two months presented to the ED with acute kidney injury with a serum creatinine of 2.93 mg/dL and Ca of 15.2 mg/dL. Her CD4 count was 145 ul and viral load 35 copies/ml. Four months prior, she was treated with amphotericin for cryptococcal lung infection and Cryptococcosis. One month prior, a right lower lobe mass histology had revealed necrotic tissue with inflammatory cells. On examination, she was alert, in no acute distress, with unremarkable physical examination. Her temperature was 36.7 degrees Celsius, heart rate 72/minute, BP 108/64 mm Hg, respiratory rate 14/minute, and oxygen saturation 100% on room air. Chest X-ray showed an interval decrease in the right lower lobe mass. Serum intact PTH was 9.7 pg/mL, PTHr peptide, SPEP and UPEP were negative. Serum 25 (OH) D was 37 ng/mL, 1,25 (OH), D3 was 17 pg/mL, and 24 hour urine Ca was 270 mg. Urine fractional excretion phosphorus was 28% with no glucosuria. She was diagnosed with IRIS and Stribild was discontinued. She was treated with IV fluids and calcitriol with an improvement in her renal function and normalization of her serum calcium over a period of 4 weeks. Lab data summarized.

<table>
<thead>
<tr>
<th>Serum Creatinine mg/dL</th>
<th>Serum Ca mg/dL</th>
<th>CD4 ul</th>
<th>HIV viral load copies/ul</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base level</td>
<td>0.70</td>
<td>9.0</td>
<td>119,698</td>
</tr>
<tr>
<td>2 weeks on StriBild</td>
<td>1.45</td>
<td>11.8</td>
<td>122,220</td>
</tr>
<tr>
<td>8 weeks on StriBild</td>
<td>2.93</td>
<td>15.2</td>
<td>145</td>
</tr>
<tr>
<td>6 weeks off StriBild</td>
<td>1.00</td>
<td>9.4</td>
<td>178,362</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Discussion: IRIS is thought to be due to increased T-lymphocyte proliferation after HAART in AIDS patients. IRIS typically manifests as a granulomatous inflammation. Corticosteroids are treatment of choice in IRIS in the setting of excess 1.25 (OH) D3. In our case, serum 1.25 (OH) D3 was low suggesting possible other mechanisms.

TH-PO117

IgA-Dominant Postinfectious Glomerulonephritis: A Case Series Pranjali Sharma,1 Anitha Vijayan,2 Tingting Li.2 1Dept of Internal Medicine, Renal Div, Washington Univ in St. Louis, St. Louis, MO; 2Dept of Internal Medicine, Renal Div, Washington Univ in St. Louis, St. Louis, MO; 3Dept of Internal Medicine, Renal Div, Washington Univ in St. Louis, St. Louis, MO.

Introduction: IgA dominant post-infectious glomerulonephritis (PIGN) is a distinct clinicopathologic entity that typically occurs in diabetic patients and in association with a recent or active staphylococcal infection. Patients usually present with hematuria, proteinuria, and AKI. Renal pathology shows an immune-complex GN with various histologic patterns and IgA-dominance or co-dominance with IgG on immunofluorescence. Here we report the clinical characteristics and outcomes of 10 patients with IgA dominant PIGN.

Case Description: After obtaining approval from the local IRB, retrospective, single-center review of data was performed and 10 patients with IgA dominant PIGN were identified.

Majority was white males, and 6/10 were diabetic. Eight patients had a Staphylococcal infection and one had active Hep C infection. Only 3/10 had low complements. 6/10 required RRT and 4 developed ESRD, of which 2 died at 2 and 5 months after initiation of RRT. Five had left with varying degree of CKD and one was lost to follow up. Three patients were treated with immunosuppression in addition to antibiotics—all had significant improvement in renal function; one patient who was initially RRT-dependent was able to come off dialysis.

Patient
Infection
C3/C4
Hematuria
Proteinuria/d
Peak Scr
RRT
Follow Up
1
Hep C
N/N
Y
7.5
1.6
No
CKD
2
MSSA
L/L
Y
0.6
6.9
Y
CKD
3
MRSA/Pseudo-
domons
L/L
Y
1.16
3.9
No
NA
4
MRSA
N/N
Y
6.5
5
Y
Died
5
MRSA
N/N
Y
3.7
10.9
Y
CKD
6
MSSA
L/L
Y
1.2
7.5
Y
ERSD
7
MRSA/RE
N/N
Y
4.1
Y
ESRD
8
MSSA
N/N
NA
6.5
Y
Died
9
MRSA
N/N
NA
3.9
No
CKD
10
Clostridium
subterminalis
N/L
Y
2.8
5.2
No
CKD

Table 1. Clinical features and outcomes of pts with IgA-dominant PIGN

Discussion: IgA-dominant PIGN is an increasingly recognized disorder that occurs most commonly in diabetic patients with Staphylococcal infections. Overall renal prognosis is poor. Treatment with immunosuppression in addition to antibiotics may be considered.

TH-PO1119

ANCA Negative Paeu-Immune Necrotizing Crescentic Glomerulonephritis in a Patient with Non Hepatitis C Mixed Essential Cryoglobulinemia Victor Nwazue,1 Ji ae Yoon,2 Balhinder S. Brar.3 1Medicine, Mercy St Vincent Medical Center, Toledo, OH; 2Nephrology, Univ of Toledo, Toledo, OH; 3Nephrology, Mercy St Vincent Medical Center, Toledo, OH.

Introduction: Mixed essential cryoglobulinemia (MC) is associated with a hepatitis C infection in 70-90% of patients and presents as membranoproliferative glomerulonephritis or rapidly progressive glomerulonephritis (RPGN) with or without crescents. We report an unusual presentation of type II MC without hepatitis C infection presenting as ANCA negative PNM and crescentic glomerulonephritis (GN). We report the clinical characteristics and outcomes of 2 different pathologically and pathogenically distinct disease entities. To our knowledge this is the first reported case with these unusual manifestations.

Case Description: A 64 year old male presented with AKI (creatinine of 5.4 from a baseline of 0.8 mg/dL, 2 weeks earlier), 12-18 month history of arthralgias, fatigue, joint pains, petchial and purpuric spots on his extremities. His symptoms were exacerbated in the winter months. Lab tests revealed elevated cryoglobulin level (338mg/dL), low C4 (5 mg/dL), positive rheumatoid factor, IgG monoclonal gammapathy (0.37g/dL). MPO ANCA, PR3 ANCA, ANA, hepatits B and C and HIV serologies were negative. Urinalysis showed 20-50 RBCs, no casts and proteinemia of 2.5. G bone marrow biopsy showed < 5% plasma cells and no T cell aberrancy or B cell monoclonality. A kidney biopsy revealed pauci-immune necrotizing C3GN. Electron microscopy (EM) showed no deposits or fibrillary or tubular structures in the glomeruli. The patient was treated with hemodialysis (HD), 5 sessions of plasmapheresis and oral cyclophosphamide for 3 months. He responded to treatment with near complete resolutions of his symptoms and near normalization of kidney function.

Discussion: Pauci-immune C3GN is associated with either microscopic polyanthus or granulomatous with polyanthus. These can present as RPGN and have either a positive MPO or PR3 ANCA but have no deposits on immunofluorescence and EM. C3GN in pauci-immune is an immunocomplex disease, has distinct tubulocapillary, fibrillary and tubular structures on EM. Our case was an unusual combination of 2 different pathologically and pathogenically distinct disease entities. To our knowledge this is the first reported case with these unusual manifestations.

TH-PO1120

Fibrillary Glomerulonephritis Presenting as Rapidly Progressive Crescentic Glomerulonephritis Pallavi D. Shirsat,1,2 Chi Chyi Chong,1,2 Ramesh Marahatta,1,2 Cherinet S. Adgeh,1,2 Neville R. Dossaboy.1,2 1Dept of Nephrology, Veterans Affairs Medical Center, Shreveport, LA; 2Dept of Nephrology, LSU School of Medicine, Shreveport, LA.

Introduction: Fibrillary glomerulonephritis is a rare disease of unclear etiology, known to be associated with malignancy, autoimmune disorders, lymphoplasmacytic disorders and hepatitis C. It is seen in 0.5 to 1.0% of native kidney biopsies.

Case Description: We report a case of a 62 year old Caucasian male veteran who had a past medical history of hepatitis C, hyperlipidemia, s/p coronary bypass, multiple colon polyps (rectal and CKA) stage 3. Patient, on a routine follow up appointment, was noted to have rapid worsening of kidney function, with creatinine increase from baseline of 1.4-1.8 up to 3.2 mg/dL. He was also noted to have 24 RBCs per HPF on urine microscopy. Urine protein:creatinine ratio was 4.5. Hepatitis C related membranous glomerulonephritis (GN) was high on the differential list. Hepatitis B and HIV serologies were negative. Complement, cryoglobulins, ANCA and serum protein electrophoresis were within normal limits. Patient underwent kidney biopsy, which showed crescentic GN, with linear pattern immunoglobulin deposition along the GBM (glomerular basement membrane) on light microscopy and immunofluorescence suggestive of anti-GBM disease. However, patient’s anti-GBM titer was negative! Electron microscopy showed thickening of GBM due to fibrillary deposits. Similar fibrillary deposits were also seen in the mesangium, with haphazard distribution of fibrils measuring about 15 nm, consistent with fibrillary GN. Conge red stain for amyloid was negative. Patient was also found to have a 2.8 x 2.5 cm well-circumscribed solid & cystic mass in right kidney on ultrasound, suspicious for renal cell carcinoma (RCC). A fine needle aspiration of the mass yielded cells consistent with RCC.

Discussion: Fibrillary GN is known to be associated with malignancy. It can rarely present clinically as rapidly progressive, crescentic GN, and masquerade as anti-GBM disease on immunofluorescence. Electron microscopy and serologic workup are needed to clinch the definitive diagnosis.

TH-PO1121

Pauci-Immune Necrotizing Crescentic Glomerulonephritis as the First Manifestation of Chronic Lymphocytic Leukemia Relapse S. Saadi Imam,1 Monia E. Werlang,1 Tatiana A. Thorn,2 Nabeel Aslam.1 1Dept of Medicine, Division of Internal Medicine, Mayo Clinic, Jacksonville, FL; 2Dept of Medicine, Div of Nephrology, Mayo Clinic, Jacksonville, FL.

Introduction: The association between hematological malignancy and auto-immune disease is a well-documented phenomenon. Chronic lymphocytic leukemia (CLL) patients have 5-10% risk of developing autoimmune cytopathies, and a rare subset of these CLL patients may present with anti-neutrophil cytoplasmic antibodies (ANCA) or Wegener’s with set of a vasculitis. Here, we present a case of a patient with treated CLL whose relapse was identified by the new diagnosis of ANCA-associated pauci-immune glomerulonephritis.
Case Description: A 73-year-old female with history of CLL, status post chemotherapy five years ago, presented with complaints of dyspea on exertion, fatigue, oral ulcers, hemoptysis, rash, arthralgias, edema, and tea-colored urine for 3 months duration. Exam showed BP 157/94, bibasilar rales and gingival ulcers. Labs showed Hb 5.4g/dL, platelets 113K, WBC 4.6k, S. creatinine 4.4mg/dL. Urinalysis showed 2+ protein, many RBCs and WBCs. ANCA, ANA, anti-PR3 and MPO were strongly positive. Kidney biopsy showed necrotizing crescentic pauci-immune glomerulonephritis in more than 50% of glomeruli. Taking into consideration the patient’s prior history of CLL, bone marrow biopsy was performed and showed scattered nodular lymphoid proliferation with flow cytometry confirming relapse of CLL. Given this finding, our patient was treated on the lines of CLL relapse with steroids and rituximab instead of using steroids, cyclophosphamide and plasmapheresis for the treatment of ANCA-associated vasculitis alone.

Discussion: The prevalence of ANCA positivity in CLL patients has been documented to be 20-25%. In our patient, ANCA-associated pauci-immune glomerulonephritis was the first manifestation of CLL relapse. Discovering CLL relapse mandated a change in the management from the standard treatment of pauci-immune glomerulonephritis to a regimen more appropriate for both conditions. Clinicians should be aware of this rare association of CLL with ANCA-associated vasculitis to choose the most appropriate treatment regimen for these patients.

TH-PO1124
A Case of Catastrophic Antiphospholipid Syndrome Treated with Plasma Exchange
Takesuki Takahashi, Fumihiko Furuya, Tetsuhiro Oku, Kenichiro Kitamura. Third Dept of Internal Medicine, Univ of Yamanashi.

Introduction: Catastrophic antiphospholipid syndrome (CAPS) is characterized by diffuse vascular thrombosis, leading to multiple organ failure within a few days and resulting to poor prognosis. Antiphospholipid syndrome (APS) is an autoimmune thrombotic syndrome with recurrent thrombosis and occurs in both artery and vein, and from large to micro vessels. CAPS is also defined as a fatal variant of APS and develop thrombosis of three different organ systems with histopathologic evidence of multiple small vessel occlusions and high titers of antiphospholipid antibodies. Treatment for CAPS has not been established, and intensive anticoagulation or immunosuppressive therapy is carried out.

Case Description: A 68-year-old female who had been diagnosed as lupus erythematosus and APS complicated with multiple cerebral infarctions and treated with 5 mg of oral prednisolone. After her admission, she developed de novo cerebral infarction and colonic perforation with ischemic enteritis. Following a partial colectomy, she developed gram-negative bacteremia, subsequently, multiple strokes, non-ST elevation myocardial infarction, renal failure, and pathological findings with multiple thrombi. These clinical findings indicated that patient’s features were consistent with CAPS. She was maintained with anti-bacterial agent, anticoagulant, and prednisolone. However, since renal failure and anuria had continued, she was treated with plasma exchange (PE) and hemodialysis. Thereafter the volume of urine output was gradually increased and her renal function was recovered.

Discussion: We report a case of CAPS with multiple organ failure and successfully treated with anticoagulant, prednisolone, and PE. The clinical manifestation of CAPS depends on the release of inflammatory cytokines from the affected organs by thrombosis and small vessel occlusion. Our patient’s successful course could be attributed to beneficial role of PE through the removal of excessive inflammatory cytokines.

TH-PO1125
Acute HIV in a HIV-Naïve Patient During Primary HIV Infection and High Viral Load
Amit N. Shah, Adam G. Winkler, Claude Bassil, Donald E. Wheeler, Jacques A. Durr. Div of Nephrology, Univ of South Florida, Tampa, FL.

Introduction: A hitherto healthy 42 yo AA male felt chills only 6 days earlier. He took a NQuil and skipped next day’s shift for body aches/GI cramps. He improved but again felt bad by HS, 48h later. Next AM in a local ER, his UA showed WBC/RBC, 3+ protein, and a SG of 1.030. Physical exam, chest X-ray, contrast abdominal CT, and eGFR, were normal. His WBC had worked full capacity again, but got admitted 48h later after a brief syncpe.

Case Description: Viral signs: T 103 °F, BP 100/60 mm Hg, and HR 76 bpm. He had transient mild diastolic. Serum albumin (Alb) was 2.1 g/d, creatinine (cr) 2 mg/dl, and WBC 3+103/ml. UA had WBC/RBC and >0.5 g/dl protein. UA was 21 mmol/l. His urine protein was ~12 g/24h. CRP was ~2 (<0.5 mg/dl), and ESR 50 mm/h. CPK was 8717 U/l and ~ half by 48h. BCP, and HIV-1/2 Ab screens were (-), but (+) for HIV p24 Ag. He had >3+106 HIV copies/ml, and 213 CD4+ cells/ml. US showed normal-sized kidneys, no obstruction, but some corticale echogenicity.

His cr first improved for 72h, but then rose to ~8 mg/dl in 1w. Dialysis and HAART were initiated. By then he had edema and Alb was 1.2 g/dl. Renal biopsy showed collapsing GN, podocyte hypertrophy/hyperplasia, microcystic tubular dilations, 3+ acute tubular injury, 2+ patchy (mostly lymphocytic) infiltrate with focal tubulitis, and no signs of chronicity. Prednisone was added. He seroconverted (HIV-1) 2w after his first chills.

Discussion: Of the case reports of primary renal HIV infection only 2 had biopsy-proven HIV. One was HIV Ab (+) but by EIA but not by Western blot, and had 70,000 HIV copies/ml (Szabo S et al. 2002). Both had advanced RF and already other infections. Our patient had normal eGFR until his acute HIV infection. The high HIV Ag load alone, not replication, is the sole likely cause for HIV, consistent with the view that a direct toxic effect of HIV gene products or podocyte dedifferentiation, since viral particle endocytosis readily occurs in podocytes (as their normal filter cleaning role?), but lack of HIV entry receptors precludes local replication (Khatua AK et al. 2010).
A Case of Hypercalcemia with Renal Failure: Renal Sarcoid?


Introduction: Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by noncaseating granulomas in involved organs. Renal involvement occurs in 35-50%, manifested by hypercalculia, hypercalcemia, nephrocalcinosis, and nephro lithiasis. Granulomatous interstitial nephritis is the most typical histological finding usually in the setting of systemic disease and rarely in the absence of extrarenal sarcoid.

Case Description: A 54 y/o male presented with AKI superimposed on CKD and severe hypercalcemia (Calcium 13.5mg/dl, Ca×1.7mmol/L, creatinine=7.59mg/dl). Six months prior he had a kidney stone removed at which time his creatinine was 2.4mg/dl with Ca=1.1 but no further work up was performed. He was taking no medications and complained of back pain. Physical exam was unremarkable. A CT scan was negative for nephrolithiasis or hydronephrosis, chest X-ray revealed no abnormality. He was aggressively treated with IV NS and then Lasix with minimal improvement in the creatinine or the serum calcium. Work up for hypercalcemia included normal serum and urine immunofixation, negative PPD, normal PSA and normal skeletal survey. 25 Hydroxyvitamin D 27.8ng/ml (30-95ng/ml). He was started on prednisone 60mg/d with rapid resolution of the hypercalcemia and slow improvement in renal function (Creatinine 2.9mg/dl). A slow steroid taper over 1 year is planned.

Discussion: The diagnosis of sarcoid interstitial nephritis was strongly suggested by the renal biopsy given that other causes of granulomatous were ruled out. The patient was started on prednisone 60mg/d with rapid resolution of the hypercalcemia and slow improvement in renal function (Creatinine 2.9mg/dl). A slow steroid taper over 1 year is planned.

FR-PO002

Pediatric Chronic Refractory SIADH: Use of Tolvaptan

Cristin Kaspar, Nianzhou Xiao, Timothy E. Bunchman, Megan M. Lo. Pediatric Nephrology, Children’s Hospital of Richmond at Virginia Commonwealth Univ, Richmond, VA.

Introduction: The syndrome of inappropriate antidiuretic hormone (SIADH) is the most common cause of euvolemic hyponatremia in hospitalized patients, and standard therapies can be limited in their effectiveness. Arginine vasopressin receptor antagonists (AVR-A) oral tolvaptan and intravenous conivaptan have been FDA approved in adults, but reports on long-term use in pediatrics are lacking. We report on the dosing and safety of chronic AVR-A treatment in two patients with chronic SIADH. Dosing regimen was extrapolated from current pediatric and adult literature.

Case Description: Case A is a 13 year old, 43.5 kg female with a 12-year history of chronic A VR-A treatment in two patients with chronic SIADH. Dosing regimen was extrapolated from current pediatric and adult literature.

Discussion: Case A is a 13 year old, 47.3 kg female who developed refractory SIADH as her initial presentation of an olfactory neuroblastoma. She was treated with conivaptan load and infusion of 0.2 mg/kg/day, titrated off after 32 hours. She received tolvaptan starting at 0.15 mg/kg/day and discontinued once the mass was excised after 27 days.

Discussion: Stable tolvaptan dosing was reached at 0.15-0.3 mg/kg/day (7.5 mg daily or twice daily) and weaned to 0.08 mg/kg (3.5 mg) daily or every other day before being discontinued in both patients. Case B had elevation of serum creatinine when on IV conivaptan and fluid restriction. Neither patient had complications of hypokalemia, hypernatremia, or liver dysfunction. Both patients required frequent monitoring of serum sodium and regular titration of dose and oral fluid intake. We recommend starting tolvaptan at 0.5-0.3 mg/kg/day. The use of tolvaptan in an outpatient setting for chronic hyponatremia is safe and effective in adolescent patients with close monitoring.

FR-PO003

Congenital Pituitary Stalk Interruption Syndrome (PSIS) Newly Diagnosed in Case of Hyponatremia in the Elderly

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Introduction: There are many diseases that cause hyponatremia. Among them, adrenal insufficiency (AI) is important due to its urgency. We present an extremely rare case of elderly-onset AI in congenital PSIS, which is highly suggestive of the mechanism of AI progression.

Case Description: A 72 year old female with a 24 year history of hypothyroidism and a 12 year history of diabetes mellitus type 2. She was diagnosed with hyponatremia (Na=115mEq/L) in December, 2015. She was admitted due to “severe” hyponatremia in March, 2016. She was transferred from another hospital where she was treated with fluid restriction and normal saline with an improvement in serum sodium but further fluid restriction caused her sodium level to fall below 120mEq/L. She was intubated and admitted to our hospital. She had a history of congestive heart failure, hypertension, hyperlipidemia, diabetes, gout, hypertension, and psoriasis.

Discussion: We present an elderly-onset AI in a congenital PSIS patient. We performed CRH/TRH/GHRH/LHRH stimulation test disclosed hypothalamic panhypopituitarism. The patient was started on hydrocoisone 60mg daily. We achieved an improvement in serum sodium level to 130 mEq/L. The improvements in serum sodium level were sustained with a daily dose of 30mg hydrocoisone. The patient’s condition improved and she was discharged home after a week of hospitalization.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

357A
the delivery of hypotensive hormones to pituitary, resulting in elderly-onset AI. Thus, blood flow disturbance of SHA can induce AI in PSIS. In conclusion, a con genital disorder can be the cause for elderly-onset adrenal insufficiency. This case suggests that pituitary stalk interruption syndrome should be taken into account as a differential diagnosis for hypopituitarism, even in the elderly, especially in short statured patients.

FR-PO005

A Family Case of Hypoparathyroidism, Deafness, and Renal Dysplasia Syndrome with a Novel Mutation of GATA3

Tomoo Yabuuchi, Shoichiro Kanda, Naoya Morisada, Keiichi Takizawa, Yuji Tomii, Naoto Kaneko, Hirotake Hama, Eiji Nakano, Norimasa Tada, Kiyonobu Ishizuka, Hiroto Chiba, Yoshihiro Kato, Yuki Tokoa, Kazumoto Iijima, Motoshi Hattori

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Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT), a major cause of end-stage renal disease in children, often present as a systemic disorder with extrarenal symptoms. Extrarenal symptoms and family history are helpful in the genetic diagnosis of CAKUT. We report here a family case of hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome with a novel mutation of GATA3.

Case Description: Soon after birth, a female patient was diagnosed as having bilateral cystic dysplastic kidneys by renal ultrasonography. She also had hearing impairment at the infancy. She received peritoneal dialysis at the age of 3 years and received a cadaveric kidney transplant at the age of 10 years. When she was 14 years old, she visited the emergency department because of acute abdomen. Detailed examinations showed hematometra associated with vaginal atresia. Branchio-oto-renal syndrome was considered as her diagnosis based on her hearing impairment, bilateral cystic dysplastic kidneys, and normocalcemia. However, we suspected that she had an HDR syndrome because we found that her mother had hypoparathyroidism after determining a detailed family history. Genetic analysis was approved by the central ethics board of Tokyo Women's Medical University and Kobe University. This analysis showed a novel mutation, c. 1013G>T (C338F) of GATA3, the causative gene for HDR syndrome.

Discussion: Our patient did not show any symptoms of hypoparathyroidism. However, based on the family history, we performed a genetic analysis and found a novel mutation of GATA3. She was then diagnosed with atypical HDR syndrome. Therefore, determining a detailed family history is important in the precise diagnosis of CAKUT patients.

FR-PO006

Hydropneumothorax: A rare cause of hypoxemia

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Introduction: Hydropneumothorax is a very rare condition, usually associated with traumatic injuries, neoplasms, or infectious processes. In this case report, we present a patient with a non-traumatic hydropneumothorax and hypoxemia, which was successfully managed conservatively.

Case Description: A 45-year-old male patient was admitted to our hospital with a history of chest pain and shortness of breath. He was found to have a large left hydropneumothorax on chest X-ray. The patient was managed conservatively and underwent spontaneous resolution with no recurrence.

Discussion: Hydropneumothorax is a rare condition that can be caused by various etiologies. It is important to differentiate it from other causes of hypoxemia to ensure appropriate management. This case highlights the importance of a multidisciplinary approach in the management of such rare conditions.
hypokalemia, following the discontinuation of the medication, especially after prolonged use. Recent literature has knowledge, suggests this to be a case report demonstrating the association between HTN, hypokalemia and drospirenone.

Case Description: A 54 year-old Indian woman, previously normotensive, noted a new rise in home BP to 200/100 mm Hg and presented to the emergency department, where she was also noted to have mild hypokalemia to 3.1 mEq/L. Given the rather new onset of severe HTN and hypokalemia, work-up for secondary causes of HTN was done, which revealed normal aldosterone level (9 ng/dL), low plasma renin activity (PRA) (0.15 ng/mL/h) and high aldosterone/PRA ratio (60). Looking back into her history, it was noted that, the timing of symptoms was closely related to discontinuing Yasmin® (3 mg estradiol and 3 mg drospirenone), which she was taking for over 6 yrs. She was thought to have rebound effect with relatively excess mineralocorticoid activity, precipitated by the abrupt discontinuance of drospirenone. With the introduction of low dose spironolactone, her symptoms significantly improved.

Discussion: Drospirenone (an analogue of spironolactone), which has antimineralocorticoid and antiandrogenic activities similar to endogenous progesterone, counteracts the estrogen-mediated stimulation of the renin-angiotensin-aldosterone system (RAAS). Due to these effects, it has the potential to decrease blood pressure and also cause hyperkalemia. At a dosage of 400 mg daily, drospirenone causes mild natriuresis, which is followed by compensatory stimulation of the RAAS (comparable to a low sodium diet). When the prolonged ongoing suppression for the RAAS is removed, there might be a potential rebound effect with (relatively) high aldosterone state, resulting in sodium retention, leading to HTN. Spironolactone appears to be useful in this situation.

FR-PO010
Acthar Induced Hypokalemie Metabolic Alkalosis
Imran Quayyum, Neil W. Lyman. Dept of Nephrology, St. Barnabas Medical Center, Livingston, NJ.

Introduction: Acthar, an ACTH formulation from porcine pituitary gland, is an effective therapy for Membranous Nephropathy (MN). A rare adverse effect of hypokalemic alkalosis has been reported infrequently only. We present an atypical report of an 87 year old Caucasian female who developed severe hypokalemia and metabolic alkalosis with Acthar therapy, and concomitant diuretic use.

Case Description: The patient presented with severe bilateral leg edema. Lower extremity doppler was negative for DVT. Echo revealed normal EF. UA showed 4+ protein and 2+ blood. Spot protein/creatinine ratio was 20. Urine sediment had no RBC casts. Her scr was 1.99 mg/dL (baseline 1.34 mg/dL). Albumin was 2.3 g/dL. Workup for malignancy was negative. Her serologies were unremarkable and a renal ultrasound was negative. Anti-Phospholipid Antibody was positive. Renal function was normal. When this laboratory evaluation was done 2 months ago, the scr was 3.0 mg/dL and urinalysis was normal. She was referred due to her advanced age. Acthar 80 units 2x/week was added to her regimen of furosemide, amiloride, losartan and hydrochlorothiazide. Protein excretion decreased from 40 g/day to less than 5 g/24 hours. Of note, the patient is on continuous venovenous hemofiltration (CVVH) for end stage liver disease. She had previously been on dialysis for 2 months. 

Discussion: ACTH increases endogenous steroid production via MelanoCortin Receptor (MCR) type 2. It also exerts direct beneficial effects on podocytes and glomerular cells via other MCR subtypes. ACTH is an effective, alternative therapeutic modality for patients with MN who are non-responders to treatment with prednisone. The mechanism of action of ACTH has not been well described. We report a unique case of severe hypokalemia/metabolic alkalosis with the use of Acthar in a patient with MN. Clinical signs of hypokalemia and metabolic alkalosis are not typically seen in hyporeninemic hypoaldosteronism. Instead, ACTH-induced alkalosis can be explained by the increased aldosterone production, leading to hypokalemia. This case highlights the importance of evaluating the possibility of ACTH-induced hypokalemia in patients with MN and similar conditions.

FR-PO011
Polycthemia in a Patient with Bartter’s Syndrome and Medullary Nephrocalcinosis
Gorigle Singian Merdega, Medicine, Philippine General Hospital, Manila, Metro Manila, Philippines.

Introduction: Bartter’s syndrome is a tubular salt wasting disorder presenting with severe hypokalemic alkalosis, hyperchloremia, and hyperreninemia with normal blood pressure. Medullary nephrocalcinosis in this disorder is an infrequent finding and is still poorly understood. Polycythemia is an unusual presentation in patients with renal diseases, but has been described in literature among patients with nephrotic syndrome and distal tubal acidosis. It is noteworthy, however, that reports on secondary erythrocytosis among patients with Bartter’s syndrome is lacking. The exact mechanism for the polycythemia observed is uncertain, although it may be related to increased production of erythropoietin. The patient demonstrated, the concomitant use of ACTH and diuretic therapy can result in severe hypokalemic metabolic alkalosis. Clinicians should closely monitor serum electrolytes after initiating Acthar.

Case Description: A 27 year old Filipina male with recurrent bouts of severe hypokalemic alkalosis since childhood presenting as bilateral lower extremity weakness necessitating recurrent hospital admissions was diagnosed with Bartter’s syndrome based on metabolic alkalosis, hypokalemic alkalosis, slight hypernatremia with normal serum calcium and magnesium levels. He had normal blood pressure and no frank hypercalciuria. His creatinine was elevated but his ultrasound revealed normal sized kidneys with no evidence of nephrocalcinosis. He was treated with hemoglobin of 190 g/L, slight leukocytosis with no thrombocytosis. AK2 mutation was negative and a bone marrow biopsy revealed mildly hypercellular marrow with trilineage hematopoiesis, making polycythemia for which the patient was on iron supplementation. His lab hemoglobin was 15 g/dL. His symptoms resolved with bicalutamide. His labs showed serum sodium 139mmol/L, chloride 103mmol/L, creatinine 83mmol/L. His arterial blood pH was 7.37 with bicarbonate 21. His plasma renin activity was suppressed at 0.2ng/ml/hr and his serum aldosterone was raised at 534.4pmol/L. The transubtural potassium gradient was 3.87. Genetic analysis of the patient and affected family members revealed a missense mutation affecting exon 13 of the gene KLHL3 (c.1492C>T p.His498Tyr) affecting a residue located in the 5 kelch motif of the protein. The patient was treated with dietary salt restriction and a thiazide diuretic.

Discussion: This man illustrates classic findings in familial hypercalciemic hypertension including hypertension, hypercalciemia, metabolic acidosis and positive family history. Cases such as this gives us further insight into the molecular pathophysiology of blood pressure control. KLHL3 gene products play a key regulatory role in distal nephron Na reabsorption and may have potential as anti-hypertensive drug targets.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

359A
FR-P0014
Renal Failure Run A-FUowl: Disseminated Histoplasmosis Eileen Smith, Rajeev Raghavan, Sreedhar A. Mandayam. Baylor College of Medicine, Houston, TX.

Introduction: In patients with fever of unknown origin (FUO) and glomerulonephritis, Histoplasma capsulatum should be considered.

Case Description: A 37-year-old man presented to the hospital with 3 weeks of fatigue, 15-pound weight loss, intermittent chest pain, dyspnea on exertion and 3 day history of erythematous pruritic rash on his neck. PMH included congenital aortic stenosis with AVR, complicated by endocarditis requiring repeat AVR. Physical exam found splenomegaly and a lacy erythematous rash on the neck and torso. On admission, creatinine was 3.15 mg/dL (baseline 1.7 mg/dL, last year) with gross hematuria, and new pancytopenia. Initial work-up for glomerular disease was non-diagnostic. He developed persistent cyclical fevers to 102°F during his hospital stay. Blood cultures, tagged WBC scan and TEE were negative. Kidney biopsy showed numerous electron-dense deposits suggestive of Membranopro-Proliferative Glomerulonephritis. H. capsulatum serology and culture were positive. CT scan of chest showed right hilar lymphadenopathy. The patient regularly cleaned a chicken coop. An infectious work-up found the patient to be strongly positive for the Histoplasma capsulatum urinary antigen. With itraconazole for histoplasmosis and concomitant steroid therapy for glomerulonephritis, he defervesced and his creatinine improved to 1.4 mg/dL.

Discussion: Infection Related Glomerulonephritis (IRGN) is an immune-mediated disease caused by non-renal pathogens. The incidence is higher in developing countries: for example, per 100,000 individuals, the incidence of cases per year is 39 in India and 0.78 in the United States. It is believed that sub-clinical IRGN is common and underdiagnosed. In a series of 1012 kidney biopsies, 10% had evidence of disease, such as subepithelial humps. Hematuria is present in > 80% of cases, and patients usually present with Nephritic Syndrome. Endemic mycoses as a cause of glomerular disease in humans are rare. An infection due to H. capsulatum can result from inhalation of aerosolized spores after disruption of chicken droppings harboring the fungus. We suspected endocarditis given his cardiac history, and kidney biopsy findings also supported infection. However, the splenomegaly, FUO, and exposure to fowls (FUOwls) established the diagnosis.

FR-P0015
Next Generation Sequencer Driven Exome Analyses Identified a MCKD1 Family with New Mutation Before VNTR Of MUC1 DNA Sequence, Suffering from Mucosal Dysfunctions Satoko Yamamoto, Jun-Ya Kaimori, Masaki Hatanaka, Naotsubo Ichiumi, Shiro Takahara, Hiroaki Rakugi, Yoshitaka Isaka. Dept of Advanced Technology of Transplantation, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.

Introduction: Hereditary tubulo-interstitial nephritis (h-TIN) is characterized by family history, bland urine, normal size kidney, hyperuricemia, renal fibrosis and gradual renal function loss. MCKD1 type h-TIN is also recognized by the difficulty to identify mutant sequence by conventional Sanger Sequencer or next generation sequencing, because the cytoseine insertion mutation locates in the GC rich valuable number tandem repeat (VNTR) region. The mutant MUC1 DNA sequence is supposed to produce truncated type protein, which is inferred to be trafficking to the cell membrane. Because of the difficulty of identification, there may be lots of unknown symptoms in MCKD1.

Case Description: We identified 5 hereditary TIN patients in a family, three of those are renal transplant recipients, and the other was CKD. The CKD patient is 23 y/o female, whose renal function is gradually reducing for 10 years. Now her serum creatinin is over 3. Her renal MRI images showed normal size kidneys with no cysts. The patients are suffering from mucosal dysfunctions including GI ulcer, sinusitis, and dysphagia. We analyzed genome DNA sequence of hereditary TIN family by next generation sequence driven trio exome analyses. They revealed that the 2 bp deletion mutation were located before VNTR. Interestingly, consequently produced mutant MUC1 protein is a truncated protein with almost the same a.a. sequence repeats with previously reported mutant protein. The results were confirmed in the further analyses of other family members by conventional Sanger sequencer.

Discussion: We could identified the totally new mutation sequence of MCKD1 family, because it located before the GC rich VNTR sequence of MUC1. The newly identified mutant protein showed the almost same a.a. repeats sequence, suggesting these repeat sequence is implicated in the pathophysiology of MCKD1 type h-TIN.

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FR-P0016
Propofol-Induced Hyperkalemia in a Hemodialysis Patient Ibrahim M. El-Ali, Chandana Shekar, Sarthak Virmuni, Ruchir D. Triivedi. Dept of Medicine, Div of Nephrology, Univ of Connecticut Health Center, Farmington, CT.

Introduction: Propofol induced hyperkalemia and propofol infusion syndrome are well described in the intensive care literature. Propofol induced sudden cardiac arrest, however, may be under recognized. We report a case in which a large bolus of propofol was associated with an acute increase in serum K+ precipitating potentially fatal cardiac arrhythmia.

Case Description: A 58 yo Caucasian male with a past history of hypertension presented a week after developing an acute hyperkalemia rash associated with fever, encephalopathy, and atrial fibrillation, which was preceded by a month history of intermittent night sweats, fever, and joint pain. The desquamating rash encompassed >30% BSA with mucosal involvement. Skin biopsy revealed acute vacuolar interface dermacits consistent with toxic epidermal necrolysis (TEN). Labs showed pancytopenia without evidence of hemolysis. Serum Cr was 2.14 mg/dL (recently 0.9) and urine Protein/Cr was 1.15. Urine microscopy showed numerous acanthocytes and a few RBC casts. Serologies revealed low C3 and C4, positive ANA 1:640 and ENA screen, but negative ANCA, cryoglobulins, infectious work up and antibodies to ds-DNA, Sm, RNP, Ro/SSA, La/SSB, Jol and Scl70. A kidney biopsy revealed acute tubular injury and mild mesangial and endothelial proliferation without crescents or tuft necrosis. Immunofluorescence revealed diffuse 1-2+ staining for IgG, IgA, IgM, C3, C1q, kappa and lambda in the mesangium and capillary walls. Electron microscopy showed mesangial and capillary deposits with 20nm non-branching fibrils. Congo red stain was negative and IgG subclass stain did not reveal monoclonality. The findings were classified as a fibribillary glomerulonephritis. After initial methylprednisolone pulse, treatment with oral prednisone and mycophenolate mofetil resulted in resolution of rash, encephalopathy, and recovery of renal function and cell counts. The unifying diagnosis was new onset SLE, with TEN (possibly precipitated by naproxen) and fibrillary glomerulopathy.

Discussion: This case illustrates an uncommon presentation of an immune complex mediated fibrillar glomerulopathy consistent with SLE in an older male patient who presented with TEN. SLE has been rarely implicated as a cause of SJS/TEN when associated with initial photodistribution, absence of genital involvement, and a prolonged course.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
We report a case of SIADH associated with acute motor and sensory axonal neuropathy (AMSAN), a variant of GBS.

**Introduction:** Although lower urinary tract and kidney malformations account for 40% of childhood ESRD it is a rare cause of kidney failure in adults. Mutation in the HNF1α gene and homozygous loss-of-function mutation of muscarinic receptor M3 (CHRM3) were described. CHRM3 is the major receptor mediating urinary bladder contraction upon micturition. These patients have normal urethral patency on cystogram and detrusor hyporeflexia with high residual volumes after micturition seen on cystometry, identical to the findings in our report. This diagnosis in a 25 year old is rare, as most patients do not survive until adulthood or they are already ESRD.

**Case Description:** A 76-year-old woman with ADPKD was again admitted by infected (1L) renal cyst (7.3 cm) on ultrasonography (US) with similar episode, 1 yr ago. She presented with a fever, dysuria and left CVA tenderness. Despite clinical and laboratory improvement with sensitive antibiotics against Klebsiella pneumonia for 14 days, the size of the infected renal cyst was paradoxically enlarged (8.9 cm) on follow-up US. Thus, percutaneous catheter was inserted for drainage and after 1 wk, tubogram showed no evidence of dye leakage (figure1-A). Following complete clinical recovery, absolute ethanol sclerotherapy was performed to prevent further recurrent cyst infection. However, she complained of severe burning pain in low abdomen at the beginning of the procedure. Tubogram dye was shown in pelvicalveal system and ureter (figure1-B). Sclerotherapy was immediately stopped and saline irrigation was followed. Then, percutaneous catheter was remained into the cyst for further draining, and double-J catheter was inserted at ureteropelvic junction to prevent a ureteral stricture. Then, she underwent uneventful hospital course, and discharged on hospital day 42.

**Discussion:** Infected renal cyst wall, despite clinical recovery, could consist of already damaged tissue that may be easily broken by ethanol. Through this unexpected adverse complication, we learned that cyst ablation therapy with ethanol may not be an appropriate modality to prevent recurrent renal cyst infection in ADPKD.

**FR-PO019**

How ‘Idiopathic’ Is Idiopathic Hyperammonemia? Esho Georges, Kakitha Vellanki. Nephrology, Loyola Univ Medical Center, Maywood, IL.

**Introduction:** Idiopathic hyperammonemia is characterized by progressive elevations in serum ammonia of unknown etiology, ultimately leading to cerebral edema and death. It is a rare fatal syndrome described in transplant setting; lung transplant recipients having the highest risk. Calcineurin inhibitors are thought to play a role but the exact mechanism is not known. Here we report an unusual case of severe hyperammonemia that has been linked to donor transmitted Ureaplasma infection.

**Case Description:** A 59-year-old Hispanic man with idiopathic pulmonary fibrosis received bilateral lung transplant at our center. His induction regimen included thymoglobulin and methylprednisolone and was maintained on tacrolimus, mycophenolate and prednisone. He received intravenous antibiotics and improved clinically.

**Discussion:** Serum ammonia levels of such a magnitude despite aggressive dialysis is unheard of. It is a rare fatal syndrome described in transplant setting; lung transplant recipients having the highest risk. Calcineurin inhibitors are thought to play a role but the exact mechanism is not known. Here we report an unusual case of severe hyperammonemia that has been linked to donor transmitted Ureaplasma infection.

**Discussion:** In conclusion; underlying infection with urea splitting organisms need of further studies, it may be worthwhile to empirically treat with azithromycin for urea-splitting organism infections.

**FR-PO020**

Pelvocalyceal Leakage on Ethanol Sclerotherapy for Recurrent Infected Renal Cyst in ADPKD Eunyoung Lee, Joo-Hark Yi, Sang-Woong Han, Ho-Jung Kim. Division of Nephrology, Dept of Internal Medicine, Hanyang Univ Guri Hospital, Guri-si, Gyeonggi-do, Republic of Korea.

**Introduction:** Though sclerotherapy has been commonly considered as a safe and effective treatment for symptomatic renal cysts, it’s effectiveness in recurrent infected renal cyst in autosomal dominant polycystic kidney disease (ADPKD) is rarely reported.

**Case Description:** A 76-year-old woman with ADPKD was again admitted by infected (1L) renal cyst (7.3 cm) on ultrasonography (US) with similar episode, 1 yr ago. She presented with a fever, dysuria and left CVA tenderness. Despite clinical and laboratory improvement with sensitive antibiotics against Klebsiella pneumonia for 14 days, the size of the infected renal cyst was paradoxically enlarged (8.9 cm) on follow-up US. Thus, percutaneous catheter was inserted for drainage and after 1 wk, tubogram showed no evidence of dye leakage (figure1-A). Following complete clinical recovery, absolute ethanol sclerotherapy was performed to prevent further recurrent cyst infection. However, she complained of severe burning pain in low abdomen at the beginning of the procedure. Tubogram dye was shown in pelvicalveal system and ureter (figure1-B). Sclerotherapy was immediately stopped and saline irrigation was followed. Then, percutaneous catheter was remained into the cyst for further draining, and double-J catheter was inserted at ureteropelvic junction to prevent a ureteral stricture. Then, she underwent uneventful hospital course, and discharged on hospital day 42.

**Discussion:** Infected renal cyst wall, despite clinical recovery, could consist of already damaged tissue that may be easily broken by ethanol. Through this unexpected adverse complication, we learned that cyst ablation therapy with ethanol may not be an appropriate modality to prevent recurrent renal cyst infection in ADPKD.

**FR-PO021**

A CD2AP Mutation (p.T374A) Associated with Cognitive Decline and Focal Segmental Glomerulosclerosis in Young Adulthood Dmitry Tsvekeyov,1 Yolanda Marie Anistan,1 Christian Harteneck,2 Maik Gollasch,1 Charité Univ Medicine Berlin, Nephrology/Intensive Care, Experimental and Clinical Research Center (ECRC) and Max Delbrück Center for Molecular Medicine, Berlin, Germany; 1Dept of Pharmacology and Experimental Therapy, Inst of Experimental and Clinical Pharmacology and Toxicology, Eberhard Karls Univ Hospitals and Clinics, and Interfaculty Center of Pharmacogenomics and Drug Research, Univ of Tübingen, Tübi.

**Introduction:** Mutations in CD2-associated protein (CD2AP) gene have been identified in patients with focal segmental glomerulosclerosis (FSGS); however, reports of CD2AP mutations remain scarce.

**Case Description:** We performed Sanger sequencing in a 32-year-old patient with steroid-resistant FSGS presented with a nephrotic syndrome (proteinuria >3.5 g/day). The patient reported that his mother and his only brother also have a kidney disease. Neurological examination showed a remarkable cognitive decline within the last 5 years. Therapy with steroid and low-intermediate doses of cyclosporine A led to a persistent reduction of proteinuria. Serum creatinine levels and glomerular filtration rate (eGFR) did not decline during this treatment.

**Discussion:** Our patient displayed mild cognitive decline, a phenotypic characteristic not previously associated with CD2AP-associated FSGS. His proteinuria was remarkably reduced by treatment with cyclosporine A. Our findings expand the genetic spectrum of CD2AP-associated disorders and broaden the associated phenotype with the co-occurrence of cognitive decline. Our case shows that cyclosporin A is a treatment option for CD2AP-associated nephropathy.

**FR-PO022**

Acute Motor and Sensory Axonal Neuropathy-Associated Syndrome of Inappropriate Antidiuretic Hormone Secretion Weeraporn Sirung,1 Aumyot Prongdong,1 Pavis Laengvejkal,2 Camilo Pena,1 Mustafa G. Aly,1 Sorot Phisitkul.1 Internal Medicine, TTUHSC; 1Neurology, TTUHSC.

**Introduction:** SIADH is associated with various conditions including Guillain–Barre’ syndrome (GBS). We report a case of SIADH associated with acute motor and sensory axonal neuropathy (AMSAN), a variant of GBS.
Case Description: A 36-year-old man presented with a 6-week history of progressive ascites, weight gain, and edema. Examination showed ascites with questionable weakness, more severe in the LLEs, muscle wasting, absent LE reflexes, dysesthesis and no cranial nerve involvement. MRI head/spine was unremarkable. CSF analysis showed albuminocytologic dissociation and ruled out infection. HIV, viral hepatitis and paraproteinemias were absent. SIADH and AMI were ruled out. However, G1 and GQ1b were negative. Nerve conduction study showed axonopathic pattern on motor and sensory fibers bilaterally. AMSAN was diagnosed. He received IV immunoglobulin with gradual improvement of his weakness. On admission, serum chemistry panel showed Na 115 mmol/L with normal Cr. Urine showed Na <20 mmol/L, and specific gravity 1.045. Urine Osm was not available initially. He received NS infusion for volume expansion. Interestingly, Na did not significantly improve after he became euvolemic. Fluid restriction was then tried with mild improvement. Endocrine work-up ruled out hypothryoidism and adrenal insufficiency. Repeat labs showed serum Na 124 mmol/L, urine Na 191 mmol/L and urine Osm 531 mOsm. Hence, SIADH was diagnosed. Other well-established causes of SIADH were ruled out thus AMSAN was believed to be the most likely cause of SIADH. Tolvaptan was started at 15 mg and resulted in significantly increased urine output (300-500 ml/hr). Na increased rapidly so DSW was started to prevent osmotic demyelination syndrome. Tolvaptan was restated at 7.5 mg 2 days later with prompt response. He was discharged on tolvaptan 7.5 mg daily with Na 130 mmol/L.

Discussion: Although GBS is a well-established cause of SIADH, but to our knowledge, AMSAN-associated SIADH has only been rarely reported in literature. We suggest that AMSAN should be high on the differential diagnosis for hyponatremia in patients with AMSAN, especially in the setting of euvolemia.

FR-P0023
Severe Renal Osteodystrophy as a Result of Fanconi Syndrome Rabie L. Adam-Eldien, Charles W. Heilig. Nephrology, Univ of Florida, Jacksonville, FL.

Introduction: Fanconi syndrome is a disease of the proximal renal tubules in which glucose, amino acids, uric acid, phosphate, bicarbonate and other substances are not reabsorbed and lost in the urine.

Case Description: 22 year old African American female with an autosomal dominant Fanconi syndrome. Her disease is clinically manifested by severe rickets and short stature. Her short stature has not responded to growth hormone. She has multiple stress fractures, and she amputates with a walker. Her disease is manifested chemically by generalized aminoaciduria, hyperchloremic metabolic acidosis, hyperphosphaturia, glucosuria, bicarbonaturia, and proteinuria. Her life compliance with the medication has been poor. She has a gastrostomy tube for medications administration. Her medications include Calcium Carbonate, Neutra-Phos, Rocaltopol, Polycitra and Zantac. Her physical examination showed: Height 98.5 cm, weight 15.8 kg, blood pressure 106/57, pulse 80. She can stand up with hips flexed and her trunk slightly forward because of the anterior and lateral bowing of the femur and the widening metaphyses of the knees and the wrists. She has rickety change, ankle prominence, and she has good range of motion. Extremities: Have severe rickety changes. Lower extremities are deformed with prominent femur curve bilaterally. The rest of her exam was uneventful.

Urinalysis shows glucose 100 mg/dL, ketones 40 mg, blood trace, pH 7, protein greater than 300 mg. Chemistry showed, Sodium 134, potassium 3.4, bicarbonate 31, chloride 112, glucose 142, BUN 5, creatinine 0.6, calcium 7.9, phosphorus 3.8. Osmolality 268.

Discussion: Acute intermittent porphyria (AIP) is a rare metabolic disorder. Polyuria is a common manifestation of many primary medical disorders. Here we present a case of Acute intermittent porphyria (AIP) with decreased urinary osmolality, and high urine sodium indicating a mechanism other than Diabetes insipidus. After the solute load was reduced the solute intake of the patient but first and foremost requires an accurate diagnosis.

FR-P0024

Introduction: Infective endocarditis can cause renal failure due to immune complex mediated glomerulonephritis. We present a case of Nontuberculous mycobacterium (NTM) endocarditis associated with acute glomerulonephritis with tubulointerstitial nephritis.

Case Description: Our patient was a 59 y/o Venezuelan man with a history of cocaine use who presented with generalized weakness, intermittent nausea, and a 40lbs weight loss. He denied taking any antibiotics or illicit drugs for the previous month. On examination, he was afibrile, HR 85, BP 112/43mmHg. Pulmonary exam was unremarkable, and heart rate was 85. Auscultation revealed a 3/6 holosystolic murmur at the right upper sternal border. JVP was not elevated. She was afebrile, HR 85, BP 112/43mmHg. Pulmonary exam was unremarkable, and heart rate was 85.

He denied taking any medications or illicit drugs for the previous month. On examination, his exam was unrevealing.

He has a gastrostomy tube for medications administration. Her medications include Calcium Carbonate, Neutra-Phos, Rocaltopol, Polycitra and Zantac. Her physical examination showed: Height 98.5 cm, weight 15.8 kg, blood pressure 106/57, pulse 80. She can stand up with hips flexed and her trunk slightly forward because of the anterior and lateral bowing of the femur and the widening metaphyses of the knees and the wrists. She has rickety change, ankle prominence, and she has good range of motion. Extremities: Have severe rickety changes. Lower extremities are deformed with prominent femur curve bilaterally. The rest of her exam was uneventful.

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Discussion: Acute intermittent porphyria (AIP) is a rare metabolic disorder. Polyuria is a common manifestation of many primary medical disorders. Here we present a case of Acute intermittent porphyria (AIP) with decreased urinary osmolality, and high urine sodium indicating a mechanism other than Diabetes insipidus. After the solute load was reduced the solute intake of the patient but first and foremost requires an accurate diagnosis.

FR-P0025
Severe Hyponatremia in a Young Patient with Recurrent Abdominal Pain Dimpu M. Patel, Manish K. Saha, Ashita J. Tolwani. Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.

Introduction: Acute intermittent porphyria (AIP) is a rare metabolic disorder. Hyponatremia due to syndrome of inappropriate secretion of diuretic hormone (SIADH) during acute attacks of AIP requires prompt diagnosis and treatment of both AIP and hyponatremia.

Case Description: A 21yo Asian female presented to the ED with sharp intermittent abdominal and flank pain. Upon arrival to the ED, she had a generalized toxic-clonic seizure requiring intubation for airway protection. She denied any medications or illicit drugs for the previous month. Her only medications were trimethoprim-sulfamethoxazole and ibuprofen prescribed 2 days prior. Clinical exam revealed tender abdomen, right upper quadrant tenderness, and high urine osmolality (350 mOsm/kg). She was treated with a carbohydrate based diet and avoidance of medications known to precipitate an acute attack.

Discussion: AIP results from a deficiency of PBG deaminase, leading to accumulation of 5,10-dihydroxy-δ-aminolevulinic acid (ALA)-delta 7 and ALA-delta 6, which are degraded by PBG deaminase. Urinary ALA-delta 7 is increased. The metabolism of ALA-delta 7 and ALA-delta 6 are mediated by hematopoietic enzymes and it can be caused by a drug or accompanies another genetic disorder. In hereditary Fanconi syndrome, proximal tubular acidosis, hyperphosphatemic rickets, hypokalemia, polyuria, and polydipsia usually appear in infancy. If a patient is unable to keep up with the replacement of these substances secondary to compliance or lack of access, adverse permanent skeletal effects might result from that.

FR-P0026
A Case of Solute Diuresis Muhammad K. Qaseem, Elizabeth A. Gilliams, James L. Bailey. ’1 Emory Univ School of Medicine, At: ’EUH.

Introduction: Polyuria is a common manifestation of many primary medical disorders. Here we present a case of Argininosuccinate Lyase Deficiency(ASLD) who presented with altered mental status and later developed polyuria.

Case Description: A 24-year old male with history of ASLD was admitted to the Intensive Care Unit (ICU) for altered mental status with an ammonia level of 347mcnmol/L. He was started on Ammonia Scavenger therapy with Ammonium/arginine, Na-benzoate and bi-phenylacetate (BPA). On hospital day 10 he developed hypokalemia, hypernatremia and polyuria of 5L. His labs are listed below.

<table>
<thead>
<tr>
<th>Day-1</th>
<th>Day-14</th>
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<tbody>
<tr>
<td>Na=140 mmol/L</td>
<td>Na=148 mmol/L</td>
</tr>
<tr>
<td>K=3.8 mmol/L</td>
<td>K=2.6 mmol/L</td>
</tr>
<tr>
<td>CI=112 mmol/L</td>
<td>CI=118 mmol/L</td>
</tr>
<tr>
<td>CO2=20 mmol/L</td>
<td>CO2=26 mmol/L</td>
</tr>
<tr>
<td>Creatinine= 0.68 mg/dL</td>
<td>Creatinine= 0.5 mg/dL</td>
</tr>
<tr>
<td>BUN= 3 mg/dL</td>
<td>BUN= 2 mg/dL</td>
</tr>
<tr>
<td>Ammonium= 347 mcnmol/L</td>
<td>Ammonium= 47 mcnmol/L</td>
</tr>
</tbody>
</table>

Urine studies showed urine Sodium of 253mmol/L, urine Potassium of 59mmol/L, urine chloride of 175 mmol/L, urine anion gap of 137, urine osmolality of 63 mOsm/kg and urine Creatinine of 63 mg/dL with a 5.3L of urine in 24 hours. He was receiving Normal Saline, Ammonium and Total Parenteral Nutrition(TPN). It was recommended to stop the infusion of ammonium to decrease the non-measured anions in the urine, stopping 5%normal saline and change the TPN to have less solute load. With these interventions his urine output and hypokalemia improved to almost back to normal.

Discussion: Argininosuccinate Lyase deficiency results in the breakdown of argininosuccinic acid to arginine and fumarate. ASLD can result in severe hyperammonemia. Treatment of acute decompensations with hyperammonemia involves discontinuing oral protein, using intravenous arginine and ammonia scavenging therapy. Polyuria in ASLD could be due to different mechanisms such as low BUN leading to poor urine concentrating ability with loss of free water or due to solute diuresis. Our patient’s high urine osmolality and high urine sodium indicated a mechanism other than Diabetes insipidus. After the solute content was decreased his urine osmolality decreased significantly along with his urine output. Hypernatremia also improved. Management of solute diuresis in this case was to reduce the solute intake of the patient but first and foremost requires an accurate diagnosis.
Life Threatening Hypokalemia and Metabolic Alkalosis Related to Paraneoplastic Cushing’s Syndrome
Chyi Chyi Chong, 1 Pallavi D. Shirsat, 1 Ramesh Marahatta, 1 Cheri N. Adgh, 2 Neville R. Dossabhoy. 2
1LSU Health Science Center, Shreveport; 2VA Medical Center, Shreveport.

Introduction: Paraneoplastic Cushing’s syndrome (CS) develops secondary to tumor-affected ACTH. In the case of severe hyponatremia, with metabolic alkalosis related to ectopic ACTH production.

Case Description: A 58 y/o African American male presented with complaints of feeling unwell, weight loss and frequent diarrhea for at least one month. On admission, he was normotensive. On physical exam, patient had mild wheezes at bases. Laboratory data was significant for Na 144 mEq/L, K 1.1 mEq/L, Cl 82 mEq/L, HCO3 50 mEq/L, BUN 14 mg/dl and Cr 1 mg/dl. Blood gas revealed pH 7.4, PCO2 92 mmHg, PO2 92.4 mmHg and HCO3 47 mmol/L. Pt unfortunately developed respiratory failure requiring intubation shortly after albuterol nebulizer treatment. He was also receiving Diamox in ICU. He required potassium supplement on average of 120 meq per day (Maximum 300 meq/day). Once diarrhea resolved and with discontinuation of Diamox, patient was still noted to be hypokalemic. Urine electrolytes performed: Na 31 mmol/L, K 107 mmol/L, Cr 41 mg/dL. Additional lab data: Renin <0.15 ng/ml/hr, Aldosterone <1 ng/dl, ACTH level 126 pg/ml and 24hr urine cortisol 3846 mg.

Discussion: This is a rare case of paraneoplastic CS associated with neuroendocrine carcinoma. Early recognition and appropriate treatment for this syndrome is important, although overall clinical outcome remains poor.

FR-PO28

Overcorrection of Hyponatremia Secondary to Diuresis in Postpartum
Maria Berenice Nava, 1 Maya K. Rao. 2 Div of Nephrology, Columbia Univ, New York, NY; Div of Nephrology, Columbia Univ, New York, NY.

Introduction: Previous case reports have described hyponatremia in pre-eclampsia particularly with twin gestations. Overcorrection in the post-partum period is a potential risk and complications manage.

Case Description: Case report.
30 yo woman G1P0 with intrauterine insemination with triplets presented at 30 weeks gestation with pre-eclampsia and nephrotic syndrome for emergent cesarean section. On presentation she was hypertensive, massively edematous found to have a serum sodium of (sNa) 126 mEq/L (no prior values), serum creatinine 0.5 mg/dL and albumin 2.4 g/dL. Urine osmolality was 159 mOsm/kg and the urine osmolality was 263 mOsm/kg, urine sodium 21 mEq/L. Spot urine protein:creatinine ratio 3.5 grams. By POD 2, her sNa decreased to a nadir of 119 mEq/L and spot protein: creatinine ratio was 0.458 grams. Free water restriction was started. She soon began to auto-diurese (2.6L in 4hrs) resulting in a rise in sNa to 127 mEq/L in 5 hrs with a urine osmolality of 159 mOsm/kg. She was started on DDAVP to 0.04IU/hr and sNa levels were checked every 4 hrs. Her subsequent sodium levels remained at 127 mEq/L over the next 12 hrs. On POD 0 she was noted to be hypokalemic. Urine output decreased to <100ml/hr on POD 4, urine osmolality was 217 mOsm/kg, therefore DSW was discontinued. She received 4 additional doses of DDAVP. The patient was ultimately discharged on POD/10 with a sNa of 143 mEq/L and off DDAVP.

Discussion: Hyponatremia in pre-eclampsia with nephrotic syndrome has been reported in the literature and it is thought to be secondary to low effective circulating plasma volume. In this case, we report rapid correction of serum sodium post-delivery likely due to volume redistribution and removal of ADH stimulus. Awareness of potential rapid correction and frequent monitoring of serum sodium is important in order to intervene early and prevent consequences of rapid sodium correction. Serum sodium post-delivery should be monitored very closely in cases such as these.

FR-PO29

Severe Hypocalemia in a Hemodialysis Patient

Introduction: Severe hypocalemia in a hemodialysis patient is rare in the absence of parathyroidectomy, vitamin D deficiency or calcitriol medications.

Case Description: A 58 year-old man was found to have severe asymptomatic hypocalemia (5.9 mg/dL) with prolonged QTC (547 ms) four weeks after starting hemodialysis. He had a history of prostate cancer treated with radical prostatectomy, bisphosphonates and a GnRH analog. Serum calcium prior to starting hemodialysis was 8.6 mg/dL; serum albumin 3.2 gm/dL, PTH 352 pg/mL, 25OH Vitamin D2 =<4ng/mL, 25OH Vitamin D3 12 ng/mL and phosphorus 6.3 mg/dL. His intravenous doxelcalciferol dose was titrated to 20 mcg thrice weekly; oral calcium carbonate and 1,25-dihydroxycholecalciferol were administered orally. Dialysate calcium concentration was increased to 3.5 mg/dL. However, despite these measures, pre-dialysis calcium was 6 mg/dL. On further review, it was found that he had been started on denosumab six weeks prior to initiation of hemodialysis for bone pain due to skeletal metastases. Denosumab is a monoclonal antibody against RANKL (a ligand for receptor of nuclear factor kappa-B ligand). Tumor cells in patients with skeletal metastases stimulate osteoblast to secrete RANKL, which stimulate osteoclast to promote osteolysis and increase calcium levels. Even after replenishing Vitamin D stores, our patient continues to need higher dialyse calcium.

Discussion: Common causes of hypocalcemia in dialysis patients include: vitamin D deficiency, autoimmune or surgical hypoparathyroidism, severe hyperphosphatemia due to tumor lysis or rhabdomyolysis and medications such as cinacalcet. Denosumab is an easily overlooked cause of hypocalcemia. Our patient had Vitamin D deficiency but normal calcium level prior to starting denosumab. It is important to replete vitamin D and calcium stores prior to initiating denosumab in patients with chronic kidney disease as they may have resistance to standard therapy for hypocalcemia. It is also recommended to check calcium levels regularly while on this medication.

FR-PO30

Central Diabetes Insipidus with Pituitary Atrophy from Chronic Lithium Use
Joe Ghata, Satish Kumar. Nephrology, Univ of Oklahoma Health Science Center; Oklahoma City, OK.

Introduction: Lithium use is commonly associated with nephrogenic diabetes insipidus (NDI) and rarely with central diabetes insipidus (CDI). The mechanism of Lithium associated CDI is unclear. We report a patient on chronic lithium therapy who developed CDI and partial NDI and who had atrophy of posterior pituitary atrophy on MRI.

Case Description: A 62 yo woman with diabetes mellitis 2 for 5 years, hypertension for 10 years, and bipolar disorder on lithium for 40 years was admitted to the ICU for altered mental status. ROS was negative for nausea, vomiting, diarrhea, acute intoxication or infectious prodrome. Physical exam was normal; she was clinically euvolemic. Urine output was 4-8 ml/hr and serum Na was 178 mEq/L. Serum creatinine was 4.84 mg/dL elevated from a baseline of 1.5 in 2012. Urine osmolality (U osm) was <100 mosm/L. Intravenous D5W at 200 ml/hour resulted in improved serum creatinine to 1.7 mg/dl but minimal reduction in serum Na. Water restriction produced a submaximal rise (<250 mosm/L) in U osm from 157 to 176. ADH levels were undetectable by RIA when serum Na was 165-175. Intravenous desmopressin produced submaximal elevation in urine osmolality from 80 to 153 (91.25%), consistent with partial NDI (U Osm = 250 mosm/L) and partial CDI (<15 to 99%). MRI demonstrated atrophy of the posterior pituitary with non-specific volume loss, straightening of the infundibulum, and absence of bright spot corresponding to the posterior pituitary. Final diagnosis was both central and nephrogenic DI associated with lithium use. Euthyremia was eventually achieved with intranasal DDAVP and liberal fluid intake.

Discussion: This is the first report of radiological evidence of posterior pituitary atrophy with lithium-associated central DI. Possible mechanisms of posterior pituitary atrophy may include “burn-out” from chronic hypersecretion of ADH caused by lithium induced nephrogenic diabetes insipidus or autoimmune hypophysitis from circulating autoantibodies developed in response to chronic high ADH levels.

FR-PO31

Iatrogenic Hyponatremia

Introduction: Vasopressin acts in the kidney via V2 receptors to regulate water resorption and on the vasculature via V1 receptors to regulate smooth muscle tone. It is often used in the management of shock, but rarely causes hyponatremia in hemodynamically unstable patients. We present here a case of a man who developed marked hyponatremia during vasopressin infusion.

Case Description: A 58 year old man with history of hypertension and coronary artery disease was admitted to intensive care unit for un-witnessed cardiac arrest. He was intubated and started on vasopressin and norepinephrine for cardiacogenic shock. His lab data on admission revealed normal serum sodium, blood urea nitrogen and creatinine. His inpatient course was significant for development of hyponatremia within 2 hours of initiation of vasopressin infusion. Patient’s sodium dropped from 142 mosm/L(normal range 136-146 meq/L) to lowest value of 124 meq/L associated with oliguria (urine output 20ml/hr). With cessation of vasopressin, urine output increased significantly to 500ml/hr and serum sodium increased from 124 meq/L to 142 meq/L. Dextrose infusion was started to prevent overly rapid correction. Please refer to graph for the changes in serum sodium and urine output with vasopressin infusion over time. Patient had normal cortisol levels and thyroid function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Discussion: Vasopressin does not usually result in hyponatremia when used in management of shock. Possible explanations include lack of renal responsiveness secondary to cardiovascular hyperperfusion/acute kidney injury, or lack of intake of hypotonic fluids. In this case, the patient developed marked hyponatremia in setting of preserved renal function.

FR-PO032

Hyperkalemia Secondary to Octreotide Use in a Patient with Normal Kidney Function
Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY.

Introduction: Octreotide, a somatostatin analogue works by reducing blood levels of a variety of hormones (e.g. growth hormone, insulin) and chemical messengers (e.g. gastrin, vasoactive intestinal peptide). Octreotide therefore has been used as an effective medication for the treatment of sulphonylurea-induced hypoglycemia, acromegaly, VIPoma and carcinoid syndrome. Octreotide-induced hyperkalemia has rarely been reported in the literature. We report a patient with normal renal function who developed hyperkalemia secondary to octreotide use.

Case Description: A 70-year-old male with long standing history of DM (since 20 years), HTN, and metastatic neuroendocrine pancreatic cancer was referred by his oncologist for evaluation of severe hyperkalemia (serum potassium level of 6.6 mmol/L). Patient was diagnosed with pancreatic neuroendocrine tumor approximately 2 years prior to his presentation for which he underwent Whipple procedure. He was also receiving subcutaneous octreotide monthly for nearly 1.5 years prior to his presentation. There was no history of kidney disease or any urinary complaints. Other medications included aspirin, insulin, creon, levotiroxine and HCTZ. BP was normal and patient was noted to have bilateral lower extremity pitting edema on examination. Other labs done 5 days prior to presentation showed normal serum bicarbonate (25 mmol/L), normal serum creatinine (1.23 mg/dL), and elevated serum glucose (263 mg/dL). On reviewing medical records, our patient was noted to have chronic and persistent hyperkalemia over the previous six months that was medically managed by intermittent oral sodium polystyrene sulfonate and potassium diet. All other causes of hyperkalemia were clinically excluded. Serum potassium normalized after receiving medical management and holding octreotide treatment.

Discussion: We present a rare case of octreotide-induced hyperkalemia in a patient with normal renal function. We believe that hyperkalemia in our patient occurred as a result of octreotide-induced insulin suppression and resultant impaired cellular potassium uptake. Based on our experience, one should be aware of this potential life-threatening side-effect of octreotide therapy.

FR-PO033

Hypercalcemia and Acute Kidney Injury due to Immune Reconstitution Syndrome in an HIV Patient on HAART and MAC Therapy
Anand Achangti, Omar M. Shahateet, Karl Berthold Pemmbur, Nithin Karakala, Juan Carlos Q. Velez.
Nephrology, Med Uni of South Carolina, Charleston, SC.

Introduction: Hypercalcemia can occur in HIV-infected patients due to several conditions such as granulomatous diseases, lymphomas, and solid tumors. HIV patients are also susceptible to causes found in the general population, such as primary hyperparathyroidism, medications, and vitamin D supplementation.

Case Description: A 48 year old male with history of HIV and disseminated Mycobacterium avium complex (MAC) was sent to the hospital after being found to have a serum calcium of 15.5 mg/dL and serum creatinine of 5.8 mg/dL on routine labs. His only complaint was weakness. Five months prior to presentation, patient had an adjustment of his highly active antiretroviral therapy (HAART) with a viral load of 76,000 copies/mL, CD4 count of 36/CLMM, serum calcium of 9.6 mL/dL, and serum creatinine of 2.6 mg/ dL at that time. Previous renal dysfunction was caused by interstitial nephritis diagnosed 6 weeks prior. Patient reported increased compliance to his new regimen for several weeks prior to presentation, reflected by an increase in CD4 count of 138 (CLMM earlier and undetectable viral load upon presentation. Workup for hypercalcemia included: low PTH of 5.8 pg/mL, low PTH-rp of 0.7 pmol/L, and a high 1,25 Vitamin D of > 200 pg/mL. Serum and urine protein electrophoresis showed a restricted kappa lambda ratio and bone marrow biopsy were normal. Imaging was negative for lymphoma. The patient was managed with volume repletion, probenecid 600 mg/d, and IV pamidronate 60 mg with gradual improvement of his calcium to 8.8 mg/dL and creatinine to 2.8 mg/dL in 9 days. Steroids were tapered and the patient remained stable 6 months later.

Discussion: Our patient developed acute kidney injury secondary to severe hypercalcemia, likely due to renal vasoconstriction and volume depletion superimposed over interstitial nephritis. The etiology of hypercalcemia was likely immune reconstitution syndrome caused by the restoration of HAART. In patients with HIV and AIDS with history of granulomatous disease, it is important to monitor for hypercalcemia when initiating HAART therapy or adjusting therapy.

FR-PO034

Hypocalcemia in Severe Malnourishment, and Acute Pancreatitis Veils Vitamin D Intoxication
Nephrology, Stony Brook Univ Medical Center, Stony Brook, NY.

Introduction: Although vitamin D has a wide therapeutic index, a routine use of high doses of vitamin D intake can cause toxicity. We report a case with severe hypocalcemia likely due to malnourishment and pancreatitis related to alcoholism followed by hypercalcemia from vitamin D toxicity.

Case Description: A 43 year-old woman with alcoholism was admitted with rhabdomyolysis and alcohol induced acute pancreatitis. On initial examination she was in moderate distress with altered mental status and diffuse abdominal pain. Her blood pressure was 102/67 mmHg, heart rate 136/min and temperature 38.3°C. Her lab data revealed WBC 54.71 mm3, Hb 16.9 g/dL, PLTs 186 mm3, serum Na 129 mEq/L, K 3.5 mEq/L, bicarbonate 19 mEq/L, BUN 23.3 mg/dL, creatinine 1.3 mg/dL, sodium 133 mEq/L, potassium 1.7 mg/dL, CPK 1089 IU/L, albumin 2.9 g/dL. She received intravenous Ca, Mg, K and phosphorus in addition to oral supplements. On day 4, her serum Ca was 8.7 mg/dL, albumin 2.5 g/dL, phosphorus 4.0 mg/dL and K 3.9 mmol/L without any supplement. Her serum Mg remained low and continued to receive oral and intravenous Mg supplements. Serum Ca was not checked between days 9-14 of her hospitalization. On day 15, her serum Ca was 12.8 mg/dL, ionized Ca 6.4 mg/dL, vitamin D 25OH 370 ng/ml, vitamin D 1-25 OH 149 pg/ml and intact PTH 11.8 pg/ml. Her TSH, T4, ACE and vitamin A levels were normal. Her 24 hours urine revealed Na 140 mEq/L, K 70 mEq/L, creatinine 1110 mg, UN 4.1 g, Ca 462 mg, Mg 403 mg , phosphorus 931 mg. She admitted taking vitamin D 50,000 units daily for many months for her psoriasis on her own. Her hypocalcemia was treated and her serum calcium stabilized over one week to 9.4 mg/dL while her vitamin D 25OH and vitamin D 1-25 OH remained elevated over the next 6 weeks.

Discussion: Her unusual presentation of hypocalcemia masked vitamin D toxicity till she resumed regular nutrition. Her hypocalcemia was likely related to malnourishment due to chronic alcoholism and possible calcium deposition due to acute pancreatitis. With proper nutrition during her hospitalization and improvement of her underlying condition led to hypocalcemia due to vitamin D toxicity.

FR-PO035

Re-Defining the Speed Limit in Osmotic Demyelination Syndrome? Malrukh Rizvi, Rebecca D. Monk.
Nephrology, Univ of Rochester Medical Center, Rochester, NY.

Introduction: Osmotic demyelination syndrome (ODS) is a severe, debilitating, possibly fatal neuroanatomical condition that results from rapid correction of severe chronic hyponatremia. Imaging reveals central pontine myelinolysis (CPM). Potential added risk factors for ODS include Sodium (Na) < 120 mM/L, alcoholism, malnutrition and liver transplant. Current recommendations advise raising serum sodium by less than 9 mM/L in 24 hours. We present a case of ODS in a patient presenting with severe hyponatremia corrected at a maximum rate of 8mEq/dL in 24 hrs.

Case Description: A 37 year old man with a history of alcohol abuse was sent in to the hospital by police after a car accident for jaundice. He endorsed two weeks of worsening jaundice and right upper quadrant (RUQ) pain. Admission vital signs were stable. Physical exam revealed marked jaundice, abdominal distention and RUQ pain. Work up revealed severe alcoholic hepatitis with cirrhosis and metabolic derangements including a Na of 105 mM/L, chloride of 69 mM/L, Na urea nitrogen of 45 mg/dL, creatinine of 2.13 mg/ dL with unknown baseline. 3% saline with dDAVP was initiated for cautious correction of severe hyponatremia. Imaging reveals central pontine myelinolysis (CPM). Potential added risk factors for ODS include Sodium (Na) < 120 mM/L, alcoholism, malnutrition and liver transplant. Current recommendations advise raising serum sodium by less than 9 mM/L in 24 hours. We present a case of ODS in a patient presenting with severe hyponatremia corrected at a maximum rate of 8mEq/dL in 24 hrs.

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Discussion: Her unusual presentation of hypocalcemia masked vitamin D toxicity till she resumed regular nutrition. Her hypocalcemia was likely related to malnourishment due to chronic alcoholism and possible calcium deposition due to acute pancreatitis. With proper nutrition during her hospitalization and improvement of her underlying condition led to hypocalcemia due to vitamin D toxicity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
364A
FR-P0036  
A Case of Axenfield-Rieger Syndrome Presenting with Elevated Serum Bicarbonate  
Rudrick V. Ledesma, Maureen E. Brogan, Venkata Buddharaju, Rahul N. Pawar, Rajat Lamba.  Westminster Medical Center, NY.

Introduction: Elevated serum bicarbonate can often be misdiagnosed as metabolic alkalosis leading to improper management. Chronic respiratory acidosis caused by central hypoventilation can lead to elevated bicarbonate secondary to renal compensation. We present a case with alkalosis caused by cerebro-pontine lesion in a patient with Axenfield-Reiger syndrome (ARS).

Case Description: A 25 yo man with PMH of glaucoma, developmental delay, schizoid affective disorder sent to the ED for respiratory failure. He was seen earlier in renal clinic for treatment of elevated serum bicarbonate. He was complaining of fatigue and insomnia. Arterial blood gas was done and showed a pH of 7.30, pCO2 of 79, pO2 of 63 and HCO3 of 38.9. He was eventually admitted for further management. While in the hospital, he continuously needed bilevel positive airway pressure. Chest ultrasound showed little to no movement of his diaphragm. EMG was negative. PFT was suboptimal as he wasn’t able to follow the instructions. MRI brain showed a mass on his right cerebro-pontine angle. He was also diagnosed with ARS during his hospital stay. The mass was resected and progressive improvement was observed in his respiratory status. He was eventually weaned off bilevel positive airway pressure and was discharged home without any need for respiratory support.

Discussion: Elevated serum bicarbonate can often pose a diagnostic challenge. Evaluation should start with an ABG which would differentiate a primary metabolic alkalosis from a renal compensation of respiratory acidosis. Differential diagnoses for respiratory acidosis include central hypoventilation, primary lung pathology, neuromuscular disease and airway pathology. Central hypoventilation could be secondary to lesions in the respiratory center. ARS presents as a spectrum of developmental disorders resulting from abnormal migration and differentiation of neural crest cells with both ocular and systemic manifestations. The reason in the brain that may be affected are forebrain and pitorinary gland. Our case is interesting as he had ARS with epidermoid cyst which we believe has led to central hypoventilation and elevated bicarbonate as compensatory mechanism.

FR-P0037  
Signet-Ring Cell Carcinoma Presenting as Frequency of Urination  
Haya Waseem Siddiqui, Daniel E. Carl, Todd W. Gehr. Nephrology, Virginia Commonwealth Univ, Richmond, VA.

Introduction: Urinary tract obstruction may occur at any site in the urinary tract and is important to recognize early since it is readily reversible if quickly corrected.

Case Description: 45 year old male with obesity, history of gastric bypass surgery, hypertension and obstructive sleep apnea who presented to our institution for evaluation of frequency of urination. He developed progressively worsening frequency of urination, occurring every hour during the day and night for 3 months prior to presentation. During this time, his serum creatinine was 1.6 mg/dL. He had been seen multiple times by an Urologist and Primary Care Providers outside our institution, and was diagnosed with prostatitis despite negative urine cultures and no pyuria. During the work up, an outpatient CT scan revealed mild bilateral hydronephrosis and mild left hydroureter. Furthermore, an office cystoscopy revealed diffuse inflammatory cystitis of the bladder and no definitive bladder wall thickening. Over the ensuing 3-4 weeks, he developed acute kidney injury with a serum Cr that peaked at 6mg/dL. This prompted an admission to an outside facility.

He was again found to have mild bilateral hydrourerter, however, ureteral stents were attempted, but unsuccessful. A repeat cystoscopy revealed severely inflamed bladder tissue but no visible abnormality. Urinary bladder biopsy was done. Patient was transferred to VCU for placement of percutaneous bilateral nephrotoomy tubes by interventional. He had successful stent placement by IR followed by post obstructive diuresis treated with intravenous fluid hydration in the form of saline. His AKI improved as evidenced by peripheral edema evident on follow-up imaging study. His serum Cr improved to 1.3 mg/dL and repeat CT scan with intravenous contrast was obtained for staging which showed circumferential bladder wall thickening with asymmetric soft tissue prominence along the right anterior dome most consistent with bladder neoplasm. Outside pathology report was consistent with signet cell carcinoma of bladder.

Discussion: Signet-ring cell carcinoma a rare bladder tumor can result in acute kidney injury secondary to bilateral ureteral obstruction.

FR-P0038  
A Case of Tenofovir-Induced Nephrotoxicity  

Introduction: Tenofovir (TFV) is a nucleotide reverse-transcriptase inhibitor used for treatment of HIV and hepatitis B. Most studies suggest that TFV has only a modest effect on estimated glomerular filtration and severe nephrotoxicity is uncommon. We describe a case of tenofovir-induced nephrotoxicity.

Case Description: A 55 year old woman with HIV on TFV for several years, presented with vomiting and abdominal pain for 4 days. Physical exam was unremarkable. Laboratory data showed BUN 65 mg/dL, creatinine 9.07 mg/dL (baseline: normal), bicarbonate 12 mmol/L, glucose 137 mg/dL, HIV RNA: 21 copies/ml and CD4: 292 cells/ml, glycosuria and proteinuria (157mg/24 hours). Serological tests for autoimmune and infectious diseases were negative. Kidney biopsy showed proximal tubule (PT) injury and eosinophilic oval cytoplasmic inclusions on trichrome stain (fig a) with no definite glomerular or mesangial abnormalities. Electron microscopy (EM) showed PT cells with cytoplasmic swelling, loss of membrane integrity, accumulation of enlarged dysorphic mitochondria with intra-cristal widening and abnormal matrix appearance and loss of cristae (fig b) consistent with mitochondrial injury (MI) seen in TFV nephrotoxicity. Despite discontinuing TFV, she remained dialysis dependent.

Discussion: Currently available data supports renal safety of TFV in HIV patients. Severe renal dysfunction has only been reported sporadically. Although nucleoside reverse transcriptase inhibitors (adefovir) are known to impart mitochondrial reprogramming by interfering with DNA polymerase-γ, evidence linking TFV specifically to MI is limited. Our case implies that TFV can cause significant renal failure and MI. Monitoring renal function and urinalysis during TFV treatment is key for early detection of nephrotoxicity.

FR-P0039  
A Case of Severe Hypomagnesaemia in a Patient Treated with Trastuzumab  
Saifullah Kazi, Ghulam Akbar, Paul Robbins. Nephrology, Lankenau Medical Center, Wynnewood, PA.

Introduction: A case of invasive ductal carcinoma that was treated with chemotherapy including Trastuzumab found to have severe hypomagnesaemia requiring very aggressive repletion strategies.

Case Description: A 36 y/o non-alcoholic female with past medical history of hypertension well controlled on diet therapy, was diagnosed with invasive ductal carcinoma of the breast requiring initiation of chemotherapy with docetaxel and carboplatin with Trastuzumab. She received a total of 6 cycles of chemotherapy every three weeks and Trastuzumab was given weekly. After completion of chemotherapy, the dose of Trastuzumab was increased to 8mg per infusion every three weeks. Her serum magnesium level which was 2.1mg/dl in the beginning of chemotherapy was noted to be low at 0.5mg/dl when she presented with generalized weakness to the hospital six months into the treatment. At this time, she had completed her chemotherapy 2 months ago and now on Trastuzumab only. She was on lasix and proton pump inhibitors at that time, both of which were stopped immediately. However her serum magnesium remained low between 0.6-1.0 mg/dl persistently for next few months requiring intravenous infusions every week. On repeated testing, fractional excretion of magnesium remained high indicating renal magnesium wasting. Although patient was hypokalemic initially, it corrected immediately after stopping loop diuretics and remained normal following treatment using tubulopathies such as Gitelman or Bartter syndrome. She remained hypomagnesaemic despite completing one year course with Trastuzumab. She is receiving once a week intravenous infusions of magnesium 500mg with no further magnesium wasting. Although her serum magnesium remained low between 0.6-1.0 mg/dl persistently for next few months requiring intravenous infusions every week. On repeated testing, fractional excretion of magnesium remained high indicating renal magnesium wasting.

Discussion: Trastuzumab is a human epidermal growth factor (HER-2) inhibitor which belongs to the family of epidermal growth factor receptor (EGFR). EGFR is involved in increasing the magnesium absorption in the distal nephron by increasing the transcription of the genes regulating TRPM6 channel. Hypomagnesaemia has been well reported in other EGFR inhibitor with Cetuximab used in colon cancer and Erlotinib used in lung cancer, but not reported in patients taking Trastuzumab, especially after escalating to higher doses.

FR-P040  
Capecitabine Induced Acquired Bartter’s-Like Syndrome  
Eric A. Kirk, Jennifer Thompson, Juan Carlos Q. Velez, Nithin Karakala. Nephrology, MUSC, Charleston, SC.

Introduction: Many forms of chemotherapy carry a risk of electrolyte abnormalities. Capecitabine is an antimetabolite of the fluoropyrimidine carbamate class of chemotherapeutic agents. Phase I and II trials have reported hypomagnesaemia, hypokalaemia with hyperkaliemia as isolated electrolyte imbalances, and there are case reports of isolated hypomagnesaemia and reports of a relatively large number of patients with hypokalaemia. A Fanconi like pattern of electrolyte disorders has also been reported with capecitabine.

Case Description: A 68 year old female with neuroendocrine pancreatic cancer treated with capcitabine and temozolomide developed back spasms and was found to have severe hypokalaemia (2.4mmol/L), hypomagnesaemia (0.7mg/dL) hypocalcaemia (4.6mg/dL) and metabolic alkalosis (bicarbonate 30mmol/L) in the absence of vomiting or diarrhea 5 weeks after starting a 2 week course of capecitabine (1400mg/m2 divided twice daily). She had evidence of renal salt wasting with sodium 256.5mEq, potassium 51.8 mEq and calcium 500ng in a 24 hour urine collection. No evidence of hypoparathyroidism, with intact PTH 67.3pg/mL, 1,25 hydroxy vitamin D was 33pg/mL. Further capecitabine therapy was withheld. 24 hr urine collection was completed 1 week later with decreased renal loss of sodium, potassium and calcium and normalization of electrolytes.

Discussion: We present a case of life threatening hypokalaemia caused secondary to capcitabine. As the patient had metabolic alkalosis it was unlikely that the patient had Fanconi’s as described in some case reports. Our case is unique as this patient developed a combination of hypokalaemia, hypocalcaemia, hypomagnesaemia and metabolic alkalosis.
caused by capcitabine. The patient exhibited Barter’s like physiology with increased renal loss of calcium, magnesium, and sodium and evidence of metabolic alkalosis. Unlike the proximal tubulopathy associated with capcitabine, the pathophysiology of acquired Barter’s with is unknown but could be caused by direct inhibition of apical NaKCC or ROMK, or activation of the calcium sensing receptor on the basolateral surface in the thick ascending loop of Henle.

FR-PO041
Uncommon Case of Severe Hypercalcemia After Renal Transplantation Rapedrat Lekkham, Gitana Bradauskaite. Nephrology, Einstein Medical Center, Philadelphia, PA.

Introduction: Following renal transplantation, hypercalcemia is frequently caused by persistent hyperparathyroidism, but other causes should be kept in mind. We report a case of hypercalcemia after renal transplant from unregulated extrarenal 1,25-dihydroxyvitamin D synthesis from disseminated tuberculosis and cryptoccocus.

Case Description: The patient was a 59-year-old male with unknown etiology of ESRD who received a living unrelated kidney transplant. He was stable on low dose immunosuppressive agents for history of BK virus infection. At 10 months post-transplant, the patient diagnosed with disseminated cryptoccocosis with granulomatous mesentric mass and positive cryptoccoccal antigen. High dose oral fluconazole was started. 10 days later, he readmitted with severe hyperonatremia, severe hypercalcemia (corrected serum Ca peak at 14.72 mg/dl) and acute renal failure (serum Cr peak at 5.8 mg/dl from baseline 1.6 mg/dl). The iPTH level was suppressed to 2.8 pg/ml. The serum 1,25(OH)D level was elevated and levels of 25(OH)D fell. Serum phosphate rose and ALP levels were elevated. PTH-related peptide was negative. Serum immunoelectrophoresis with immunofixation showed elevated kappa monoclonal gammopathy with normal ratio of free kappa and lambda light chain. Kidney biopsy revealed acute tubular necrosis, no evidence of granulomatous or lymphoproliferative disease. CT chest revealed right upper lobe mass with calcified granuloma at lung base. Culture from lung biopsy showed strongly positive for Mycobacterium Tuberculosis. Anti-tuberculosis drugs were started and mycobacterium motefil was held. Elevated calcium levels were unresponsive to calcitonin, fluid neither helped. After his aperiodic AFB became negative, the oral prednisone was increased to 20mg/day. Hypercalcemia and hyperphosphatemia normalized upon one month follow up and remained stable until finished 6 months course of anti-tuberculosis drugs and the creatinine returned to baseline.

Discussion: Unlike persistent hyperparathyroidism, underlying diseases of PTH independent hypercalcemia after renal transplantation like a granulomatous disease can lead to significant morbidity and mortality. Early recognition and prompt treatment is necessary.

FR-PO042
Treatment of Malignancy-Associated Hypercalcemia with Low Calcium Hemodialysis Yields Several Benefits for Cancer Patient Rozina B. Ali, Akshitha Rao, Suzanne Boyle, Jesse M. Goldman. Div of Nephrology and Hypertension, Drexel Univ College of Medicine, Philadelphia, PA.

Introduction: Hypercalcemia of malignancy can be fatal. In literature, primary treatment remains forced saline diuresis while dialysis is seldom considered. We present a case of severe, refractory hypercalcemia associated with diffuse large B-cell lymphoma that was treated with low calcium (Ca) hemodialysis (HD).

Case Description: A 56 year-old male presented with 3 weeks of weakness and constipation. He noted a serum creatinine (Cr) of 1.45mg/dL, Ca of 2.1mg/dL, and ionized Ca of 2.3. Urine microscopy had granular casts. Cause of acute kidney injury (AKI) was attributed to hypovolemia, acute tubular necrosis and Ca-induced vasoconstriction. He had a PTH of 7pg/ml, PTH-ep of 2.1pmol/L, vitamin D 25,OH of 25.9ng/mL and 1,25(OH)2 of 18pg/mL. Non-contrast CT chest demonstrated diffuse lichenoid nephropathy with LN biopsy showing diffuse large B-cell lymphoma. On day 1, patient received several liters of normal saline, calcitonin, and pamidronate. Despite maximal medical therapy, he had delirium, persistent AKI with Cr peak to 2.6 mg/dL and elevated Ca at 15mg/dL. On days 3, 4, and 5, he received consecutive 4-hour sessions of intermittent HD with low Ca (2mg/L) dialysate using a 0180 high flux dialyzer with blood flow of 400mL/hr. On day 6, Ca decreased to 10.4 mg/dL and mental status improved. He received induction chemotherapy on day 13 with cyclophosphamide, doxorubicin, rituximab, and vincristine. At discharge, Cr was 1.66mg/dL and Ca level was 12mg/dL.

Discussion: Serum/urine Cr PCR: consecutively negative. Immunohistochemistry on tissue sections: positive for BK (SV40 T antigen which cross reacts with JC). In-situ hybridization for JC and BK viruses: positive in medullary tubular epithelial cell nuclei. Reduction in immunosuppression resulted in renal improvement.

FR-PO043
Case Description: 41 year old female with history of thyroidectomy for cancer, parathyroidectomy, hypothyroidism, and gastro-esophageal reflux disease (GERD) referred to our nephrology clinic for severe symptomatic hypokalemia for a decade. She has poor appetite and weighs around 330 pounds but denies vomiting or diarrhea. Home BP’s is low 90’s /60’s mmHg. She denies licorice, diuretic or excessive alcohol use. She was adopted as a child with unknown family history. She was admitted for further work up. Her serum potassium (K) was 3.5 and Mg was 1.2. 24 hour urine collection was done and levels of sodium, K, Mg and aldosterone were found to be 48 mmol, 21 mmol, 49.6 mmol, and 7.5 mg/di respectively. Fractional excretion of Mg using the formula FEMg = 100 * (UrineMg / PlasmaMg) / (0.7 * PlasmaMg + UrineCr) was 121% confirming renal Mg wasting. Her serum bicarbonate of 22mmol/L and absence of salt wasting ruled out Gitelman syndrome. Review of medications revealed that she was chronically on esomeprazole 40 mg daily for presumed GERD. Esomeprazole was stopped, and with continued magnesium supplementation her repeat K and Mg were within normal range as outpatient. Repeat 24 hour urinary Mg was pending at the time of abstract submission.

Discussion: The kidneys are highly efficient organs in Mg conservation with most of filtered Mg being reabsorbed in the thick ascending limb of the loop of Henle. It is speculated that patients who develop hypomagnesemia on long-term PPI treatment may harbor one or more heterozygous mutation(s) of the gene TMPRE6, FXVYD2, KCN310, or KCN1A1 involved in the modulation of Mg reabsorption in the distal nephron, leading to diminished efficiency of the encoded protein(s). This situation could involve a continuous low-grade Mg leak and facilitate the development of Mg depletion when combined with factors that decreases intestinal magnesium absorption.
FR-PO045
Successful Treatment of Anti-Angiotensin II Type 1 Receptor Antibodies Associated with Refractory Antibody-Mediated Rejection and AcuteCellular Rejection in Kidney Transplantation: A Case Report
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Introduction: Angiotensin II type 1 receptor (AT1R) antibody has been proved that it can be detrimental to kidney allograft. Similar to HLA-antibody, patients who have AT1R antibody are at risk for rejection and poor allograft outcome. There is no standard treatment in this situation but the aim is to remove pathologic antibodies and suppress antibodies production. Outcomes after treatment are unsatisfactory and not well established. Herein we present a successful treatment kidney transplant patient who experienced AT1R antibody mediated rejection.

Case Description: A 50-year-old male with hypertension and ESRD underwent a disease donor kidney transplantation using a graft from acute kidney injury donor with peak serum creatinine of 1.24 mg/dl. No intraoperative complication occurred, urine flow rate of 300 ml/hr was observed immediate postoperative but abruptly decreased to 20 ml/hr at 8 hours posttransplantation. Acute rejection was suspected, thus allograft biopsy was done. The histopathological findings were compatible with acute cellular rejection combined with antibody-mediated rejection (ABMR). AT1-R antibody was detected at level of 15.0 ml/ml. Anti-rejection therapies were offered with steroid, IVIG, plasmapheresis, anti-thymocyte globulin and rituximab. At 8 weeks posttransplantation, rejection was well controlled with stable serum creatinine of 1.5 mg/dl.

Discussion: Although AT1R antibody associated rejection has rarely been reported, the outcomes after rejection are unsatisfactory. Early detecting rejection and rapid antibody removal seem to be the most effective treatment that prolong allograft function in present time. There are limited and controversial data about long term graft survival by treating patient with angiotensin receptor blocker.

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FR-PO046
Hemodiafiltration for Hepatic Encephalopathy Induced by Budd-Chiari Syndrome in a Patient with End-Stage Kidney Disease
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Introduction: Budd-Chiari Syndrome (BCS) is defined as portal hypertension caused by obstruction of the inferior vena cava at the liver. Severe BCS induces hepatic encephalopathy, and has been known to be exacerbated by HD due to removal of protein-bound tryptophan is removed by HD. Therefore, one of the reasons why HDF ameliorates hepatic encephalopathy is increased removal of protein-bound AAAs, leading to increased BCAA/AAA ratio.

FR-PO047
De Novo Lupus Nephritis in a Stable Kidney Transplant Recipient
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Introduction: De novo Lupus Nephritis (LN) is an exceedingly rare complication in kidney transplant recipients. We present a case of histoplasmosis with clinical manifestations of SEL. The scarcity of autoimmune disease in this population is not fully understood, but has been attributed to the maintenance immunosuppression used to prevent allogreception and rejection.

Case Description: Herein we present de novo LN in a 55-year-old woman with post streptococcus glomerulonephritis and HTN; 28 years status-post living-related kidney transplant. The patient had no personal or family history of autoimmune disease at time of transplant. Three years ago, she began complaining of episodic carpo-pedal spasm and scoliosis; laboratory abnormalities included mildly low albumin and stable Ig proteinemia. Medications were stable and no potentially provocative antigens, vaccines or transfusions, were given during this period. Immunosuppression included cyclosporine and low dose prednisone. Seven months ago, the patient developed malar rash and hemo-proteinuria prompting immunological studies and kidney allograft biopsy. Anti-nuclear, double stranded DNA, Smith and histone antibodies were all strongly positive with low serum complement levels. Serum creatinine increased by 0.5 mg/dl; from baseline; urine protein to creatinine ratio revealed nephrotic range proteinuria peaking at 9.6grams. Immunofluorescence revealed granular “full house” pattern, C4d negative; Electron microscopy revealed intranembranous deposits. The patient was treated with high dose prednisone, continued cyclosporine and addition of mycophenolate mofetil.

Discussion: Although rare, de novo auto-immune disease should be considered for transplant patients despite maintenance immunosuppression.

FR-PO048
Atypical Hemolytic Uremic Syndrome Allograft Outcome in the Post Eculizumab Era
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Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is an exceedingly rare etiology of renal failure. Two forms of HUS are often linked to underlying viral illness or particular classes of immunosuppression in transplant recipients. Exceedingly rare are genetic etiologies of aHUS for which transplantation is undesirable due to very high recurrence rates of disease.

Case Description: Herein we describe a case of misdiagnosis; 78 year old man initially diagnosed with rapidly progressive glomerulonephritis (RPGN) by kidney biopsy developed anuria necessitating hemodialysis. The patient had no family history of kidney disease. Immunological work-up was negative for Anti-nuclear or cytoplasmic antibodies; complement deemed within normal limits. Pt received a living-unrelated kidney transplant from a 40 year old healthy donor. Standard induction solumedrol and thymoglobulin. Initiation of maintenance calcineurin inhibitor (CNI), steroid, antimalabite. Favorable outcomes were observed, creatinine 1.77 mg/dl and urine output upon discharge. One week post-transplant, patient was observed to have increased creatinine, peak 4mg/dl, not amenable to discontinuation of CNI or typical offending agents; prompting renal biopsy. Histologically Thrombotic Microangiopathy (TMA), C4d (-) observed and deemed comparable to native biopsy slides. Laboratory studies confirmed aHUS (-) ADAMST13; low lactate dehydrogenase, elevated haptoglobin; peripheral smear hightocytes. Negative viral studies including Shiga toxin. Pt was treated with high dose solumedrol, plasma exchange and eculizumab; resolution of kidney function, creatinine 1.88 mg/dl, month post-transplant period. Interim six month follow-up, with twice monthly eculizumab reveal no recurrent TMA on biopsy; despite bouts of acute kidney injury related to CNI levels or viral fluctuations.

Discussion: aHUS, as presented above, may be misdiagnosed and therefore present at the time of post-transplant recurrence. With the advent of treatment, alternative pathway complement inhibitor eculizumab; a high degree of suspicion must be maintained when managing post-transplant dysfunction.

FR-PO049
An Unusual Manifestation of Disseminated Histoplasmosis in a Renal Transplant Patient
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Introduction: Disseminated histoplasmosis is rare but can develop in immunocompromised patients. We present a case of disseminated histoplasmosis in a renal transplant patient with unknown origin with oral and gastrointestinal (GI) manifestations.

Case Description: The patient is a 42 year-old man with ESRD secondary to unclear etiology, who had a living related renal transplant from his cousin 4 years ago in Mexico. He was born in El Salvador, moved to California at age 7, and had traveled to Mexico and Cuba (last travel 1 year ago). His post-transplant course was complicated by antibody mediated rejection and borderline acute cell mediated rejection 2 years ago, for which he was successfully treated with IVIG, plasma exchange, and rituximab. His medication included tacrolimus, MMF, and prednisone. He presented with 2-3 weeks of fever and chronic abdominal pain after unsuccessful treatment with ciprofloxacin. He had a WBC of 38.7
It has been postulated that complement activation might have a role, but this patient had normal complement levels.

Hyponatremia, but low Na histoplasma antigen was positive. He improved soon after oral itraconazole was started.

Hemodialysis (HD) using a standard Na\textsuperscript{+} mEq/L to 131 mEq/L on day 2, and reached 137 mEq/L by day 3. The patient was then corrected of Na\textsuperscript{+} rise was > 0.5 mEq/hr or 6 mEq in 24 hrs. It was to be reduced if the correction


Introduction: Anuric acute kidney injury (AKI) with hyponatremia presents a therapeutic challenge. Hemodialysis (HD) using a standard Na\textsuperscript{+} bath can cause excessive correction of Na\textsuperscript{+}, and a risk of osmotic demyelination. We report the controlled correction of hyponatremia via continuous venous venous hemodialysis (CVVHD) against a standard bath using an infusion of dextrose 5% in water (DSW) to blunt the Na\textsuperscript{+} shift.

An 83 year old male with respiratory failure developed altered mentation and oliguria. Labs demonstrated severe hyponatremia with Na\textsuperscript{+} 119 mEq/L, K\textsuperscript{+} 6.8 mEq/L, and AKI with BUN 46 mg/dL, creatinine 3.08 mg/dL. Emergent renal replacement therapy (RRT) was required, but HD would have risked overly rapid correction of Na\textsuperscript{+}. Instead, we started CVVHD with a Na\textsuperscript{+} 140 mEq/L bath. The dialysate rate was 2 L/hr and blood flow rate was 200 cc/min. Net target was zero, with all drips included in the calculation. We simultaneously infused DSW at 100 cc/hour. [Na\textsuperscript{+}] was monitored every 4 hrs. The DSW flow was increased if the [Na\textsuperscript{+}] rise was > 0.5 mEq/hr or 6 mEq in 24 hrs. It was to be reduced if the correction was suboptimal. The patient’s [Na\textsuperscript{+}] rose from 118 mEq/L to 125 mEq/L on day 1, 125 mEq/L to 131 mEq/L on day 2, and reached 137 mEq/L by day 3. The patient was then safely converted to HD.

Discussion: CVVHD is a safer option for RRT than HD in the setting of severe hyponatremia, but low Na\textsuperscript{+} CVVHD is not available. Some have suggested adjusting the dialysate [Na\textsuperscript{+}] using sterile water to achieve the desired [Na\textsuperscript{+}] prior to treatment. This may produce a predictable response in Na\textsuperscript{+}, but there are concerns for infection and/or dosing error which makes this strategy problematic. Reducing dialysate or effluent flow, though effective, often results in unacceptable clearances. We demonstrated, that CVVHD with a standard Na\textsuperscript{+} bath, a separate D5W drip, and strict monitoring of [Na\textsuperscript{+}], can yield a predictable response in [Na\textsuperscript{+}], obviating the cumbersome and risky point of care manipulations of the dialysate formula.

Case Report: Renal Squamous Cell Carcinoma of a Native Kidney After Renal Transplant Adam Daniel Jakes,1 Poornam Jani,1 Mini Menon,1 Kate Adams,1 Matthew Edley,1 Stewart Fleming,1 Sunil Bhandari,1 1 Dept of Renal Medicine, Hammersmith Hospital, London, United Kingdom; 2 Hull York Medical School, Hull, United Kingdom; 3 Dept of Renal Medicine, Hull Royal Infirmary, Hull, United Kingdom; 4 Dept of Infection & Tropical Medicine, Castle Hill Hospital, Hull, United Kingdom; 5 St. James’s Univ Hospital, Leeds, United Kingdom; 6 Cellular and Molecular Pathology, Ninewells Hospital, Dundee, United Kingdom.

Introduction: Renal squamous cell carcinoma is a rare primary tumour of the kidney, which rapidly invades local structures and has a poor prognosis. Presentation is usually non-specific and is associated with renal stone disease and chronic infection. We present a case of squamous cell carcinoma of a native kidney in a renal transplant recipient, which has not previously been described in the literature.

Case Description: A 46-year-old white male with previous renal stones and recurrent urinary infections underwent a right nephrectomy and subsequent renal transplantation due to failure of the remaining kidney. Five years post-transplant, an abdominal ultrasound scan was performed due to recurrent urinary infections and ongoing pyuria. This was reported as normal, but he later developed a discharging sinus in his left flank. A CT scan revealed a right perinephric abscess with an associated cystic lesion. A left nephrectomy was performed and histological examination suggested an invasive squamous cell carcinoma of the renal pelvis. The patient later required major surgery for chronic infection, and further imaging revealed metastatic disease, resulting in the decision to treat him symptomatically.

Discussion: Renal transplant recipients are three-four times more likely to develop a malignancy than the general population. The patient also had renal stone disease and recurrent urinary infections; further increasing his risk of developing this condition. Abdominal ultrasound was suboptimal and only a later CT scan revealed the underlying malignancy. Given the non-specific nature of the symptoms and the poor prognosis, healthcare professionals should have a lower threshold for diagnostic imaging in these patients. This should be expedited if there is a persistent abnormality on urinalysis.

A Case of Hydronephrosis due to Adenovirus Hemorrhagic Cystitis following Peripheral Blood Stem Cell Transplantation for Malignant Lymphoma Rio Noto,1 Hideki Yokoi,2 Akhiro Yoshimoto,3 Motoyo Yanagita.2 1 Clinical Nephrology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan; 2 Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.

Introduction: In patients receiving stem cell transplantation (SCT), adenoviral infection is associated with mortality and morbidity. Cystitis is the most common presentation of adenoviral urinar tract infection, which unusually causes inflammation of the upper urinary tract. We report a rare case of adenoviral urethritis accompanied by hydronephrosis due to autologous peripheral blood SCT.

Case Description: A 50-year-old female, who had undergone SCT 4 months ago for the treatment of nasal-type extranodal NK/T cell lymphoma and received tacrolimus as prophylaxis for graft-versus-host disease, developed fever, right back pain and dysuria. Computed tomography (CT) showed perirenal and periureteral fat heterogeneity and dilatation of the right ureter. He was diagnosed as pyelonephritis caused by ureteral stones (already dropped), but antibiotics did not relieve symptoms. In addition, he exhibited a left solitaiary pulmonary mass, which was diagnosed as Mycobacterium avium complex (MAC) infection by lung needle biopsy. Cystoscopy and retrograde pyelography revealed hemorrhagic cystitis and right ureteral stenosis, where a catheter was placed. Viral PCR test was performed for differentiating hemorrhagic cystitis, and adenovirus was detected both in urine and in blood. Symptoms and abnormal findings on CT were improved by the placement of a catheter and the decrease of tacrolimus dosage.

Discussion: Differential diagnoses were urethral carcinoma, recurrence of malignant lymphoma, retroperitoneal fibrosis and disseminated MAC disease. Urine cytology result was negative for malignant. Gallium scintigraphy excluded recurrence of malignant lymphoma. Fat heterogeneity disappeared after catheter placement, suggesting that malignant lymphoma and retroperitoneal fibrosis were unlikely. MAC was not detected from blood and urine cultures. Clinical course and laboratory data indicated that inflammation of adenoviral hemorrhagic cystitis spread to the right ureter, leading to ureteral stenosis and hydronephrosis in an immunocompromised patient after SCT.

Unusual Cause of Thrombocytopenia in a Dialysis Patient Rahul N. Pawar, Savneek S. Chugh, Amy R. Patel, Rudrick V. Ledesma, Rajat Lamba. Nephrology, Westchester Medical Center, NY.

Introduction: Hemodialysis (HD) is an invasive treatment with many adverse effects, thrombocytopenia being one of them. Most of the cases of thrombocytopenia on dialysis are related to the use of heparin creating auto-antibodies leading to heparin induced thrombocytopenia (HIT). Here we report a case of severe thrombocytopenia, which was initially thought to be due to HIT, but later revealed to be secondary to a specific dialyzer membrane.

An 81 year old female started on HD 2 months prior for progressive CKD was sent to the HD unit for excessive bleeding. She was on a new platelet (PLT) count of 27 K/uL. When she was first started on inpatient HD, she was found to be thrombocytopenic and heparin autoantibodies were weakly positive so she was started on argatroban. At the 1st outpatient HD unit, her PLT count increased to 200 K/uL. After transferring to a 2nd outpatient HD center, her PLT count, once again, dropped to 27 K/uL, along with recurrent bleeding at the catheter site. This prompted investigation of heparin exposure as a cause, but it was revealed that the patient never received heparin during any of her treatments. Despite being restarted on argatroban, her PLT count remained in the 20 K/uL range. The argatroban release assay was negative. It was noted that the hospital and the 2nd outpatient unit both used a F160NR dialyzer, different from the dialyzer used in the first outpatient unit. With the suspicion of a possible dialyzer reactor, the membrane was switched from F160NR to Gambro Revaclear. Her PLTs increased to 125 K/uL in 4 days. Discharge instructions were indicated that the patient must use a Revaclear dialyzer. A week later, repeat PLT count was noted to be 200 K/uL.

Discussion: This case demonstrates a rare dialyzer reaction, in which a specific dialyzer membrane leads to severe thrombocytopenia and bleeding. It has been postulated that complement activation might have a role, but this patient had normal complement levels.
FR-PO054

Calcium Free Dialysis for Hypercalcemic Crisis

Introduction:
Hypercalcemic crisis, a potentially life-threatening condition, has been defined as a calcium of 14 mg/dl or more with evidence of multi-organ dysfunction including cardiovascular, renal or CNS involvement. We describe a case of hypercalcemic crisis due to primary hyperparathyroidism treated with low calcium/calcium free dialysis.

Case Description:
A 62 year old healthy man was brought by his wife to the ED for lethargy, worsening confusion over 3 days, weight loss and constipation. On exam, he was hemodynamically stable, had flat jugular veins and dry mucous membranes. His corrected calcium was 23.58 mg/dl with a creatinine of 3.60 mg/dl. He was aggressively hydrated with normal saline and received a total of 2 doses of Calcitriol 240 IU IM with no improvement in his mental status or in his calcium levels. He was then given Denosumab 60 mg SQ and underwent a 3 hour session of low calcium dialysis (Ca bath 1.0 mEq/L). During the treatment, he was given NS boluses in addition to his maintenance NS 250 cc/hr to avoid hypotension. He subsequently underwent 3 additional treatments (Treatments 2 and 4- using calcium free dialysate and Treatment 3- using Ca 1.0 mEq/L) that were well tolerated. Following his 2nd treatment, his mental status improved significantly. After his 4th treatment, his calcium was 12.26 mg/dl. His intact PTH level was 1324 pg/mL. A Sestamibi thyroid scan showed a large left parathyroid mass. The patient underwent surgical resection of a 13 gm parathyroid adenoma after which his calcium normalized to 9.8 mg/dl. His clinical course and a blood pressure trend during hemodialysis is reported below.

Discussion:
Calcium free dialysis and the use of low calcium dialysate was tolerated with no hemodynamic instability. Aggressive hydration is important to maintain tolerability. It can be safely used as a bridge to definitive surgical treatment in the setting of primary hyperparathyroidism.

FR-PO055

Antineutrophil Cytoplasmatic Antibody Crescentic Allograft Glomerulonephritis following Sofosbuvir Therapy

Introduction:
Sofosbuvir is used for the treatment of hepatitis C virus infection. We report first case of ANCA/RPGN following Sofosbuvir in a kidney transplant recipient.

Case Description:
51 yo male had a living unrelated donor kidney transplant, received alentezumab induction, and tacrolimus and mycophenolate maintenance. sCr was 1.4, 1 week after transplant. 12 weeks post-transplant, sCr was 2.0; renal biopsy showed ATN and tubular isometric vacuolization. Tacrolimus was replaced with cyclosporine. His sCr stabilized at 1.6. He had HCV genotype 1a and high viral load. At week 40 after transplant, his sCr was started on ribavirin and sofosbuvir. At 12 weeks of HCV treatment, sCr was 3.7, UA with 30 protein and 131 RBCs, and PCR was 0.6. Allograft biopsy showed TMA. Therefore, sofosbuvir, ribavirin and cyclosporine were stopped. He was started on prednisone and continued on mycophenolate. His sCr was at 2.4. 70 weeks after transplant (30 weeks after initiation of sofosbuvir), he had a sCr of 1.4, p-ANCA titer was 1:320 and MPO ab >100. He was diagnosed with p-ANCA associated crescentic GN in the allograft. The patient was treated with sulfamethoxazole, trimethoprim and a course of plasmapheresis. He later started HD and Rituximab was added. He remains dialysis-dependent despite of our efforts in treating his RPGN.

Discussion:
Renal biopsy showed 3 different pathologies. Initially tubular toxicity of tacrolimus. After sofosbuvir and ribavirin, he had TMA, we stopped his HCV treatment, although the concurrent cyclosporine use was implicated. 30 weeks after the initiation of sofosbuvir and ribavirin therapy he had ANCA-associated crescentic GN. Ribavirin had no reported cases of ANCA vasculitis. Sofosbuvir was approved in 2013 and we suspect it as likely cause of ANCA vasculitis. Therefore, our case represents the first case of drug-associated ANCA vasculitis in an allograft kidney. Further drug monitoring is necessary to elucidate the degree of association and possible causal effect of sofosbuvir and p-ANCA vasculitis.

FR-PO056

Malignant PEComa Post Combined Kidney and Pancreas Transplantation

Case Description:
The patient was a 44-year-old Hispanic female with a history of DM type 1 with living related kidney transplant back in 1998 and followed by a pancreas transplant in 1999 with transplant pancreatectomy and retransplant of the second pancreas in 2010. Her immunosuppressive agents were mycophenolic acid, prednisone and tacrolimus. Fifteen years post-kidney-transplant, she developed fever with chronic cough for a month. CT of the chest revealed multiple, bilateral, solid, non-cavitating pulmonary masses with mediastinal lymphadenopathy. CT of the abdomen showed right native kidney mass measured 5.2x8x cm. Right lower lobe lung biopsy showed perivascular epithelioid cell neoplasm. The PEComas of the lung are traditionally considered benign. To investigate the nature of the renal mass, the patient underwent right open radical nephrectomy. Again, the right nephrectomy pathology showed malignant PEComa, 10 cm with pure epithelioid with carcinoma-like growth pattern, involving the entire kidney. The tumor is histologically identical to the patient’s lung mass and confirms that the kidney mass is the primary tumor and the lung tumor is a metastasis. The patient also found metastatic osteolytic lesions involved pelvis, proximal femurs, cervical and thoracic spines. After confirmed the diagnosis of malignant PEComas, mycophenolic acid was stopped. She was started on Temsirolimus 25 mg intravenous weekly, taclarim was changed to rapamycin and continue with oral prednisone. Unfortunately 3 weeks later patient became unresponsive, cardiac arrest and passed away.

Discussion:
Although the majority of PEComas is recognized as benign, but in the immunocompromised patient, especially with a history of multiple solid organ transplants like in our patient, the tumor could be presented in advance and aggressive way with fatal outcomes.

FR-PO057

A Case of Post-Transplant Kaposi Sarcoma Treated with Combination Chemotherapy and mTOR Inhibitor

Case Description:
A 43 y old African American male with history of ESRD s/p deceased donor kidney transplant in 2013 induced with alentezumab, maintained on tacrolimus, mycophenolate and prednisone was admitted with worsening shortness of breath and productive cough. His course was complicated by hypoxemic respiratory failure requiring intubation. He received broad-spectrum antibiotics initially and his anti-
FR-PO058

Warfarin-Related Nephropathy in a Kidney Transplant Patient
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Introduction: Anticoagulant-related nephropathy is a new entity manifesting as AKI in the setting of excessive anticoagulation. Initial cases were related to warfarin use; however, more recently AKI is reported with direct thrombin inhibitors. We present biopsy-proven warfarin-related nephropathy (WRN) in a transplant patient on anticoagulation for atrial fibrillation with INR<2.

Case Description: A 69y old man with hypertension, atrial fibrillation (on warfarin), T2DM and ESRD s/p living unrelated kidney transplant with baseline sCr 2.0 mg/dL (on cyclosporine, mycophenolate and prednisone) presented with nausea, vomiting and abdominal pain. Acute cholecystitis was diagnosed and percutaneous cholecystostomy drainage performed. Initial labs revealed leukocytosis and AKI on CKD with sCr 2.7 mg/dL. INR was 1.8. Urinalysis revealed 3+ blood, 2+ protein with 179 RBCs/HPF, urine sediment 1-2 RBC casts/LPF. Transplant kidney ultrasounds was unremarkable. Complements were normal. Urine microscopy demonstrated persistent RBC casts and kidney biopsy was performed. Acute tubular injury with numerous occlusive RBC casts suggestive of WRN was observed. Kidney function slowly improved but sCr remained above baseline upon discharge. Warfarin was resumed due to high stroke risk.

Discussion: Our patient’s presentation with AKI in the setting of acute cholecystitis raised the possibility of sepsis-induced AKI. However, the presence of microscopic hematuria and numerous RBC casts suggested a glomerular process. Biopsy suggested WRN developing in the setting of CKD and anticoagulation. Our case is somewhat unusual given the INR<2. Most cases of WRN have an INR>3. However, the patient had risk factors that had been linked to WRN including CKD, diabetes mellitus and hypertension. Interestingly, INR levels several months prior were all consistently below 2 yet the patient had 2 bleeding episodes requiring hospitalizations (GI bleed and thigh hemATOMA) suggesting an underlying bleeding predisposition. It is reasonable to consider WRN in cases of unexplained AKI with RBC casts in a patient with INR<3 in the presence of other risk factors and bleeding tendency.

FR-PO059

Successful Preemptive Kidney Transplantation Using Rituximab Induction in a Young Patient with Focal Segmental Glomerulosclerosis and Nephrotic Syndrome – Case Report
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Introduction: Focal segmental glomerulosclerosis (FSGS) recurs in 30% of patients receiving their first kidney transplant and often leads to graft loss. In the past, patients with FSGS and overt nephrotic syndrome were rarely transplanted, mostly due to the worries about its relapse. Rituximab (RTX), an anti-CD20-specific monoclonal antibody, was previously reported to be a valuable option in resistant nephrotic syndrome and relapsing FSGS after second kidney transplantation. Hereby, we present a successful first kidney transplantation of a young patient with FSGS and full-blown nephrotic syndrome, treated with RTX induction.

Case Description: The patient is a 24-year-old woman, who developed nephrotic syndrome at the age of 4. FSGS was confirmed early by renal biopsy, she was treated with cyclosporine A, mycophenolate mofetil (MMF), and steroids, with no remission. She was referred to preemptive, deceased donor kidney transplantation despite of 10 y/day proteinuria. She received a kidney transplant with two doses of RTX (375 mg in ad 1 and 7, followed by tacrolimus 5 mg BID, MMF 500 mg BID, and steroids therapy after transplantation. We observed immediate kidney graft function and protein-absent diuresis since 6 day post-transplant. Pre-transplant soluble urokinase plasminogen-type activator receptor (suPAR) was 1750 pg/ml. His kidney function was at baseline. Imaging revealed diffuse lung 13th and was 2073 pg/ml at 6 months post-transplant. Steroids were tapered and discontinued at 10 months post-transplant. Twenty months after transplantation serum creatinine is 0.8 mg/dL and no proteinuria is observed.

Conclusion: Successful kidney transplantation in a patient with pretransplant overt nephrotic syndrome secondary to FSGS, using rituximab as an induction therapy strongly suggest the need for larger clinical trials in such patients.

FR-PO060

Black Appearing Peritoneal Effluent
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Introduction: Endoscopic tattooing with India ink is a useful and safe tool for localizing small colorectal lesions.

Case Description: 60 year old man with End Stage Renal Disease due to Lupus Nephritis on continuous Ambulatory Peritoneal Dialysis (CAPD), developed black effluent from the peritoneal dialysis drain bag following screening colonoscopy. Findings included an ulcerated tumor occupying 25% to 49% of the colon circumference. There was no evidence of bleeding and multiple forceps biopsies were taken. The tumor area was marked using tattoos with 3 injections (5 ml each) of India ink. He returned CAPD and noticed his dialysate effluent was “black”. He presented to the ER with nausea, vomiting and black colored peritoneal fluid. Examination revealed a mild tender abdomen without rebound or guarding. Vitals were stable and he was afebrile. CT scan of abdomen revealed subcutaneous fluid, free intraperitoneal air and metastatic peritoneal disease. Peritoneal effluent cell count was elevated at 0.619 K/uL and WBC count of 5.5 K/uL. His presentation was consistent with peritonitis (cloudy dark-gray/black peritoneal effluent and elevated cell count)and empiric antibiotics were initiated with vancomycin, cefepime and metronidazole.

Within 48 hours the peritoneal effluent was clear (cell count down to 0.105 K/uL). The effluent culture grew Escherichia coli and Providencia Staurti. Dialysate remained normal. At the time of partial colectomy performed one month later, dark dye was still visible on mesenteric transverse colon, but no abscesses was identified.

Discussion: Complications associated with India ink tattooing include abscesses, inflammatory pseudotumor, focal peritonitis and peritoneal staining, most of which have been attributed to inadequate dilation or sterilization of the India ink dye. Dye spillage into the peritoneal cavity has been reported to occur at a rate between 2.4% and 13%. This occurrence has been attributed to injection technique (deep), and the possibility of trans- splanchnic migration of the dye. In our patient, drug administration, inadequate accurate drug site and bacterial peritonitis with gram-negative organisms is consistent with microperforation of the colon during the tattooing procedure.

FR-PO061

Sevelamer-Induced Colonic Ulceration – A Unique Case of Gastrointestinal Bleeding in End Stage Renal Disease Patient
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Introduction: End stage kidney disease patients experience significant morbidity and mortality. One common complication in this population is Gastro-intestinal bleeding(GIB). The causes of GIB in patients on chronic dialysis include use of aspirin and NSAIDs, Angiodysplasias and malignancies. Also medications like Sodium-poly-styrene-sulfonate can cause direct mucosa damage. We report a case of GIB in Hemodialysis-patient attributed to Sevelamer-induced colonic-ulceration.

Case Description: 56Y/0 ESRD-Hemodialysis patient with multiple comorbidities including hypertension, systolic cardiac-dysfunction, Atrial-fibrillation, H/o Breast Cancer s/p mastectomy/chemo(2005),presented to the hospital with passage of bright red blood per rectum,accompanied with syncope and shortness of breath. Her medications included Antibiotics, Aspirin, Baby-Aspirin, Carvedilol, Diltilazem, Pantoprazole, Sevelamer, Cinacalcet. Her clinical examination was unremarkable(excluding neurologic exam)except for palor. Orthostatic vital signs not checked due to dizziness, Significant labs findings were-hemoglobin-5.7mg/dl, Serum Potassium-5.5meq/L,BUN and Serum-Creatinine 46mg/dl, which were respectively and INR-1.1. CT head- no acute abnormalities, Mesenteric angiogram-no source identified, Endoscopic-Gastro-duodeno-scopy-normal, colonoscopy-no active bleeder, multiple diverticulosis1. Bleeding scan showed activity near the hepatic flexure. She underwent emergent right-hemicolecystectomy for the continued bleeding. Pathology report showed metastatic Carcinoma involving proximal Colon. Colonic-Mucosa inflammation and ulcerated,cluster of organophilic Fish scale like crystals suggestive of Sevelamer crystals were noted in colonic mucosa. Patient improved post surgery.

Discussion: There is only handful of literature on the Sevelamer colonic toxicity. This case highlight the fact that with widespread use of sevelamer in dialysis patient, physicians should be aware of this entity. Our understanding of Sevelamer-associated mucosal injury is limited and there are no known prevention strategies available.

FR-PO062

Successful Eculizumab Therapy in De Novo Atypical Hemolytic Uremic Syndrome in a Renal Transplant Recipient
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Introduction: The use of terminal complement inhibitor eculizumab has not been well described in the treatment of de novo atypical hemolytic uremic syndrome (aHUS) post renal transplantation.

Case Description: We present a 47 years old female with end-stage renal disease due to reflux nephropathy who had received a living-donor renal transplant from her sister 18 months previously. Her maintenance immunosuppression medications included tacrolimus 6mg twice daily, mycophenolate sodium 720mg (AM) and 360mg (PM), and prednisone on Continuous Ambulatory Dialysis. Her prednisone was tapered and dehydrated. Admission biochemistry revealed stage III acute kidney injury with a serum creatinine of 640 µmol/l (baseline 90 µmol/l). She was anemic (Hb 90 g/l) and proliferative was held. His exam was unremarkable except for an exophytic gingival lesion on his right mandible. His blood work revealed a mild anemia, elevated liver function tests, and liver nodularities with bulky lymphadenopathy. An axillar lymph node biopsy was performed and was consistent with Kaposi sarcoma (HHV8+). Tacrolimus was stopped and the patient was transitioned to the mTOR inhibitor: sirolimus. He was initiated on liposomal doxorubicin for his extranodal disease and metastatic disease after four cycles. His renal function remained stable on sirolimus and prednisone.

Discussion: Post-transplant malignancies are common and constitute a major burden. Adjustment of immunosuppression is the mainstay of therapy in these cases. It is standard of practice to switch from calcineurin inhibitors to sirolimus upon the diagnosis of Kaposi sarcoma. However, there’s no literature regarding chemotherapy in transplant-associated Kaposi sarcoma. Most of the available data is from the AIDS population which we extrapolated to our patient. His bulky disease triggered us to explore aggressive therapy. Combination chemotherapy and sirolimus seem to be a good therapeutic strategy that should be considered in cases of disseminated post-transplant Kaposi sarcoma.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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required multiple blood transfusions. Her trough tacrolimus level was raised to 22 ng/L. Stool microscopy and culture was negative for shiga-toxin producing bacteria. Blood film showed red cell fragments; serum lactate dehydrogenase was raised at 752 u/L. ADAMS-13 activity was normal. Renal biopsy was consistent with thrombotic microangiopathy. Complement genetic analyses (factors H, I, B and MCP tested) did not reveal any pathogenic mutations. Antibody H antibody was negative. She was treated, first with four cycles of plasma exchange and then commenced on eculizumab at 900mg infusion weekly for first four doses and then 1200mg fortnightly. Her renal and anemia parameters normally normalized.

hyperterglyceridemia, elevated LDL and D-dimer. Patient met the clinical criterion for HLRH. His nephrotic syndrome was attributed to HLRH associated with CMV infection. Treatment was started with anakinra 100 mg subcutaneously daily. Patient responded to the therapy with initial decline in serum Cr to 2.4 mg/dl. At 2 months follow up, proteinuria has improved to 2.1 g/g. ferritin to 1875 ng/ml, but Cr remains elevated at 3.6 mg/dl.

Discussion: Most cases of HLRH in kidney transplant recipients are triggered by CMV infection or other herpesviruses. This is a unique case of HLRH and nephrotic syndrome caused by CMV infection which is likely secondary to cytokine storm and histioctye proliferation. Treatment with anakinra could be beneficial in these patients.

FR-PO065

BK Nephropathy in Allogeneic Stem Cell Transplant Recipient without Thrombotic Microangiopathy and Graft-Versus-Host Disease: A Unique Observation

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Introduction: BK virus is emerging as an important pathogen in allogeneic stem cell transplant (SCT) recipients and more prevalent in patients of Graft versus Host Disease (GVHD) and Thrombotic microangiopathy (TMA). Due to immunosuppression, different drugs and/or drug combinations have been associated with BK nephropathy such as tacrolimus. BK virus causes chronic kidney disease, ureteral stenosis and hemorrhagic cystitis in stem cell transplant patients leading to increase mortality and long hospital stay. We present a unique case of BK nephropathy that has occurred in patient who was asymptomatic and without any co-infections, TMA, or GVHD. The patient was tapered off tacrolimus which showed improvement in the BK viral urine and serum load.

Case Description: A 31-year-old female with history of Acute Myeloid Leukemia (AML) underwent an allogeneic stem cell transplant a year ago. Patient was treated with 4 cycles of Fludarabine, IDArubicin, CYTarabine (FIA) and sorafenib regimen. Post-transplant course was complicated by GVHD of gastrointestinal tract and skin (Grade I). Patient was maintained on tacrolimus and later tapered off. She remained asymptomatic; however, kidney function worsened with elevated creatinine at 1.8. BK Serum viral Load of 10,800 was seen. Therefore, renal biopsy was done which was consistent with BK nephritis. With limited effective therapeutic options, immunosuppression by tacrolimus was tapered off and Leflunomide was started showing a decrease in viral load and creatinine stabilizing to 1.37.

Discussion: A definitive diagnosis of BK nephritis is confirmed with a kidney biopsy.

FR-PO066

Pharmacokinetics and Total Removal of Fosfomycin in a Patient with Chronic Kidney Failure Undergoing Haemodialysis

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Introduction: Fosfomycin shows bactericidal activity against various gram-positive, gram-negative and anaerobic pathogens, including antibiotic resistant S. aureus. However, dosing of fosfomycin in critically ill patients undergoing renal replacement is based on scarce data.

Case Description: A female chronic dialysis patient (76 years, BMI 20) was admitted to our hospital due to distinct dorsalgia. Computed tomography of the lumbar spine unveiled spondylodiscitis of the thoracic vertebrae 11/12. A punch biopsy of the affected bone region showed focal osteomyelitis. As the patient was allergic to penicillin, antibiotic therapy with cindamycin and fosfomycin sodium (8 g per day, 3 g before, 5 g after IHD session) was initiated. Maximum plasma concentration after the 3 infusion was 496 mg/L. IHD led to a distinct reduction of fosfomycin plasma levels of 61%, with a dialyzer clearance of 75 ml/min. The total amount of fosfomycin in the total collected dialysate was 2430 mg. Ccr after the additional administration of 5 g of fosfomycin after IHD treatment was 467 mg/L.
FR-PO067
Tumoral Calcification – A Rarely Seen Complication in Dialysis Patients
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Introduction: Tumoral calcification is characterized by solitary or multiple painless, periarticular soft-tissue calcium deposits. Tumoral calcification was first described by Giard and Duret in 1898 and 1899. There are two categories, a familial variant also called Tschlaender disease and Secondary tumoral calcification also called Uremic tumoral calcification.

Case Description: Case : 50 year old female with end stage renal disease secondary to hypertension presented for evaluation of painful left shoulder mass. She has been on dialysis for 12 yrs. Has multiple painful swellings on her hands, elbow and feet. States that her shoulder mass appeared 2 years ago and has progressively increased in size. Also complained excruciating pain causing trouble carrying out her daily activities. Her surgical history significant for a right neck dissection for a neck mass, parathyroidectomy and a remote history of partial thyroidectomy.

Physical examination significant for multiple soft immobile nodular swellings on the left shoulder, dorsum of left foot, right elbow and index finger. Mass on the left shoulder about 12 X 10 cm in size, immobile, tender and firm to palpation. The swelling on the right elbow non tender to palpation and the one on the left index finger involved the distal and proximal interphalangeal joints. Imaging studies showed nodular swellings with significant calcification. Excision of the left shoulder mass showed exudation of a chalky white material. Pathology results were consistent with tumoral calcification.

Discussion: Secondary tumoral calcification is associated with high serum Ca X P in dialysis patients, secondary or tertiary hyperparathyroidism, aluminium intoxication and vitamin D overload. These lesions are painless but massive swellings can cause mechanical limitation, pain and neurovascular symptoms due to compression of adjacent structures. Management includes dietary phosphate restriction, noncalcemic phosphate binders, intense dialysis with a low-calcium dialysate and calcimetics. Surgical excision is indicated in symptomatic lesions. Parathyroidectomy recommended in patients with persistently elevated PTH levels. Tumoral calcification resolves after successful renal transplantation.

FR-PO068
Palate Nodule in a Hemodialysis Patient: A Long and Winding Road Until Diagnosis
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Introduction: Secondary hyperparathyroidism (SHPT) is a common condition in end-stage renal disease patients. We highlighted a complication that usually affects long bones, a brown tumor (BT). We report a case of a patient with SHPT, with a palate nodule, which diagnosis investigation led to a BT of maxilla.

Case Description: A 25 years-old female, previously hypertensive, who returned to hemodialysis after her kidney transplant failed. She was referred to our CKD-MBD service with a 3-month history of a progressively enlarging submucosal nodule with hard consistency on her posterior left palate. The mass was painful since the beginning, and presented progressive growth. She had no fever, neither consumptive symptoms nor palpable lymph nodes. Before coming to our service, she was referred to a maxillofacial surgery service, where a computed tomography (CT) and a biopsy were requested, as no initial suspected diagnosis was done. CT disclosed a lytic bone lesion located in alveolar process of maxilla, measuring 3.0 X 2.5cm, and damaging the superior molar roots, producing a bulging in the left maxillary sinus, nasal cavity and palate. Microscopy view evidenced the presence of multinucleated giant cells among ovoid and fusiform mesenchymal cells, large amount of hemorrhage and trabecular of lamellar bone tissue, being compatible with Brown Tumor. On review of her case, she confirmed that Sveveler's 1,8 g thrice a day, but the administration of Vitamin D analogs was not possible due to hyperphosphatemia. Her serum intact Parathormone levels were 1,500pg/ml, Vitamin D 36ng/ml, ionized calcium: 4,8mg/dl, phosphorus: 6,1mg/dl. Technetium sestamibi parathyroid scan revealed hyperactive glands at both superior thyroid lobes and at the low cervical region. The patient was submitted to total parathyroidectomy, and the lesion is progressively decreasing despite of other modalities of treatment.

Discussion: Brown Tumors must be kept in mind as a differential diagnosis in patients with SHPT even when these lesions are located in unusual sites such as the maxilla.

FR-PO069
A Case of Levofloxacin Toxicity Treated with Continuous Veno-Venous Hemofiltration
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Introduction: Levofloxacin is a commonly prescribed antibiotic. Multiple adverse events such as central nervous system and cardiovascular toxicity have been described. Cardiovascular toxicity, namely QT prolongation when present can be particularly dangerous and requires urgent management. Aside from stopping the drug there is paucity of data regarding other urgent treatment modalities such as CVVH when potential toxicity is suspected.

Case Description: A 53 year-old African American female with a history of ESRD on peritoneal dialysis (PD) for 2 years was admitted for concern of levofloxacin toxicity. She had been admitted to an outside hospital and discharged approximately 1 week prior to presentation with a levofloxacin prescription for presumed bronchitis. During initial evaluation, she admitted to taking levofloxacin 500 mg every 8h1 for the preceding 5 days. She admitted she had been performing PD every other day as she was concerned she was volume depleted. After 3 days she developed nausea, vomiting, left heel pain, left hand tremor, and palpitations. She had not performed peritoneal dialysis since the onset of her symptoms. Her initial physical exam was consistent for left hand tremor and Achilles tendon tenderness. Her QTc upon initial evaluation was 534. Serum levofloxacin level was ordered and a decision was made to start continuous veno-venous hemofiltration (CVVH) to increase clearance of levofloxacin. CVVH was stopped after clinical recovery of her symptoms and normalization of QTc. Her initial levofloxacin level was 36.65 mcg/mL (normal therapeutic range 8-12 mcg/mL) and serum creatinine was 1.7mg/dL. During the duration of treatment every 12 hours. Below is a graphical trend of her levofloxacin levels.

Discussion: Levofloxacin toxicity represents a unique and dangerous clinical challenge. This case report shows successful and effective treatment of critical toxicity with the use of CVVH.

FR-PO070
Utility of Cystatin C in the Setting of Urinoma
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Introduction: Urinomas (i.e. presence of urine outside of the urinary tract) are common in the setting of urologic/pelvic surgery. Due to the resorption of extravasated urinary constituents such as urea nitrogen and creatinine, determination of renal function is typically confusing and often leads to the false impression of acute renal failure, a situation referred to as pseudo-renal failure. We describe the superior precision of cystatin C (CysC) vs serum creatinine (SCr) in estimating renal function in a patient with urinoma.

Case Description: 79 yo M with a history of urinary retention requiring a chronic indwelling Foley catheter presented with catheter obstruction leading to bladder rupture and apparent acute renal failure. Presenting Scr was 5.8mg/dl (baseline 1.5mg/dl). A cystogram was consistent with urinoma. Treatment of the bladder leak consisted of urinary catheter replacement and he maintained urine output > 2L/24h for several days. Scr decreased to 2.0mg/dl. A second episode of catheter obstruction subsequently occurred resulting in a significant increase of the extraperitoneal bladder leak and acute rise of creatinine to 4.6mg/dl. After placement of a larger catheter, his Scr decreased to 1.7mg/dl. During the second episode of urine leakage, simultaneous CysC levels were obtained. In contrast to
the marked variation of Scr during the onset and resolution of the urinoma, CysC levels demonstrated increasing modulating effect. In contrast, followed by return to near baseline level of 1.7 mg/L on catheter replacement. CysC-based eGFR values using CKD-EPI demonstrated similar relative stability, decreasing from 39 to 29 mL/min during the recurrent bladder rupture, followed by an increase to 36 mL/min after treatment. In contrast, the eGFR decline based upon Scr-based CKD-EPI equation was notably flatter declining from 20 to 11 mL/min during episode then increased to 38 mL/min with treatment.

**Discussion:** These findings imply superiority of CysC over Scr in estimating renal function in patients with urinoma and pseudo-renal failure. Discordant estimates of eGFR between CysC and Scr may be indicative of urinoma.

**FR-PO071**

Two Cases of Nonocclusive Mesenteric Ischemia Triggered by Intradialytic Hypotension

**Introduction:** Among dialysis patients, non-occlusive mesenteric ischemia (NOMI), defined as diffuse intestinal ischemia without any organic blood vessels occlusion, is rare (1%patient-year) but has a very high mortality (56-90%). The factors associated with mortality from this disease include age, diabetes, hypertension, intradialytic hypotension, atherosclerosis, medications, etc. Early diagnosis and treatment are important for improving survival in patients with this disease.

**Case Description:** We here report two cases of NOMI, who were triggered by hypotension during hemodialysis. Case 1: A 52-year-old man who had a left ventricular ejection fraction after cardiac infarction showed intradialytic prolonged hypotension. On physical examination, he was hypotensive with diffuse abrupt abdominal tenderness. The laboratory investigation showed a high blood white count of 20,000. Case 2: A 88-year-old woman on maintenance hemodialysis for 5 years had hemorrhagic shock. On physical examination, she was also hypotensive with mild abdominal tenderness. The laboratory investigation showed a high white blood count of 16,000. We performed multiple detector computed tomography (MDCT) and found patent mesenteric vessels in both cases. Subsequent surgical procedure revealed the necrosis of terminal ileum in case 1 and autopsy revealed necrosis of occluded in Case 2. Finally, we diagnosed them as having NOMI. The former underwent surgical procedure and was discharged alive from the hospital but the latter was dead.

**Discussion:** Considering the fact that NOMI is a very high mortality disease, early diagnosis and treatment is important. However, a diagnosis of this disease is very difficult because clinical manifestations are nonspecific. We speculated that the profile of hemodialysis is very different from other hospital but the latter was dead.

**FR-PO072**

Aggressive Renal Cell Carcinoma in a Renal Allograft

**Introduction:** Kidney cancers arising in renal allografts are very rare and most oncologic institutions lack experience in their management. We report a case of aggressive renal cell carcinoma (RCC) in a renal allograft in a patient with rare disease. Short post-transplantation.

**Case Description:** A 46-years-old man with a history of ESRD due to diabetic nephropathy underwent hemodialysis for one year prior to receiving a Living Un-Related Renal Transplant from his brother—in law, a 36 year healthy male in 2001. The patient had immediate graft function post-transplant and was maintained on MMF, Cyclosporine and Prednisone. He underwent renal allograft biopsy in 2004 for a gradual decline in renal allograft function; this biopsy showed chronic transplant glomerulopathy. The patient had very gradual decline in renal allograft (CKD G3a) until Jan 2015, when he developed mild lower abdominal pain over several weeks. Imaging including abdominal US and CT revealed a 14 X 12 X 12 cm mass arising from the transplant kidney with extensive regional adenopathy involving the right common iliac vein and IVC with evidence of lung metastasis. Biopsy showed RCC, clear cell type with extensive necrosis. The venous involvement precluded surgical excision. The patient was treated with sunitinib. Several weeks later, he developed extensive bilateral pulmonary embolism treated with heparin infusion. IVC filter was inserted and the initiation of treatment he developed grade 3 anemia. Alcoholic embolization of the tumor was then performed. Immunosuppressive medications were tapered and the patient returned to hemodialysis.

**Conclusion:** Characteristic of de novo kidney allograft RCC in a case currently unknown. These tumors can be de novo or transmitted by the donor and differentiation between these 2 modes of transmission may be difficult. The most common reported histologic type of graft tumor is papillary carcinoma; clear cell type as in our case is very rare. Tumors occurring in renal transplants are usually incidental, asymptomatic, low grade and small but may be symptomatic or with vapor clinical picture, high grade, aggressive and very large as in our case. Frequent and continued surveillance imaging of both the renal allograft and native kidneys is paramount.

**FR-PO073**

A Case of Acute Allograft Rejection Combined with BK Virus-Associated Nephropathy

**Introduction:** Rejection and BK virus-associated nephropathy (BKVAN) are major causes of renal allograft dysfunction. Treatment can be difficult when both conditions coexist, because potent immunosuppression is required in acute rejection and reduction of immunosuppressive agents is essential in BKVN. We present a case of acute allograft rejection combined with BKVN.

**Case Description:** A 41-year-old male with end stage renal disease because of hypertensive nephrosclerosis received a deceased donor renal transplantation. Immunosuppressive therapy was started with mycophenolate mofetil, tacrolimus, methylprednisolone, and anti-thymocyte globulin. On post-operative day (POD) 19, serum creatinine (Scr) level was 1.89 mg/dL but was elevated to 2.4 mg/dL on POD 25. Diffuse C4d staining in peritubular capillaries was noted on kidney biopsy and acute antibody-mediated rejection was diagnosed. Plasmapheresis was initiated and intravenous immunoglobulin (IVIG) and rituximab were administered. After 10 days of treatment, Scr was decreased to 1.5 mg/dL. Additional episodes of Scr elevation occurred and more sessions of plasmapheresis and IVIG administration were done, but Scr was elevated to 2.48 mg/dL on POD 67. Decoy cells were detected on urine cytology and high levels of vituria and viremia were found on polymerase chain reaction for BK virus DNA. On second kidney biopsy, findings of acute cellular rejection were noted and viral inclusion bodies in tubular epithelium were seen, suggestive of BKVN. For treatment of BKVN, reduction of immunosuppressive agents and administration of IVIG and leflunomide were performed. Steroid pulse therapy was done in regard of acute cellular rejection. Despite therapy, his renal function did not recover completely and Scr was elevated to 3.2mg/dL on POD 138.

**Discussion:** It is difficult to treat when BKVN and acute rejection coexist. In our patient, IVIG and leflunomide was administered and immunosuppression was reduced for BKVN while steroid pulse therapy was performed for acute rejection, but his allograft function deteriorated. Studies are required to optimize the management of these difficult cases.

**FR-PO074**

Decreased Ultrafiltration in an End-Stage Renal Disease Patient with Sickle Cell Anemia: A Potential Strategy to Facilitate Kidney Transplantation

**Introduction:** Sickle cell crisis (SC) leads to mortality and morbidity in sickle cell disease (SCD) patients. Vascular occlusion in a common precipitating cause. Volume overload may require increasing ultrafiltration(UF). We report a case of SCA patient with acute kidney injury (AKI) who suffered from recurrent episodes of SC and acute hemolytic anemia requiring blood transfusions after hemodialysis(HD) was initiated. She became more sensitized from blood transfusions. Decreased UF reduced episodes of SC and blood transfusions.

**Case Description:** A 39-year-old African American woman with a longstanding history of SCA presented with a severe episode of SC complicated by AKI requiring chronic HD 5 years ago. Since starting HD, she had more episodes of SC from once a year up to every other month and required more blood transfusions. She presented for a pre-kidney transplant evaluation. Her panel reactive antibody(PRA) increased from 28 and 0 to 44 and 10, for class I and II, respectively. Upon interview, she has HD 3 times/week. Her estimated dry weight was 62 kg and intradialytic weight gain was 2-2.3 kg. She sometimes had mild diastolic hypertension with BP of 90s/50s. As concern for over UF being a potential cause of volume depletion and subsequently precipitating SC, the UF was decreased. She had fewer episodes of SC and blood transfusions. She remained on the kidney transplant waiting list with this HD prescription and stable hemoglobin.

**Discussion:** Our patient presented with more frequent episodes of SC after HD initiation. Intradialytic hypotension indicates intravascular volume depletion which subsequently precipitating SC and hemolytic anemia. Volume management in SCA patients with ESRD is challenging and critical to avoid intravascular volume depletion. SC and acute hemolysis may be surrogate markers of over UF. Avoiding over fluid removal can prevent SC, acute hemolysis, and blood transfusion which potentially increases immunological barrier for kidney transplantation from sensitization.

**FR-PO075**

Recurrent Catastrophic Antiphospholipid Syndrome Treated with Eculizumab in a Peritoneal Dialysis Patient

**Introduction:** Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by recurrent arterial and/or venous thromboses in presence of elevated titers of antiphospholipid antibodies (APL). These autoantibodies, promote thrombosis by activating endothelial cells and platelets. We describe a case of a clinical remission in recurrent APS via inhibition of terminal complement with Eculizumab in a Peritoneal Dialysis (PD) patient.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underlines represent presenting author.
Case Description: A 48-year-old man has shown recurrent CAPS characterized by diffuse vasculitis, glomerulonephritis, and infarction in the heart, kidneys, liver and lung tissues by positron of aPL. Angiography revealed a bilateral subclavian arterial thrombosis, a right iliac arterial stenosis that was treated with a stent and a left renal arterial occlusion. The patient’s renal function was decreased until End Stage Renal Disease, secondary to chronic thrombotic microangiopathy, and PD therapy was started. During 16 months, our patient presented 8 recurrent episodes of disease with pulmonary involvement characterized by multiple alveolar hemorrhages in concomitance with liver necrosis (biopsy proven) and myocardial ischemia. The patient was treated with high-dose pulse corticosteroids (methylprednisolone 500 mg/day IV followed byPrednisone (1 mg/kg/day), plasma exchange (5 series with a total of 74 sessions), IV immunoglobulin (400 mg/kg/day for 5 days), IV Rituximab (initial therapy and maintenance after 6 months), clopidogrel, aspirin and anticoagulation. Despite this standard therapy, we did not observe a sustained remission.

In conclusion of the literature, we chose to administer Eculizumab, a monoclonal antibody against complement C5, that blocks and prevents the generation of the proinflammatory molecules C5a and membrane attack complex C5b-9. The patient has been in remission with long-term Eculizumab treatment and anticoagulation therapy, without further thrombotic events during 1 year of follow-up.

Funding: Private Foundation Support

FR-PO076
A Case Report of Post-Transplant Lymphoproliferative Disorder in Kidney Allograft
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Introduction: Renal tumors are rare in transplanted kidneys. Nephrectomy is the traditional approach for renal masses. We are reporting a renal mass that was found to be post-transplant lymphoproliferative disorder in the renal allograft which we chose to biopsy instead of using traditional surgical resection.

Case Description: A 63 year old female with past medical history of renal cell carcinoma (RCC), was postoperative kidney transplant by right nephrectomy. ESRD secondary to MPGN status post living donor kidney transplant presented with abdominal pain, fever and diarrhea. Ultrasound of renal allograft showed a solid appearing 4.8x5.6x4.3 cm mass in the upper pole of the transplanted kidney which was predominantly homogeneous with internal vascularity. MRI revealed a 6.2 x 4.9 x 4.5 cm mass with solid enhancing and non-enhancing components within the transplanted kidney concerning for renal cell carcinoma. Given her previous history of RCC there was an increased concern for recurrence. Nephrectomy would have been the traditional approach but that would have meant sacrificing her allograft and initiating hemodialysis. The mass was biopsied and pathology revealed post-transplant lymphoproliferative disorder. Microscopic description showed a small kidney portion with tubules and glomeruli overrun by a dense lymphoid infiltrate. Immunohistochemical stains revealed that the large atypical cells were positive for CD20, CD-2, Mum-1 and CD30 but negative for Bcl-2, Bcl-6 and CD138. C-myc stained approximately 10-20% of cells and Ki-67 30-40%. In situ hybridization for Epstein Barr virus encoded RNA (EBER) was positive. Patient received 6 cycles of R-CHOP, follow-up MRI showed decrease in mass size.

Discussion: The biopsy of renal tumors for the diagnosis of small masses has not been widely adopted despite recent safety reports with advanced techniques and physicians’ expertise. It has been shown to be safe and reliable and should be considered in all patients with small masses especially in transplanted kidneys to decrease the risk of unnecessary surgical intervention.

FR-PO077
Renal Replacement Therapy for Severe Hypoanamotra (PNA 99mEq/L), Using 5% Dextrose Solution Infusion Method
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Introduction: Dialysis therapy for patients with severe hypoanamotra poses risk of osmotic demeylination syndrome due to rapid correction of serum sodium concentration. To prevent rapid correction, low sodium dialysate or filtration fluid can be used; however, dialysate sodium concentration needs to be changed frequently as patient’s serum sodium concentration rises. Instead of using low sodium dialysate, infusion of 5% dextrose solution (DFW) to the dialysis circuit after dialyzer/hemofilter can adjust the serum sodium concentration of returning blood to the desired level (D5W infusion method). We successfully treated a patient with severe hypoanamotra therapy for severe hyperkalemia and acute kidney injury (AKI), using continuous venovenous hemofiltration (CVVH) with D5W infusion method.

Case Description: A 46 year-old woman presented to the emergency department with confusion and dysarthria, due to severe hypoanamotra (PNA 99mEq/L). She also had anuric AKI and severe hyperkalemia. Decision of dialysis therapy was made, but that would have been the traditional approach but that would have meant sacrificing her allograft and initiating hemodialysis. The mass was biopsied and pathology revealed post-transplant lymphoproliferative disorder. Microscopic description showed a small kidney portion with tubules and glomeruli overrun by a dense lymphoid infiltrate. Immunohistochemical stains revealed that the large atypical cells were positive for CD20, CD-2, Mum-1 and CD30 but negative for Bcl-2, Bcl-6 and CD138. C-myc stained approximately 10-20% of cells and Ki-67 30-40%. In situ hybridization for Epstein Barr virus encoded RNA (EBER) was positive. Patient received 6 cycles of R-CHOP, follow-up MRI showed decrease in mass size.

Discussion: The biopsy of renal tumors for the diagnosis of small masses has not been widely adopted despite recent safety reports with advanced techniques and physicians’ expertise. It has been shown to be safe and reliable and should be considered in all patients with small masses especially in transplanted kidneys to decrease the risk of unnecessary surgical intervention.

FR-PO078
Performing Chronic Hemodialysis Therapy in a Patient with Total Artificial Heart
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Introduction: Total Artificial Heart (TAH) is an implantable artificial heart usually used as a temporary bridge till heart transplantation. Recently a review showed that bleeding (47%), AKI requiring hemodialysis (40%) and infection (33%) are the most common complications following implantation of a TAH. Currently there are no data in the literature on long term renal function outcome and on management of ESRD related complications.

We present our experience on a patient with TAH in chronic hemodialysis therapy.

Case Description: A 55 years old Caucaisan man was admitted on 1st March 2012 at our Hospital ER with cardiac failure for AMI with rupture of the papillary muscle. His medical history included hypertension and dyslipidemia in good pharmacological control. On 9th March TAH has been implanted in order to replace the lost heart function. From the day of admission to ICU, the patient developed oliguric AKI and CRRT was started.

Subsequently, the patient was switched to four times a week haemodialysis. To maintain an appropriate circulating volume for the operation of cardiac device, atrial filling pressures were maintained between 5.5-5.5 mmHg and 6.0-6.5 mmHg in the right and left atrium respectively. At the same time it was decided to record the change of hematocrit which the patient was subjected during the dialysis sessions (via Blood Volume Monitor (BVM)) in order to identify the critical BVM value for the functioning of the cardiac device. In this way we were able to manage the patient’s dialysis sessions even once he was discharged from the hospital with the portable version of TAH.

Discussion: This patient received dialysis therapy four times a week in order to maintain a more constant and content weight till March 2015, when he underwent to combined heart and kidney transplantation. To the best of our knowledge this is the longer case of continuous dialysis therapy in a patient with total artificial heart. Total Artificial Heart is not considered a valid therapeutic option for those patients waiting for heart transplantation even for long periods of time.

FR-PO079
Severe Varicella Zoster Virus Encephalitis and Retinal Necrosis in a Renal Allograft Recipient
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Introduction: Varicella zoster virus infection (VZV) has devastating potential complications and should be considered more often for testing by clinicians. Our case reflects the need to maintain a higher degree of suspicion for VZV by clinicians treating the immunosuppressed population.

Case Description: A 31-year-old man underwent living related renal transplantation in 2008 for chronic glomerulosclerosis. The clinical course was uneventful until January 2015, when he was diagnosed with grade 1A rejection after admitting to four months of nonadherence to his prescribed immunosuppression regimen, consisting of tacrolimus, mycophenolate mofetil, and prednisone. The rejection was addressed with pulse IV steroids and reumontation of his oral immunosuppressant regimen. Over the next four months, the patient sought medical attention for worsening and persistent occipital headache. Lumbar puncture was performed and suggested a viral etiology.MRI imaging was performed and revealed a large cerebellar infarct and diffuse vasculitis. Upon transfer to our institution, the patient underwent emergent neuroradiology evaluation which revealed hydrocephalus with decompressive craniotomy. Polymerase chain reaction (PCR) testing in the cerebrospinal fluid was positive for VZV. The patient was started on acetylov and steroids for treatment of VZV encephalitis and diffuse vasculitis. Ophthalmologic evaluation revealed retinal necrosis of the left eye, with PCR testing of the anterior chamber fluid also positive for VZV. After four weeks of acute care, the patient is currently in rehabilitation.

Discussion: Varicella Zoster Virus infection requires timely diagnosis and treatment for positive outcomes in the immunosuppressed patient. Clinical presentation can vary dramatically, from subtle rash to encephalitis. Therefore, clinicians caring for immunosuppressed patients should more routinely consider VZV as part of the differential diagnosis. Our case raises several questions including consideration for lengthening duration of VZV prophylaxis in allograft recipients and consideration for resuming VZV prophylaxis when resuming immunosuppression after extended periods of nonadherence.

FR-PO080
Hemodialysis Related Acute Thrombocytopenia During Pregnancy
Nikul Kumar Chandhuri, Belinda Bun Jim, Anjali Acharya. Dept of Nephrology, Jacobi Medical Center, Bronx, NY.

Introduction: Thrombocytopenia is not uncommon during pregnancy. It could be multifactorial and range from a mild asymptomatic condition to severe thrombocytopenia with fetal effects.

Case Description: A 29 year old woman with hypertension, CKD-IV from primary FSGS, presented at 10th week of gestation. Intermittent hemodialysis had to be initiated at 20th gestation week. Thrombocytopenia developed as described in the table below.

| Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only | Underline represents presenting author. |
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FR-PO081
A Rare Case of Nephrocalcinosis Caused by Hereditary Renal Hypouricaemia

Three Months After Kidney Transplantation

Yo Komatsuzaki, Takashi Yokoo.

Introduction: Renal hypouricaemia (MIM: 220150) is a syndrome that involves a defect in urate transporter 1 (URAT1) for urate reabsorption at the brush border of the proximal tubule. Nephrocalcinosis and exercise-induced acute renal failure are two major complications affecting renal function. A C889T mutation in SLCA21A2 encoding URAT1 is the rare mutation in Japanese. Here we report a rare case of nephrocalcinosis caused by hereditary renal hypouricaemia three months after kidney transplantation.

Case Description: A 41-year-old man had undergone living-related kidney transplantation because of Henoch–Schönlein purpura nephritis. Three month protocol biopsy showed several localized nephrocalcinosis determined by either von kossa or Goldner’s stain (staining for urate crystals). The evaluation for nephrocalcinosis showed hypouricaemia at 1.9 mg/dl with a high fractional excretion of uric acid at 26.8% (normal range, 6–10%). DNA direct sequencing followed by restriction fragment length polymorphism showed that both the recipient and donor were heterozygous for C889T. This mutation induce stop codon, thereby subsequent immunostaining were performed to show that both the recipient and donor were heterozygous for C889T. This mutation induce stop codon, therefore subsequent immunostaining were performed to show that both the recipient and donor were heterozygous for C889T. This mutation induce stop codon, therefore subsequent immunostaining were performed to show that both the recipient and donor were heterozygous for C889T. This mutation induce stop codon, therefore subsequent immunostaining were performed to show that both the recipient and donor were heterozygous for C889T.

Discussion: The patient was asymptomatic throughout hospitalization. Hematological evaluation ruled out all routine causes of nephrocalcinosis during pregnancy such as gestational thrombocytopenia, preeclampsia, HELLP, TTP/ITP and autoimmune causes. Given the chronological correlation of plateau decrease and hemodialysis it was concluded that thrombocytopenia was induced by the mutation in URAT1. Patient was switched from a Frenesius dialyzer to Exeltra 210 high flux dialyzer.

FR-PO082
An Unusual Case of Lymphadenopathy in a Renal Transplant Patient

Anna Bertram, Marcus Hiss, Jan H. Bræsen, Philip F. Halloran, Gunilla Einecke.

Introduction: We report an uncommon cause of lymphadenopathy in a kidney transplant patient.

Case Description: The 28y old male patient presented 18y after living donor kidney transplantation with painful inguinal swelling. He had returned to dialysis 8 months ago due to repeated infection. He was diagnosed with his first renal allograft rejection 12y ago. He has been on blood and platelet transfusions with an immunosuppressive regimen consisting of a calcineurin inhibitor and corticosteroids. He had a history of nephrocalcinosis and renal hypouricaemia but did not show any symptoms. He had an ESRD from hypertension and DM2 and received a living donor kidney transplant 22mo ago. He took atorvastatin, tacrolimus, mycophenolate mofetil, and prednisone. He had fever, abdominal pain, diarrhea, bleeding episodes, neurological deficits, and thrombocytopenia. We performed a biopsy of the allograft with a calcineurin inhibitor and corticosteroids.

Discussion: This case illustrates that severe allograft rejection, confirmed on histopathological and molecular level, can in rare cases present with pronounced lymphadenopathy.

FR-PO083
Prevnar 13 Associated Immune Thrombocytopenic Purpura in a Renal Transplant Recipient

Sagar Gupta, Daniel C. Brennan. Renal, WashU, St. Louis, MO.

Introduction: ACIP recommends all adults with immunocompromising conditions should receive PCV13 to prevent invasive disease caused by 5serotypes of S. pneumoniae. We describe here a case of ITP associated with Prevnar 13 administration in a renal allograft recipient, which is the first reported case of its kind.

Case Description: A 77 year old Caucasian male presented with chief complaint of increased bruising at insulin injection sites for one week. There was no history of fever, abdominal pain, diarrhea, bleeding episodes, neurological deficits, new medications or insect bites. He had ESRD secondary to hypertension and DM2. He received a living unrelated kidney allograft 22mo ago. He was on tacrolimus, MMF, prednisone, MMF or insect bites. He had ESRD secondary to hypertension and DM2. He received a living unrelated kidney allograft 22mo ago. He was on tacrolimus, MMF, prednisone, MMF or insect bites. He had ESRD secondary to hypertension and DM2. He received a living unrelated kidney allograft 22mo ago. He was on tacrolimus, MMF, prednisone, MMF or insect bites. He had ESRD secondary to hypertension and DM2. He received a living unrelated kidney allograft 22mo ago. He was on tacrolimus, MMF, prednisone, MMF or insect bites. He had ESRD secondary to hypertension and DM2.

The isolated thrombocytopenia was diagnosed as ITP and was attributed to the Prevnar 13 vaccine. He was started on pulse prednisone and IVIG. He received 6 units platelets with counts increasing to 94000, later discharged on a prednisone taper. Weekly blood counts showed improvement to his baseline of 140,000 in 3 weeks.

Discussion: PCV13 contains the S. pneumoniae serotypes’ capsular polysaccharide covalently linked to an immunogenic carrier protein resulting in a T-cell dependent antigen that elicits a T helper-cell response. The pathogenesis of ITP involves antibody production driven by CD4+ helper T cells reacting to platelet surface glycoproteins. Antibodies formed during viral or bacterial infections may also cross-react with normal platelet antigens (a form of molecular mimicry). Isolated cases of ITP have been reported but are relatively rare. Our case is further unique to occur in a patient on immunosuppression with a calcineurin inhibitor and corticosteroids.

FR-PO084
Placement of a Tunneled Hemodialysis Catheter in the Superior Vena Cava for Multiple Central Venous Occlusions

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Introduction: A tunneled hemodialysis catheter is essential for dialysis access when the use of a functioning arteriovenous fistula is not possible. In extreme situations of multiple central venous occlusions, it remains a challenge to establish durable vascular access.

Case Description: A 49 year-old diabetic male who had been diagnosed with ESRD one year prior came to our medical center because of temporary catheter occlusion. CT venography revealed occlusion of the bilateral brachiopheliac, internal jugular and the common femoral veins, and central venography showed occlusion of the bilateral jugular and innominate veins. Guided by ultrasound, a percutaneous transhepatic route, as well as local ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy showed an unusually severe form of intimal hyperplasia and intima-media thickening (fig. 1A). De novo-associated thrombocytopenia and no sign of malignancy. Because the allograft in his right fossa iliaca was tender, we performed a biopsy, as well, although ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy showed an unusually severe form of intimal hyperplasia and intima-media thickening (fig. 1A) and it was performed. However, histology showed lymphangiitis and no sign of malignancy. Because the allograft in his right fossa iliaca was tender, we performed a biopsy, as well, although ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy showed an unusually severe form of intimal hyperplasia and intima-media thickening (fig. 1A) and it was performed. However, histology showed lymphangiitis and no sign of malignancy. Because the allograft in his right fossa iliaca was tender, we performed a biopsy, as well, although ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy showed an unusually severe form of intimal hyperplasia and intima-media thickening (fig. 1A) and it was performed. However, histology showed lymphangiitis and no sign of malignancy. Because the allograft in his right fossa iliaca was tender, we performed a biopsy, as well, although ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy showed an unusually severe form of intimal hyperplasia and intima-media thickening (fig. 1A) and it was performed. However, histology showed lymphangiitis and no sign of malignancy. Because the allograft in his right fossa iliaca was tender, we performed a biopsy, as well, although ultrasound showed signs of chronic damage. Histology revealed severe ongoing cellular and AMR. Molecular analysis of the biopsy showed an unusually severe form of intimal hyperplasia and intima-media thickening (fig. 1A) and it was performed. However, histology showed lymphangiitis and no sign of malignancy.
the SVC (Figure 2A). The puncture point of the skin was beneath and 0.5-1.0 cm outside of the middle third of the clavicle and the needle was guided to the direction of the subcutaneous tunnel was along the distal end of the SVC, which was marked by a 5F indwelling catheter. Under fluoroscopic guidance, a micro-21G needle (Cook) was used to puncture the stent occlusion of the SVC, dark red blood was drawn when the micro-21G needle (depth approximating 15 cm) met the stent indwelling catheter. Additionally, under anteroposterior and lateral fluoroscopic guidance, a 21G needle was punctured into the SVC (Figure 2B-C), and the tunnelled hemodialysis catheter (cuff to tip 23 cm, Bard) was then exchanged with a 0.035-inch guide wire in the SVC. Chest radiography showed positioning of the right atrium and hemodialysis catheter tip into the right atrium (Figure 2D). CT showed that the needle did not enter the chest. 

Funding: Clinical Revenue Support

FR-PO085
Crystal Nephropathy in a Kidney Transplant Recipient due to Excessive Consumption of Oxalate Rich Diet and Vitamin C
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Introduction: Acute kidney injury due to crystal nephropathy has been reported mainly in patients with gastrointestinal (GI) malabsorption or GI surgery. We present a rare case of crystal nephropathy in the kidney transplant recipient (KTR) without obvious GI risk factors.

Case Description: 68 year old obese female, who is living-unrelated KTR for five years, with a stable post-transplant course and a baseline serum creatinine (sCr) of 1.1 mg/dl, presents to our hospital with tiredness and diarrhea for one week. She had extensive work up in the past for chronic diarrhea which is described as “soft stool”. 24 hour fecal fat, serum amylase and serum lipase were normal. Upon presentation, serum was 7.1 mg/dl which prompted us to perform an allograft kidney biopsy demonstrating multiple oxalate crystals deposited in the renal tubules. Reviewing her history further revealed that she was consuming 3 gm vitamin C (over the counter) daily for the last one month. Her preferred diet always consisted of oxalate rich foods (spinach). Renal functions improved in one month (sCr 2mg/dl) with hydration, discontinuation of vitamin C, and changes in dietary habits. Urine studies obtained after one week of treatment showed normal urine calcium, low urine oxalate and citrate.

Discussion: Oxalate nephropathy may occur from hyperoxaluria due to ingestion of oxalate rich diet or substances which metabolize to oxalate like vitamin C or from enteric causes like malabsorption. In our patient, we ruled out enteric causes and determined oxalate nephropathy was secondary to ingestion of oxalate rich diet and excess vitamin C. C renal functions improved with modification of diet, hydration and discontinuation of offending agents. Although vitamin C and high oxalate diet are rare causes of oxalate nephropathy in patients with normal renal function, it may cause significant nephropathies in KTR. KTR patients therefore, should follow low oxalate diet and avoid excessive vitamin C even with normal renal functions to avoid development of crystal nephropathy.

FR-PO086
The Conundrum of Dry Weight in a Pregnant Dialysis Patient

Introduction: The frequency of pregnancy in women bearing age who are on dialysis ranges from 0.3-1.5% per year. When a dialysis patient does become pregnant, nephrologists become extra vigilant to ensure a successful outcome for both mother and child. An important question that often arises is how to adjust a patient’s dry weight as pregnancy progresses.

Case Description: We present a case of a 23 year old pregnant dialysis patient who was admitted to the hospital with shortness of breath at 26 weeks gestation. She had a past medical history of a miscarriage, hypertension, and a failed deceased donor renal transplant.

At her outpatient dialysis unit, she was being dialyzed 6 times per week. Her dry weight was increased by 1.5 kg during the first trimester and during the second trimester by 1 pound a week to account for normal pregnancy weight gain. On this admission, her weight was 113.5 kg and her estimated dry weight was 114 kg. Her vital signs on admission revealed that she was mildly hypertensive with a blood pressure of 150/94 and her oxygen saturation was 90% on room air. After other etiologies were excluded, it was determined that the patient’s hypertension and hypoxia were due to volume overload despite the patient being below her expected dry weight. A feticard monitor was placed in the patient, which confirmed fetal activity every 24 hours. Approximately 2 weeks after discharge, the patient returned for her next dialysis with a weight of 108 kg, which was 6 kg below her expected dry weight. The patient delivered a baby weighing 5.4 lbs at 37 weeks with Appgar scores of 8 and 9 at 1 and 5 minutes, respectively.

Discussion: In a pregnant dialysis patient, it is difficult to distinguish between normal pregnancy weight gain and extra fluid. A fetal monitor and uterine artery doppler during dialysis are useful tools that nephrologists can employ to titrate ultrafiltration goals. Better volume management in turn could avoid pre-term delivery.

FR-PO087
A Rare Cause of AKI in a Renal Transplant Recipient
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Case Description: We present a 66 year-old African American woman who underwent pre-emptive living related donor kidney transplant for ESRD secondary to DMII and hypertension. She had immediate graft function and was discharged on the fourth post-operative day. Labs at discharge showed Na 136 mEq/L, K 3.5 mEq/L, Cl 102 mEq/L, HCO3 19 mEq/L, creatinine 1.3mg/dL and urine pH 7.0. Baseline renal biopsy was normal. Her medications on discharge included Prograf, Cilostat, Prednisone, Bactrim, Valcyte and sodium bicarbonate. She presented 10 days later with complaints of nausea, and vomiting as many as 10 times. Serum chemistries revealed the following: Na 136 mEq/L, K 5.9 mEq/L, Cl 105 mEq/L, HCO3 27 mEq/L, and total CO2 20 mEq/L, consistent with a high-anion gap metabolic acidosis (AG 21). Serum creatinine was 1.3 mg/dl and urinalysis revealed a urine pH of 7.5, pyuria and bacteriuria. Urine culture grew E. Faecalis and renal transplant ultrasound was normal. She was started on IV antibiotics and IV fluids, including sodium bicarbonate. Her chemistries revealed her anion gap metabolic acidosis had resolved, with total CO2 rising to 27 mEq/L. However, serum creatinine increased to 1.8 mg/dL, and continued to rise further despite treatment. A renal allograft biopsy was performed. Microscopic examination of the biopsy revealed widespread nephrocalcinosis with calcium-phosphate deposition. PT/INR at the time was 255 pg/mL, Ca 8.5 mg/dL, IP 4.1 mg/dL and fractional excretion (FE) of Ca 0.15%, FEIIP 29%, and urine anion gap was 29.

Discussion: We propose that our patient had developed post-transplant RTA, given the presence of a non-anion gap metabolic acidosis, low K, and urine pH of 7.0 in the immediate post-transplant period. Positive urine anion gap is suggestive of decreased ammonium excretion (although it should be confirmed with measurement of the urine osmolal gap and urinary Pco2). The combination of high urine pH, as a consequence of bicarbonate administration and decreased bicarbonate reabsorption, in conjunction with hyperparathyroidism and consequent increased phosphate excretion, provided the perfect medium for calcium phosphate precipitation.

FR-PO088
A Rare Case of Rabbit Anti-Thymocyte Globulin Induced Dissociated Intravascular Coagulation
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Introduction: Rabbit anti-thymocyte globulin (RATG) is a purified polyclonal immunoglobulin used for induction therapy in renal transplantation. Adverse effects include cytokine release syndrome, leukopenia, thrombocytopenia and serum sickness. We report a rare case of renal transplant recipient who developed severe coagulopathy and post-operative bleeding in whom RATG was used for induction.

Case Description: A 61 year old female with end stage renal disease received a deceased donor renal transplant. RATG (2 mg/kg) was initiated intraoperatively. Over the ensuing 2 hours, the patient became hemodynamically unstable with excessive bloody output from the surgical site drain. Exploration of the renal transplant revealed diffuse oozing from surrounding tissues but no bleeding from the arterial or venous anastomosis. Labs revealed an elevated prothrombin time of 27.0 sec, thrombin time of 36.4 sec, INR of 1.7, and fibrinogen level was 273 mg/dl, reduced thrombin level of 135 mg/dl and platelet count of 66000/cmcm. The RATG infusion was stopped. Multiple units of packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate were transfused. There was persistent bloody output. A reexploration revealed persistent diffuse oozing which required packing of the transplant bed. On postoperative day 4, the patient’s condition improved.

Discussion: We suspect Dissociated Intravascular Coagulation(DIC) may be secondary to RATG in our case. The donor biopsy showed no evidence of DIC. Other causes including calcineurin inhibitors, hyperacute rejection and sepsis were ruled out. Only a few case reports of RATG induced coagulopathy exist in the literature. Weber et al reported 12 hematopoietic stem cell transplant patients having coagulopathy after using RATG therapy. These cases had elevated D-dimer, tissue factor, thrombin-antithrombin III complex, and thrombomodulin, but had no bleeding, thromboembolic or vaso-occlusive complications. We contemplate that DIC is a rare but potential life threatening complication of RATG induction and awareness of this potential complication is important.

FR-PO089
A Page Transplant Kidney
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Introduction: Page kidney occurs by extrinsic compression of the renal parenchyma from a herniated or a mass, leading to activation of the renin-angiotensin-aldosterone system and resulting in systemic hypertension.

Case Description: A young-adult male, with ESRD of uncertain etiology underwent living related kidney transplantation 3-months prior to presentation. His post-transplant serum creatinine stabilized at 1.4 mg/dl. He was maintained on a low immunosuppressive regimen including tacrolimus, prednisone and mycopholic. The patient presented to the hospital with pain over allograft site and low grade fever.He reported an alteration with a family member without clear direct trauma to his right lower quadrant and subsequently referred to blunt trauma. Patient was hemodynamically stable with a blood pressure in the 170-180/100-110 mm Hg range. Labs revealed a Scr of 4.1 mg/dl, potassium of 5.7 mmol/L, hemoglobin of 10.8g/dl from a baseline of 12g/
FR-PO090
Black Colored Dialysate: A Rare Complication of Peritoneal Dialysis due to Cholecystitis
Yi Xin, Basmaah A. Abdulla, Pang-Yen Fan. Dept of Internal Medicine, Univ of Massachusetts Medical School; Dept of Nephrology, Univ of Massachusetts Medical School.

Introduction: We report a rare complication of black colored dialysate in a patient with ESRD on peritoneal dialysis (PD) with black cholecystitis.

Case Description: A 73 year old man was undergoing peritoneal dialysis for ESRD secondary to obstructive uropathy. He presented with black discoloration of his PD effluent due to a subcapsular renal transplant subcapsular/perinephric hematoma. The patient was managed conservatively and by hospital day 3, the renal function started improving. The patient was discharged with a SCr of 2.1mg/dl on hospital day 4 on his home regimen of amlopidine and labetalol. Most recently his SCr was 1.4mg/dl.

Discussion: The clinical syndrome of Page kidney in a kidney allograft due to subcapsular/perinephric hematoma following trauma or biopsy is characterized by acute hypertension with a concomitant acute decrease in kidney function. Our cases illustrates that this syndrome may occur without a history of direct trauma to the kidney, and that despite severe acute kidney injury, can be managed conservatively in some cases, with a good long term outcome.

FR-PO091
Acute Kidney Injury from Biopsy Proven Oxalate Nephropathy in a Combined Kidney and Lung Transplant Recipient
Minesh Patel, Saji Abraham. Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Introduction: We report the only known case of late AON of a transplanted kidney in a combined kidney and lung transplant patient without CF after undergoing medical and surgical management of infective endocarditis.

Case Description: A 62 year old Caucasian male with a remote history of Hodgkin’s disease complicated by radiation-induced pulmonary fibrosis and aortic stenosis underwent a simultaneous double lung transplant and bioprosthetic aortic valve replacement (AVR) in February 2013. His post operative course was complicated by recurrent bronchopneumonias secondary to MSAA requiring prolonged oxacillin as well as ESRD secondary to presumed unrecovered acute tubular necrosis (ATN). The patient subsequently underwent a successful left deceased renal transplantation from his wife in October 2014 with baseline creatinine of 1.4mg/dl. Unfortunately, he developed E. faecalis bacteremia secondary to urosepsis and subsequent finding of multivalvular endocarditis with superior vena cava involvement. This was treated with a prolonged antibiotic course, but recurrent admissions thereafter for CHF and concomitant AKI necessitated a redo AVR along with mitral valve replacement and tricuspid valve repair, “Commando Procedure” on 3-9-2015. Immediate post-operative AKI occurred and was thought due to ATN given the presence of muddly brown casts on sediment exam along with hemodynamic instability requiring temporary intra- and post-operative vasopressor support. Amuric AKI persisted for four weeks leading to a surveillance kidney biopsy to investigate for superimposed rejection. Notable histologic findings were tubular injury consistent with ATN, but more prominent was that of extensive calcium oxalate deposits consistent with AON.

Conclusion: In summary we report the first known case of AKI due to AON in a lung and renal transplant recipient after infective endocarditis requiring prolonged antibiotics and the Commando heart procedure. Though the clinical presentation mimics ATN it is important for clinicians to include AON in the differential diagnosis.

FR-PO092
New-Onset Diabetes After Transplantation in a Pediatric Patient with Congenital Anomalies of the Kidney and Urinary Tract: The Role of Hepatocyte Nuclear Factor 1β
Naoto Kaneko, Naoya Morisada, Keichi Tukizawa, Tomoo Yabuchi, Hirohata Hama, Norimasa Tada, Eiji Nakano, Shoichiro Kanda, Kyiomyobu Ishizuka, Hiroko Chikamoto, Yuko Akioka, Jumpei Iijima, Motozaki Hattori. Dept of Pediatric Nephrology, Tokyo Women’s Medical Univ, Tokyo, Japan; Dept of Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Japan.

Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most frequent cause of end-stage renal disease (ESRD) in children. New-onset diabetes after transplantation (NODAT) is one of the major complications following kidney transplantation (KTs). Mutations of hepatocyte nuclear factor 1β (HNF1B), a transcriptional factor involved in both the development of the liver and pancreas, have been reported to cause a multi-system disorder, including CAKUT, diabetes, liver dysfunction. We report a pediatric patient with renal hypodysplasia carrying a novel mutation of HNF1B who developed NODAT and liver dysfunction.

Case Description: The patient was a 14-year-old girl. She was diagnosed with bilateral hypodysplastic kidney in the newborn period. At the age of 3 years, she received living-related KTs from her mother preemptively. At the age of 4 years, a steroid pulse for acute rejection resulted in development of diabetes mellitus (NODAT). At the age of 13 years, she complained of acute right flank pain and fever. Laboratory data showed elevated transaminase levels and computed tomography showed malformation of the bile duct. The causes of NODAT were initially thought to be steroid and tacrolimus. However, based on her clinical features, including CAKUT, NODAT, and liver dysfunction, screening for a mutation of HNF1B was done by the central ethics board (Tokyo Women’s Medical University and Kobe University) was performed. Direct sequencing identified a novel splicing mutation of HNF1B, c.344+2T>C.

Discussion: CAKUT is the leading cause of ESRD in children and HNF1B is the most frequently mutated gene of CAKUT. Therefore, the contribution of HNF1B mutations to the development of NODAT appears to be large in the field of pediatric KTs. An oral glucose tolerance test and screening for HNF1B mutations may be advisable before KTs in CAKUT patients.
mice results in a concentrating defect in part related to a reduction of AVPR2 expression. As Pax2 and PTIP deletion, Pax2 and PTIP expression in the inner medulla, we hypothesized that Pax2 and PTIP are required for AVPR2 expression.

Methods: In IMCD-3 cells with control, Pax2 or PTIP deletion, we determined Pax2 and AVPR2 expression at the mRNA and protein level in response to normal and elevated osmolality. By ChIP analysis, we identified sites of Pax2 and PTIP enrichment on the AVPR2 promoter and determined changes in histone modifications, PolII occupancy in both IMCD and murine medulla tissue.

Results: Pax2 mRNA peaks 8 hours after an increase in osmolality, Pax2 protein peaks at 12 hours, and PTIP peaks at 20 hours. Pax2 deletion in the HMT activating complex localizes to a 100 bp fragment of the AVPR2 promoter, resulting in increases in activation marks, recruitment of PolII to this locus and an increase in gene expression in both cell lines and murine tissue. We identify the minimal promoter that Pax2 binds to and drives expression of the AVPR2 locus. Deletion of this 100 bp region of DNA results in lack of gene expression in the absence and presence of Pax2. Deletion of PTIP results in loss of gene expression even though Pax2 localizes to the promoter region, as histone activation marks are not increased and PolII is not recruited to this locus.

Conclusions: Thus, Pax2 and PTIP both regulate expression of AVPR2 in the murine inner medulla and in cells derived from this tissue. Pax2 provides the loci specificity for PTIP recruitment of the HMT activating complex and gene expression.

Funding: NIDDK Support

FR-PO095

Adenine Downregulates NKCC2 and AQP2 in the Rat Kidney and Causes Early Nephrogenic Diabetes Insipidus

Hassane Amjal, Rose P. Webster, Ingrid Fernandes dos Santos. Internal Medicine, Univ of Cincinnati, Cincinnati, OH.

Background: Long-term feeding of adenine is extensively used to develop animal models of chronic renal failure with metabolic features resembling those observed in humans. However, the mechanisms by which adenine induces renal failure are poorly understood.

Methods: In this study, we examined the early effects of adenine (ADN) feeding on water metabolism and renal function in rats placed in metabolic cages. Rats were fed control diet or diet supplemented with 0.25% or 0.50% ADN, or 0.50% adenosine ad libitum with free access to dH2O, and monitored daily for food intake, water balance and urine osmolarity, and euthanized for blood an kidney collections after 7 days.

Results: ADN-treated rats exhibited a sharp polyuria and polydipsia and decreased urine osmolarity as early as 3 days, and the magnitude of these effects is dose-dependent. Further, ADN caused a significant reduction in food intake and body weight at 0.50% but not at 0.25%. None of these physiologic parameters was altered by adenosine treatment.

dDAVP treatment induced a significant increase in urine osmolarity in control but not in ADN-treated rats. Immunoblotting experiments demonstrated a sharp reduction in AQP2/actin expression (75%). Outer medulla (OM) and inner medulla (IM) tip/OM and inner medulla (IM) tip.

Conclusions: In conclusion, adenine acts on renal tubules as a signaling molecule in which AQP2 both regulates as a candidate NDI treatment. Metformin was used to stimulate AMPK activation in control and V2R-blocked rats. Immunochemistry showed that AQP2 and p-AQP2-Ser256 appear to be localized on the cell membrane with acute and chronic AMPK stimulation, both in control and V2R-blocked rats.

Conclusions: AMPK stimulation in V2R-blocked rats is able to reduce the urine concentrating defect by increasing UT-A1 and AQP2. These results indicate that specific AMPK pathway activators might provide a promising treatment for congenital NDI.

Funding: NIDDK Support

FR-PO097

HYAL2 Disruption Leads to Impaired Urinary Dilution Capacity in Mice

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Background: Hyaluronan (HA) is a glycosaminoglycan present in high amount in the inner medulla of the kidney but almost absent in the cortex. Hyaluronidase 2 (HYAL2) is one of the two major hyaluronidases acting synergistically to degrade HA. Recently, it has been shown that Hyal2−/−mice display HA accumulation in the kidney. Renal HA content is known to vary with hydration status. Therefore, our study was set up to characterize the renal excretory capacities and renal water handling in response to water deprivation and acute water loading in Hyal2−/−mice.

Methods: Experiments were performed in Hyal2−/−mice and in their wild-type controls. After appropriate acclimation, water deprivation was performed during 24 hours. The capacity to excrete a water load was tested on an hourly basis for the next 6h after i.p. injection of 2 ml of sterile water. Diuresis and urinary osmolarity were measured.

Results: After water deprivation, Hyal2−/−mice showed the same ability to concentrate urine as wild-type (WT) mice. On the other hand, Hyal2−/−mice had a significant delay in the diuretic response induced by an acute water load. As for renal HA content, Hyal2−/−mice maintained higher HA concentration than WT mice after both water deprivation and acute water loading. HA was present around tubules in all kidney zones including cortex. Pre-treatment with HA depletion, kidney AQP2 and kidney p-Ser75 AQP2 expressions were increased after water deprivation and decreased after acute water loading to the same extent in KO and WT mice.

Conclusions: HYAL2 deficiency and/or increased renal interstitial HA delays the diuretic response to acute water load without any increase in plasma AVP or lowering AQP2 expression.

FR-PO098

Phosphorylated AQP2 and NR3A Reduce NSAID-Induced Urinary Concentration Defect

Huiwen Ren,1 Baoxue Yang,2 Patrick A. Molina,1 Jeff M. Sands,1 Janet D. Klein,1 Medicine, Renal Div, Emory Univ School of Medicine, Atlanta, GA; 2. Pharmacology, School of Basic Medical Sciences, Peking Univ, Beijing, China.

Background: Vasopressin increases urine concentration through activation of aquaporin-2 (AQP2) in the collecting duct. Nonsteroidal anti-inflammatory drugs (NSAIDs) block PGE2 synthesis, and may suppress AQP2, producing a urine concentrating defect.

Methods: We treated rats with a nonselective NSAID, ibuprofen, and a COX-2-selective NSAID, celecoxib, daily for 3 days. Renal AQP2 and V2R expression was assessed using immunohistochemistry and immunoblotting. Results: After water deprivation, Hyal2−/−mice showed the same ability to concentrate urine as wild-type (WT) mice. On the other hand, Hyal2−/−mice had a significant delay in the diuretic response induced by an acute water load.

Conclusions: Results: Both NSAIDs significantly increased urine output and decreased urine osmolarity by days 7 - 14. Meloxicam significantly reduced total AQP2 in inner medulla (IM) tip to 64% and base to 63% of control. Ibuprofen decreased total AQP2 in IM tip to 76%, with no change in base. Meloxicam significantly increased the ratios of pSer256-AQP2 and pThr264-AQP2 to total AQP2 in IM tip (to 44% and 40%, respectively). Ibuprofen increased the ratio of pThr264-AQP2 to total AQP2 in IM tip but did not affect pSer256-AQP2 total AQP2. Both NSAIDs increased pSer256-AQP2 and pThr264-AQP2 ratios in IM tip and base. Ibuprofen increased UT-A1 levels in IM tip, but not base. NR3A, present in rat IM tip and base, was significantly decreased in the meloxicam and ibuprofen treated IM mice (37% and 20%, respectively), but unchanged in IM tip. AQP2 and UT-A1 abundances were decreased both in wild type (AQP2: 76%, UT-A1: to 62%) and NR3A−/− mice (AQP2: 52%, UT-A1: to 33%) by ibuprofen treatment. Meloxicam did not show any changes either in wild type or in NR3A−/− mice. Notably, ibuprofen treatment caused AQP2 and UT-A1 to decrease more in NR3A−/− mice than in wild type mice.

Conclusions: We conclude that NSAIDs reduce AQP2 abundance contributing to decreased urine concentrating ability. In compensation, p-AQP2 increases, resulting in increased AQP2 membrane insertion. The beneficial effects of NR3A may reflect the altered Ca2+ entry that could be limiting dephosphorylation of AQP2 and promoting improved water homeostasis.

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

FR-PO099

AMPK Activation Increases Urine Concentrating Ability in a Rat Model of Congenital Nephrogenic Diabetes Insipidus

Orhan EK, Huwien Ren, Lauren M. Lorocque, Janet D. Klein, Jeff M. Sands. Medicine, Renal Div, Emory Univ School of Medicine, Atlanta, GA.

Background: The urine concentrating mechanism is primarily regulated by vasopressin which activates NKCC2 and urea transporters to generate a hypertonic interstitium that promotes water reabsorption through AQP2. Congenital nephrogenic diabetes insipidus (NDI) is caused by vasopressin V2 receptor (V2R) mutations. Present treatment options are limited. We studied AMPK as an alternate pathway to stimulate transporters involved in urine concentration.

Methods: Tolbutam (10 mg/kg/day), a selective V2R antagonist, was given by oral gavage to rats for 4 days, +/- metformin (800 mg/kg/day). Urine volume and osmolarity were measured daily. Following sacrifice, kidneys were dissected into inner medullary tip, base and outer medulla, and UT-A1, AQP2, and NKCC2 were analyzed by Western blot. Immunohistochemistry was used to localize AQP2, pAQP2, pAMPK, and NKCC2.

Results: Tolbutam was used to produce a rat model of NDI. Urine volumes of tolbutam-treated rats increased 105% within 24 h. Metformin was used to stimulate AMPK as a candidate NDI treatment. Metformin decreased urine volume by 110% back to control levels in 3 days. Urine osmolarity in control rats (mean: 210 mOsm/kg) was decreased by tolbutam (mean: 1303 mOsm/kg, p<0.05) and returned to near control levels by metformin (mean: 2335 mOsm/kg, p<0.05). Metformin increased protein abundance of IM tip UT-A1 by 61% in tolbutam treated rats (p<0.05). IM tip AQP2 was also increased 44% but failed to reach statistical significance (p=0.057). In contrast, IM base UT-A1 and AQP2 protein levels were not changed with AMPK stimulation. Outer medullary NKCC2 abundance was increased 117% with AMPK stimulation in control rats (p<0.004) but not in V2R-blocked rats. Immunochemistry showed that AQP2 and p-AQP2Ser256 appear to be localized on the cell membrane with acute and chronic AMPK stimulation, both in control and V2R-blocked rats.

Conclusions: AMPK stimulation in V2R-blocked rats is able to reduce the urine concentrating defect by increasing UT-A1 and AQP2. These results indicate that specific AMPK pathway activators might provide a promising treatment for congenital NDI.

Funding: NIDDK Support

FR-PO107

Synaptic Modulation of Osmoregulatory Impulsivity in the Suprachiasmatic Nucleus

Fernandes dos Santos.

Funding: NIDDK Support
FR-PO099

The Role of Klotho in Renal Sodium and Water Transport
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Background: Klotho (Kl), a transmembrane protein hormone, counteracts aging. Aging is often paralleled by dehydration, which could promote age-related disorders, because it decreases renal KI protein abundance, as well as increasing plasma osmolarity, antidiuretic hormone (ADH), aldosterone, and 1,25 vitamin D. ADH and aldosterone decrease Kl transmembrane in HEK293 cells and are elevated in the sera of Kl knockout mice. We explored the effects of Kl deficiency on renal transporters.

Methods: 8-12 week old male Kl−/−, Kl−/- and Kl+/- mice (n=6/group) were fed standard mouse chow and given to aquatic access to tap water. We evaluated serum levels of Na, K, Cl, Mg, creatinine and urea. We immunoblotted for sodium/hydrogen exchanger isoform 3 (NHE3), renal outer medullary potassium channel (ROMK), the Na-K-Cl cotransporter (NKCC2), alpha subunit of the epithelial sodium channel (αENaC) and aquaporin 2 (AQP2) measured in many clinical water-balance disorders as a potential biomarker for diagnosis and treatment. However, Kl knockout mouse present reduced sensitivity to elevated plasma aldosterone levels with no increase in oENaC or ROMK protein expression. A lack of Kl can deregulate the adaptive response (FAPESP).

Results: Data are mean±SEM.

<table>
<thead>
<tr>
<th>Kl−/−</th>
<th>Kl−/-</th>
<th>Kl+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>25.1±3.4</td>
<td>24.5±3.0</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>148±6.0</td>
<td>144±0.6</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.6±0.2</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>114±1.4</td>
<td>111±1.5</td>
</tr>
<tr>
<td>Mg (mg/dL)</td>
<td>1.6±0.1</td>
<td>1.7±0.0</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>50.5±3.3</td>
<td>52.0±2.1</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.1±0.0</td>
<td>0.1±0.0</td>
</tr>
<tr>
<td>NHE3*</td>
<td>99.1±1.1</td>
<td>92.5±2.2</td>
</tr>
<tr>
<td>ROMK*</td>
<td>99.3±2.4</td>
<td>92.3±4.7</td>
</tr>
<tr>
<td>KCC2*</td>
<td>97.5±1.1</td>
<td>97.8±1.4</td>
</tr>
<tr>
<td>oENaC*</td>
<td>99.0±4.3</td>
<td>98.0±9.0</td>
</tr>
<tr>
<td>AQP2*</td>
<td>98.5±0.8</td>
<td>98.3±0.4</td>
</tr>
<tr>
<td>pGSK3β*</td>
<td>100.0±7.7</td>
<td>98.3±0.7</td>
</tr>
</tbody>
</table>

* p<0.05 vs. Kl−/− and Kl−/-; *% Kl−/− protein expression

Conclusions: In Kl knockout mice, there seems to be normal regulation of NKCC2 and trafficking of AQP2 to the apical plasma membrane in response to ADH. However, Kl knockout mouse present reduced sensitivity to elevated plasma aldosterone levels with no increase in oENaC or ROMK protein expression. A lack of Kl can deregulate the adaptive response (FAPESP).

FR-PO101

Inhibition of EGFR Activity Increases Aquaporin 2 Phosphorylation and Increases Water Reabsorption in Lithium Treated Mice
Pui Cheung, Naohiro Nomura, Anil V. Nair, Hua Ann Jenny Lu, Richard Bouley, Dennis Brown. Medicine, Massachusetts General Hospital, Boston, MA.

Background: Impairment of vasopressin (VP) receptor type 2 signaling in the kidney is detrimental to water homeostasis. However, strategies targeting cAMP signaling to treat diseases associated with water balance have so far been unsuccessful in humans, prompting a search for alternative pathways that modulate AQP2 trafficking.

Methods: The effect of erlotinib (Erl) oral gavage in a lithium induced nephrogenic diabetes insipidus mice model was analyzed by measuring urine volume and osmolality. The effect of Erl on aquaporin 2 trafficking and expression in kidneys was studied by immunostaining and western blot analyses. EGFR and Erl regulation of AQP2 trafficking and phosphorylation were studied using selective kinase inhibitors and phospho-specific antibodies on AQP2-expressing LLC-PK1 cells.

Results: Erl alone had only a subtle effect on AQP2 trafficking, but it exerted a significant antagonizing effect on VP-induced AQP2 phosphorylation and membrane accumulation. Conversely, erlotinib (Erl), an EGFR inhibitor, led to a VP-independent increase of apical AQP2 accumulation in collecting ducts, and significantly reduced urine volume by more than 40% after 4 days of treatment in lithium-induced NDI mice. Erl enhanced AQP2 plasma membrane localization in cells by increasing AQP2 exocytosis and decreasing endocytosis. This effect was cAMP, cGMP, and PKA independent. Despite apparently bypassing cAMP pathways, Erl resulted in AQP2 phosphorylation in a dose dependent manner at serine 256, an essential step in VP-induced AQP2 membrane accumulation. We propose that EGFR has a tonic inhibitory effect on VP action, and that relief of such inhibition enhances AQP2 phosphorylation and results in membrane accumulation.

Conclusions: We showed a crosstalk between EGFR and VP in the modulation of AQP2 trafficking. EGFR inhibition increases AQP2 membrane expression bypassing the canonical VP/CAMP/PKA pathway and ameliorates lithium-induced NDI in mice. This study improves our understanding of the diversity of mechanisms that regulate water reabsorption in the body, and uncovers a novel pathway for potential therapeutic targets for NDI.

Funding: NIDDK Support

FR-PO102

ChiP-seq Analysis of Genomic Binding Sites for the Transcription Factor E11 in mmpCkd Cells
Hyun Jun Jung, Viswanathan Raghu Ram, Jae Wook Lee, Mark A. Knepper. Systems Biology Center, NHLBI, NIH.

Background: Collecting duct cells selectively express a number of transport proteins (aquaporins and ion channels) vital to water and electrolyte balance. Previous studies of tissue-specific gene expression in collecting duct cells have implicated Ets family transcription factors (TFs) (Yu et al. PNAS 2009;106:2441). We integrated data from prior proteomics and transcriptomics studies of mouse mpkCCD cells using Bayes’ Rule to create a probability-based ranking of all known TFs with regard to likelihood of a role in collecting duct-specific gene expression. Among the top-ranked TFs were several Ets family TFs including E11.

Methods: To identify genomic binding sites for E11 in mmpCkd cells, we carried out ChiP-seq analysis using an antibody successfully employed in the Mouse ENCODE Project. The mmpCkd cells were treated with the vasopressin analog dDAVP (100pM) for 24 hr prior to crosslinking and chromatin immuno-precipitation (ChiP) (n=3). DNA libraries were prepared from immunoprecipitated DNA and sequenced using an Illumina HiSeq 2000 sequence to identify TF-enriched genomic regions. Control ChiP was carried out with nonspecific IgG.

Results: The analysis (MACS peak-calling software) identified >2000 binding sites seen in all three replicates and not seen in IgG-only controls. The identified sites mapped to within 2000 bp of annotated transcription start sites (TSSs) of several genes whose transcript abundances were previously demonstrated to be regulated by vasopressin including Id3, Tgfb1, Nfkb1 and Spag9 (Sanches et al. Plos One 2011;6:10110). There was no E11 binding in the vicinity of any aquaporin or any ENaC subunit, indicating that any role of E11 in regulating these targets is likely to be indirect. However, E11 binding was mapped to additional TFs that are predicted to bind within 1000 bp upstream of TSSs for aquaporin-2, β-ENaC or γ-ENaC (Genomatix motif analysis). These TFs were C/EBP, Gata3, Sox4, Junb, Sp1, Sp3, Gabpa, Nkhi1, Hmxbox1, Breb1 and Rrma.

Conclusions: These data provide an initial step in identification of the transcriptional network that determines cell-type-specific expression in renal collecting duct cells.

Funding: Other NIH Support - NHLBI Intramural Research Program
Deletion of Aquaporin 11 in Transgenic Mice prior to Post-Natal Day 12 Results in Proximal Tubule Injury and Cyst Formation 

Soren Nielsen,1 Mads Vammen Damgaard,1,2 Michael R. Rutzler,1 Robert A. Fenton,2 Aleksandra M. Rojek,3 Dept of Health Science and Technology, Aalborg Univ, Aalborg, Denmark; 1Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark.

Background: AQP11 is expressed in the proximal tubule (PT). Neutone AQP11 KO mice show PT vacuolization and cysts, resulting in renal failure and death. This study examined whether the kidney injury is important for PT injury and cyst formation, and whether the cyst formation is related to the recycling of AQP11 to PT, as reported in the literature (J Am Soc Nephrol. 16: 1985, 2005), the expression of Casps was examined by real-time PCR in the kidney of AQP11 null mice before the polycyst development. We speculated that cisplatin may play an important role in the development of cisplatin nephrotoxicity. The enhancing the AQP11 expression in the kidney will be a renoprotective strategy in cisplatin nephrotoxicity.

Funding: Government Support - Non-U.S.

FR-PO106 Development of a Model on Chronic SIADH: Effect of Water Challenge and Treatment on Behavior, Learning, Memory and Brain Edema 

Marta Tejedor, Ana Duran Vila, Carmen Grande, Margarita Fernandez, Teba Gonzalez, Maria Melendo, Ana Morales, Cristina Vila, Juan Carlos Jado, Ignacio Lizardo, Alberto Tejedor Jorge, Nephrology, Hospital_Gregorio_Mara, Madrid, Spain.

Background: AIM: to develop a model on chronic SIADH and study the effects of acute water overload on behavior, brain edema and response to treatment.

Methods: We induced chronic SIADH by daily injection of ddAVP and water over a 3-5 day period to balb-c mice. We induced acute on chronic SIADH by giving an acute i.p. water challenge of 5% of body weight. We assessed behavioral changes by filming spontaneous ambulations of mice and under challenge conditions in a Morris water maze. We also studied brain edema by means of continuous Perfusor gradients to fraction grey and white brain substance. We administered tolvaptan to evaluate their effects in the abovementioned conditions.

Results: ddAVP administration alone was able to induce significant changes in spontaneous behavior despite minimal changes in natriuresis (3%)(2). These changes were earlier and more severe if a chronic water overload was given. Overall, learning and memory improved over time with training, measured by times of resolution (p<0.004) and trajectory (p<0.002) in a water maze. This was more evident in the control group than in the SIADH group (learning (p=0.06), memory (p=0.08)). The mean trajectory length to resolve the maze was 185.5±5 cm in the control group, 360±44 cm in SIADH with no acute water overload (p<0.05) and 808±94 cm in SIADH with an acute water challenge of 5% (p<0.05). Treatment with tolvaptan significantly shortens the length of the trajectory to nearly baseline values. The SIADH group who received a 5% water challenge developed significant brain edema which was reduced by tolvaptan. No significant changes were seen in animals who did not receive the water challenge. An acute water overload of 5% in SIADH was equivalent to a 10% one in controls, as shown by similar worsening in the water maze.

Conclusions: ddAVP injection alone is enough to induce subtle behavioral changes, even in the absence of significant hypotension. Acute on chronic SIADH significantly worsens brain edema and resolution of a water maze, and such changes can be reverted by tolvaptan.

Funding: Government Support - Non-U.S.

FR-PO107 Warburg-Like Proliferation Underlies Lithium-Induced Nephrogenic Diabetes Insipidus 

Teun de Groot, Peter M.T. Deen, Mohammad Alsady, Dept of Physiology, Radboud Univ Medical Center, Netherlands.

Background: Lithium is the first-choice medication for treatment of bipolar disorders and is used by 0.1% of the western population. Unfortunately, lithium treatment is associated with development of severe renal side effects. In approximately 50% of treated patients, lithium causes an urinary concentrating defect, which develops in 20% of patients into symptomatic Nephrogenic Diabetes Insipidus (NDI). This disorder is characterized by polyuria and polydipsia and is caused by downregulation of AQP2 water channels in principal cells of the renal collecting duct. Furthermore, lithium induces proliferation of the renal collecting duct and in vivo. Cell proliferation is often characterized by aerobic glycolysis (Warburg effect). Here, we investigated whether lithium may induce Warburg-like aerobic glycolysis and whether inhibition of this Warburg effect may rescue lithium-induced-NDI (Li-NDI).

Methods: Polarized mouse cortical collecting duct (mCCkD) cells were cultured as a 2D transwell model and exposed to lithium chloride on the apical side (10 mM) and basolateral side (1 mM) to mimic clinical conditions in patients. C57BL/6J mice were fed a normal rodent diet or a diet with lithium chloride in a concentration of 40 mM/kg of chow for the last 48 hours of the experiment, mice were housed in metabolic cages in order to determine water intake and urine output/osmolality during the last 24 hours.

Results: Lithium induced proliferation of mCCkD cells as shown by increased levels of the proliferation markers PCNA and cyclin D1. In addition, lactate and succinate, main products of the Warburg effect were increased in lithium-treated mCCkD cells and mice. This was accompanied by a decrease in the ratio of phospho-pyruvate dehydrogenase (pPDH)/PDH, confirming the induction of aerobic glycolysis by lithium in mice. Interestingly, inhibition of lithium-induced glycolysis with 2-deoxyglucose (2DG) attenuated lithium-induced AQP2 downregulation in mCCkD cells.

Conclusions: Our results reveal that lithium induces aerobic glycolysis in mCCkD cells and mice. Targeting of aerobic glycolysis with 2-deoxyglucose rescued lithium-induced AQP2 downregulation and may represent a potential therapy for Li-NDI.

Funding: Government Support - Non-U.S.
Machinery (kinase inhibitor (Bethesda, MD; Evolutionary Physiology and Biochemistry, St. Petersburg, Russian Federation; Pathways FR-PO109 J Am Soc Nephrol 26: 2015)

Mechanism involved in remodeling of the CCD to restore water homeostasis as a part of vasopressin escape.

Sequence depths were 40-65 million reads, with 80% of reads mapping to Ensembl genes were used for differential-expression analysis.

Universe of Lausanne, Lausanne, Switzerland; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER); Gobierno de Aragón, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER).

Funding: Government Support - Non-U.S.

Background: Vasopressin escape is a protective mechanism that limits hyponatremia in the syndrome of inappropriate antidiuresis (SIADH). In vasopressin escape, transcripts of aquaporin-2 and aquaporin-3 were significantly downregulated at day 1, 2, and 4. Among downregulated transcripts were transcription factors (Hes1, Hmx2, Hosb5, Hosb6, Hosb7, Jun, and Fox3) and a cyclin-dependent kinase inhibitor (Cdk1b).

Methods: FR-PO111 Mouse Monocarboxylate Transporter 9 Functions as a Urate Transporter Promu itself, Radikul. Otake, Motoshik Ouchi, Naohiko Anzai. Dept of Pharmacology and Toxicology, Dokkyo Medical Univ School of Medicine, Mibu, Tochigi, Japan.

Background: Monocarboxylate transporter 9 (MCT9/SLC16A9) has been suggested to be involved in the onset of hyperuricemia or gout by genome-wide association studies (GWAS). Since no experimental data about MCT9 function has been reported, we tried to clarify its physiological roles.

Results: The expression of SLC16A9 was investigated by quantitative RT-PCR (qRT-PCR) against human tissue cDNAs. Using oocyte expression system, we injected mouse MCT9 (mMCT9) cRNA to perform the functional characterization of mMCT9.

Methods: The expression of SLC16A9 was investigated by quantitative RT-PCR (qRT-PCR) against human tissue cDNAs. Using oocyte expression system, we injected mouse MCT9 (mMCT9) cRNA to perform the functional characterization of mMCT9.

Results: mMCT9 cRNA injection did not cause hyperuricemia in mice. However, mMCT9 cRNA injection resulted in a significant decrease in the plasma uric acid levels and increased plasma levels of several phosphatidylcholine and sphingomyelin species; and (iv) a significant reduction in plasma carnitine levels, a significant decrease in the expression levels of carnitine palmitoyl transferase (CPT1) and crestdinase, a significant decrease in the expression levels of carnitine palmitoyl transferase (CPT1) and crestdinase. These results revealed a separate, hitherto undescribed heterozygous mutation in SGLT2 (c.265G>A; p.Glu89Lys) in a patient with juvenile cataracts, microcornea and glucosuria. While the MCT12 mutation co-segregated with the eye phenotype, poor correlation with the glucosuria phenotype questioned a pathogenic role of the mutation in the kidney. Here we show that MCT12 resides on basolateral membranes of proximal tubule epithelial cells. Therefore, MCT12-mediated cellular creatine efflux contributes to the kidney phenotype.

Results: Results revealed 13 genes whose expression was relevant for the AQP2 redistribution. One of them is a recently identified member of the cyclin-dependent kinase family. Its knockdown blocks the AQP2 translocation and simultaneously increases the AQP2 protein abundance.

Results: Results revealed 13 genes whose expression was relevant for the AQP2 redistribution. One of them is a recently identified member of the cyclin-dependent kinase family. Its knockdown blocks the AQP2 translocation and simultaneously increases the AQP2 protein abundance.

Conclusions: Our approach contributes to understanding the molecular mechanisms underlying the control of AQP2 trafficking and to identify potential therapeutic targets for the treatment of diseases caused by or associated with aberrant AVP-mediated water reabsorption such as diabetes insipidus or heart failure.

Funding: Government Support - Non-U.S.

Conclusions: These results suggest that the local renal circadian clock control a variety of metabolic processes both on the intra-renal and systemic levels.

Funding: Government Support - Non-U.S.

FR-PO110 The Circadian Clock in the Kidney Controls Several Essential Metabolic Pathways Nyworks, Fuster, Fuster, Abalos, Virgili, Alfonso, and Inatomi.

The circadian clock is the central mechanism for regulating body metabolism and energy homeostasis. However, the role of the intrinsic circadian system in the control of renal and/or systemic metabolic pathways remains elusive.

Results: These results suggest that the local renal circadian clock control a variety of metabolic processes both on the intra-renal and systemic levels.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO113
NaDC1 Knockout: Effects on Blood Pressure and Urine pH
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Background: NaDC1 reabsorbs filtered citrate (Cit); thus its regulation is important in preventing calcium nephrolithiasis. Importantly NaDC1 reabsorbs other Krebs cycle intermediates such as succinate (Suc) and αKG. Recently Suc and αKG have been found to be potent in paracrine signaling as their luminal presence stimulates distal nephron G-protein coupled receptors GPRC9R and GPCR9 respectively. Luminal Suc via GPCR9 has been found to stimulate renal renin; while αKG via GPCR9 stimulates bicarbonate secretion by type I intercalated cells. The purpose was to determine whether knockout of NaDC1 produces hemodynamic or urine pH changes that might be anticipated by activation of these receptors.

Methods: Adult NaDC1 KO, heterozygous (Het), and wild-type mice (WT), under normal or acid diet for 72 hr, were studied using standard clearance techniques. After anesthetization different measurements of hemodynamic parameters were determined and rats were allowed to recover for 24 hr. Urine, blood and tissue were collected for assessment of NaDC, Cit, αKG, and pH.

Results: NaDC1 KO produced 2, 4, and 10-fold increases in urine Suc, Cit, and αKG, respectively. There was substantial residual reabsorption of Cit and Suc in KO mice, indicating other transporters involved in reabsorption of these substrates. Despite the increase in normal αKG there was no significant increase in urine pH (normal or acid diet); in fact on normal diet urine pH was lower in KO mice (5.10 ≤ 0.04 vs 5.90 ± 0.13 WT; p < 0.001). The lower urine pH in KO mice on normal diet may be a response to loss of potential driving force for increased Krebs cycle intermediate excretion. There was no change in the ability of KO animals to excrete acid. In regard to potential hemodynamic effects mediated by NaDC1 KO and increased urine Suc, no change in MAP was determined comparing WT, Het or KO either on normal or acid diet.

Conclusions: In sum, NaDC1 is responsible for significant reabsorption of normal αKG and Suc, but knockout of NaDC1 does not impair acid-base homeostasis or BP changes on normal or acid diets. Funding: NIDDK Support

FR-PO114
The Ablation of Dendritic Cells Prevents the Upregulation of the Intrarenal Renin-Angiotensin System and Renal Sodium Transporters in Response to Angiotensin II and High Salt Diet
Patricia A. Araras,1 Daniel E. Hevia,1 Carolina E. Prado,1 Eugenia L. Fuentes,1 Rodrigo Pacheco,1 Luis F. Michea.1 1Univ de Chile, Chile; 2Fundación Ciencia y Vida, Chile.

Background: Blood pressure depends on the renal sodium reabsorption mediated by the tubular transporters that are modulated by the intrarenal renin-angiotensin system (iRAS). Angiotensin II (AngII) and a high salt diet (HS) cause hypertension (HT) and the hemodynamic effects mediated by NaDC1 KO and increased urinary Suc, no change in MAP was determined comparing WT, Het or KO either on normal or acid diet.

Methods: CD11c DOG mice, for selective loss of DCs (CD11cLy), and CD11c COL% mice were euthanized 14 days after induction of HTN. Heart weight/body weight (H/BW) ratios were calculated and kidney leukocyte infiltration was analyzed by flow cytometry. We conclude that DCs are required for the modulation of iRAS and TLR4, renal NF-κB and plasma IL-6.

Conclusions: Interleukin-6 Inhibition Attenuates Hypertension and Proteinuria in Dahl Salt-Sensitive (SS) Rats
Shireen Hashmat,1 Scott K. Van Why,1 Shieen Hashman,1 Justin M. Abais-Battad,1 Hayley Lund,1 Scott K. Van Why,2 David L. Mattson. 1Pediatrics, Medical College of Wisconsin; 2Physiology, Medical College of Wisconsin, Milwaukee, WI.

Background: Interleukin-6 (IL6) inhibits the inflammatory response to injury. The current study is to determine whether prior splenectomy (SPLX) significantly alters tissue inflammation; however the effect of SPLX on HTN remains unclear. Therefore, the objective of the current study is to determine whether prior splenectomy influences the development of HTN in 2 different mouse models.

Methods: Mice underwent SPLX or sham surgery 7 days prior to the induction of HTN using angiotensin-II (AngII, 400ng/kg/d) or nitric oxide synthase inhibition using L-NAME (30mg/kg/d). Systolic blood pressure (SBP) was measured by tail-cuff manometer daily and mice were randomized 14 days after induction of HTN. Heart weight/body weight (H/BW) ratios were calculated and kidney leukocyte infiltration was analyzed by flow cytometry.

Results: Mice with prior SPLX+AngII had significantly lower (P<0.05) SBP at both week 1 (148±7) and week 2 (135±7) as compared to Sham+AngII (174±7/173±7mmHg). Similarly, SPLX+AngII mice had significantly smaller (P<0.007) H/BW (4.3±0.3) as compared to Sham+AngII treated mice (5.2±0.4mg/g BW). Interestingly, no difference was observed in renal CD45+ (9.8±3 vs 10.6±3x10^5 cells/g, P=0.64) or CD3+ T-cell infiltration (8.8±0.2 vs 9.6±0.1x10^5 cells/g, P=0.64) between Sham+AngII and SPLX+AngII treated mice respectively. Furthermore, SPLX did not appear to influence the development of L-NAMe HTN. SPLX+L-NAMe mice had similar P=0.84 SBP (145±9mmHg) as the Sham+L-NAMe group (146±4mmHg, n=6) after 2 weeks. Relative heart weights were also similar (P=0.45) between SPLX+L-NAMe (4.9±0.2) and Sham+L-NAMe treated mice (4.8±0.3mg/g BW).

Conclusions: Our data suggests that the full pressor response to AngII is dependent on the spleen. However, the effect of the spleen appears to be independent of renal inflammation. Moreover, the protective effect of the spleen is specific to AngII-dependent HTN and does not appear to be generalizable to all mouse models of hypertension. Further studies are needed to understand the putative link between lymphoid organs (such as the spleen), renal inflammation, and the development of chronic HTN.

FR-PO116
Salt Overload Promotes Severe Renal Injury and Activates AngII, Renal NF-κB and Other Components of Innate Immunity in a Model of Arterial Hypertension
Víctor F. Ávila,1 Orestes Foresto-Neto, Simone CA Arias, Camila Fanelli, Flavia G. Machado, Mariliza V. Rodrigues, Claudia R. Sena, Viviane D. Faustino, Líssiény CT Rempel, Gizely CS Moreira, Vivian L. Viana, Denise M. Malheiros, José E. Krieger, Roberto Zutz, Clarice K. Fujihara. 1Univ de Sao Paulo, Sao Paulo, Brazil.

Background: Hypertension (HTN) develops in rats that received the NF-κB inhibitor pyrrolidinedithiocarbamate (PDTC) during lactation. High salt (HS) and uninephrectomy (UNx) aggravate HTN, increase renal AngII and lead to severe renal injury. Here, we further investigated the mechanisms of renal injury and the effect of Lactotransferrin (L) in this model.

Methods: Munich-Wistar pups received PDTC (PDTClact), or no treatment (C) during lactation. At 10 weeks of age, all rats underwent UNx and were divided in: C, given normal salt diet (NS); PDTClact; given HS; PDTClact+HS; given HS and L; 50 mg/kg/d. After 3 mo, we assessed: tail-cuff pressure (TCP, mmHg), glomerulosclerosis (GS), interstitial collagen (COL), arteriolar lesions (AL), interstitial AngII+, macrophages (Mo) and lymphocytes (Ly), cells/mm², TLR4 and nuclear NF-κB (nC) in serum IL-6 (ng/mL).

Results:

<table>
<thead>
<tr>
<th></th>
<th>PDTC l</th>
<th>PDTC l+HS</th>
<th>PDTC l+HS-L</th>
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<tbody>
<tr>
<td>TCP</td>
<td>144±2</td>
<td>167±3</td>
<td>195±4</td>
</tr>
<tr>
<td>GS%</td>
<td>2±1</td>
<td>1±1</td>
<td>12±2*</td>
</tr>
<tr>
<td>AL%</td>
<td>0±0</td>
<td>1±1</td>
<td>175±5*</td>
</tr>
<tr>
<td>AngII+</td>
<td>2±1</td>
<td>2±1</td>
<td>7±1a</td>
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<tr>
<td>Me</td>
<td>33±3</td>
<td>34±4</td>
<td>140±21a</td>
</tr>
<tr>
<td>Ly</td>
<td>37±3</td>
<td>43±4</td>
<td>141±25*</td>
</tr>
<tr>
<td>COL%</td>
<td>2.8±0.2</td>
<td>2.8±0.4</td>
<td>7.3±1.2</td>
</tr>
<tr>
<td>NF-kB</td>
<td>1.0±0.2</td>
<td>1.7±0.4</td>
<td>2.6±0.5</td>
</tr>
<tr>
<td>TLR4</td>
<td>23±3</td>
<td>32±3</td>
<td>40±4</td>
</tr>
<tr>
<td>TLR4-l</td>
<td>1.0±0.1</td>
<td>1.5±0.4</td>
<td>2.9±0.7*</td>
</tr>
</tbody>
</table>

Means±S.E., *P<0.05 vs C, **P<0.05 vs PDTC l, ***P<0.05 vs PDTC l+HS-L

HS+UNx led to severe HTN and renal vascular injury, intense Mo Ly infiltration, increased AngII+ and TLR4, and NF-kB activation, with increased plasma IL-6, all correlating positively with TCP. L strongly attenuated renal damage, normalizing renal TLR4, renal NF-kB and plasma IL-6.

Conclusions: In PDTC l, renal injury caused by HS+UNx involves activation of renal AngII and innate immunity, including the NF-kB system. FAPESP/CNPq.
Methods: Experiments were performed to assess the potential role of IL-6 in Dahl hypertensive rats. In these experiments, rats were administered anti-IL-6 neutralizing antibody (anti-IL-6; 4 μg/day; IP: R&D Systems, Minneapolis, MN) or normal goat IgG control (4 μg/day, IP) for 11 days.

Results: The MAP and urine protein excretion rates (Up) were similar between the groups of SS rats (n=13-16/group) when fed low salt (0.4% NaCl) chow. Following 11 days of high salt (4% NaCl) chow, the rats receiving anti-IL-6 demonstrated a significant reduction in intraocular IL-6 in the renal medulla compared to control group (954±133 pg/ml vs 1802±336 pg/ml). Moreover, the increase in MAP following 11 days of 4% NaCl intake was significantly attenuated in treated (MAP=138±3 mmHg) vs control group (MAP=172±3 mmHg). Anti-IL-6 also attenuated IS-induced expression of CCL5 (4-fold), TNFα mRNA expression 1.25-fold. Moreover, the increase in MAP following 11 days of 4% NaCl intake was significantly attenuated in treated (MAP=138±3 mmHg) vs control group (MAP=172±3 mmHg). Anti-IL-6 also attenuated IS-induced expression of CCL5 (4-fold), TNFα mRNA expression 1.25-fold.

Conclusions: These results suggest that IL-6 may play an important role in the development of SS hypertension and end-organ damage by mediating the infiltration of leukocytes into the kidney.

FR-PO119
Indoxyl Sulfate Uregulates Aortic Expression of (Pro)renin Receptor by Reactive Oxygen Species and Activation of AhR/NF-κB Pathway in Vascular Smooth Muscle Cells
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Background: Chronic kidney disease (CKD) is considered major causes of death in cardiovascular disease (CVD) patients. (Pro)renin receptor (PRR) is significantly expressed in the vascular smooth muscle cells (VSMCs).

Methods: CKD rats and IS-administrated rats were subjected for in vivo experiments. Human aortic smooth muscle cells (HASMCs) was treated with or without indoxyl sulfate (IS).

Results: Indoxyl sulfate (IS) significantly increased NOS and PRR expression at all time points. IS significantly activated AhR and NF-κB in HASMCs.

Conclusions: IS stimulates aortic expression of PRR and NOS, and hence, may contribute to the physiological response to high dietary salt and salt-sensitive hypertension.

FR-PO120
Role of Skin and Endothelial Surface Layer Heparan Sulfates in Blood Pressure Regulation
Rik Hg Olde Engberink,1 Naomi Van Vliet,2 Bert-Jan Van den Born,3 Ed van Bavel,4 Liffert Vogt.1 Nephrology, AMC, Amsterdam, Netherlands; 2Laboratory of Genetic Medicine, AMC, Amsterdam, Netherlands; 3Vascular Medicine, AMC, Amsterdam, Netherlands; 4Biomedical Engineering and Physics, AMC, Amsterdam, Netherlands.

Background: Besides the skin, the endothelial surface layer (ESL) contains many glycosaminoglycans (GAGs) that can osmotically inactivate Na+ and may affect blood pressure (BP). GAGs regulate heparan sulfate (HS) polymerization, the predominant ESL GAG. In mice with heterozygous loss of EXT1 and EXT2 (EXT), and wildtype (WT) mice, we investigated the role of HS in the skin and ESL in BP regulation after an acute and chronic NaCl load.

Methods: We investigated BP effects of a 7-d normal (0.3%), NSD and high (8.0%) HS). NaCl diet, with tail cuff measurements, and an acute 1.8% NaCl load (8 μl/g) with intracardiac measurements. We used intravital microscopy to estimate ESL thickness in <40 µm crenal vessels on both diets. We used high performance liquid chromatography-mass spectrometry to measure skin HS disaccharide concentration.

Results: Baseline BP was equal in WT and EXT mice (p=0.9), with no difference between NSD and HSD. Relative to WT, acute NaCl infusion increased BP in EXT mice (p=0.02), while heart rate remained equal (p=0.5). After a NSD and HSD, EXT mice had a 78% reduction of ESL thickness compared to WT mice (Fig A). HSD increased ESL thickness in WT, especially in 20-40 µm vessels, but not in EXT mice (Fig BC). Skin HS concentration and sulfation patterns were equal between diets in WT mice (Fig DE). On NSD, EXT mice had more highly sulfated HS compared to WT (Fig DE). Ext mice on a HSD had the highest skin HS concentration, of which most were low-sulfated.

Conclusions: An intact ESL is pivotal to prevent a BP increase during acute NaCl excess. Skin GAGs may be particularly important to prevent detrimental NaCl effects on the long-term, especially when the ESL is damaged.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 383A
Hypertension: Basic

FR-PO122

Adenosine A1 Receptor Exacerbates Water-Sodium Retention in Deoxycorticoesterone Acetate-Salt Hypertensive Mice Janet Yanqing Mei,1 Xiaoxiao Shi,1 Dongli Tian,1 Xiaoyan Peng,1 Wei Chen,2 Limeng Chen.1
1Nephrology Dept, Peking Union Medical College Hospital, Beijing, China; 2Cardiology Dept, Peking Union Medical College Hospital, Beijing, China

Background: Adenosine receptor (A1AR) engages in tubuloglomerular feedback; its activation is followed by increased secretion of atrial natriuretic peptide (ANP) in the heart. We aim to study the function of A1AR in water-sodium retention.

Methods: DOCA-salt hypertensive model was established by removal of left kidney, implantation of a DOCA pellet (200mg, 60-day release), and feeding with high salt diet (8%NaCl). Arterial blood pressure and heart rate were measured by tail-cuff method. Urine samples were collected using metabolic cage. The CD73 (an adenosine synthetase), A1AR, ANP and Corin (a protease cleaves pro-ANP, producing ANP) mRNA expression were measured by real-time PCR.

Results: Wildtype DOCA-salt mice showed higher blood pressure (124.7±20.3 vs. 105.8±14.1 mmHg, P<0.01), slower heart rate (562.0±90.8 vs. 681.5±90.1, P<0.01), and increase in 24h urine output (3606.2±2359 vs. 1399:752 ml, P<0.01). The adenosine pathway was activated in DOCA-salt mice evidenced by increased CD73 (2.22 and 17.7 times increased expression in kidney and heart, P=0.034 and 0.009). The cardiac mRNA expression of ANP and Corin were also significantly higher in DOCA-salt mice (176.6 and 30.93 times increased expression, P=0.030 or 0.005). The A1AR mice showed no significant changes in blood pressure or heart rate between DOCA-salt and sham group. The elevation of 24h urine output (7003:3742 vs. 3606.2±2359 ml, P=0.031) and 24h sodium excrection (1246.5±860.5 vs. 1479.7±48.9 mmol/d, P=0.028) was more prominent compared to wildtype DOCA-salt mice. There was no change in either ANP or Corin mRNA expression.

Conclusions: A1AR may exacerbate water-sodium retention in salt sensitive hypertension. The reduction in glomerular hyperperfusion and hyperfiltration through podocyte injury, abnormally increased filtered load of Na and Cl transport and induces neuroexcitation, both of which may increase blood pressure. Here we tested the hypothesis that fructose-fed rats fed a high salt diet is a critical component of fructose-induced salt-sensitive hypertension.

FR-PO123

Dietary Fructose Increases Renal Sympathetic Nerve Activity in Response to High Salt Diet in Awake Freely Moving Rats Noreen F. Rosal,1,2 Lorenz Sellin,1,2 Pablo A. Ortiz,1,2 William H. Beierwaltes.1,2
1Nephrology, Wayne State Univ School of Medicine, Detroit, MI; 2Physiology, Wayne State Univ School of Medicine, Detroit, MI

Background: High consumption of fructose containing foods is increasingly prevalent. Fructose intake is associated with metabolic syndrome including hypertension. Fructose upregulates renal Na and Cl transport and induces neuroexcitation, both of which may increase blood pressure. Here we tested the hypothesis that fructose-fed rats fed a high salt diet will have higher plasma renin activity (PRA), renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) than glucose-fed rats on similar diet.

Methods: Male Sprague Dawley rats were instrumented for telemetric MAP and RSNA measurements. They were placed on 20% glucose (GF) or 20% fructose (FF) in drinking water. Blood pressure (BP) were measured for 3 weeks by radiotelemetry, starting one week prior to implantation. Histological and mRNA analysis were performed at the end of the observation period. Renal vascular function was evaluated in the isolated perfused kidney.

Results: Blood pressure in FF rats was 120.1±9.1 mmHg vs. 106.4±7.5 mmHg in GF rats (P<0.05). FF rats had higher plasma renin and MAP, however no differences were seen in heart rate. FF rats had higher RSNA than GF rats (P<0.05).

Conclusions: These indicate that, in podocyte injury, abnormally increased filtered load of Agt is reabsorbed via proximal tubular cells mainly dependently on melanin. In the present study, we tested whether melanin is involved in intrarenal AGT generation. For this purpose, we generated proximal tubule specific melanin knockout (KO) mice by crossing melanin-loxp, Ndr1-Cre, and Kap-Cre mice. Renal AngII contents were measured by radioimmunoassay.

Results: In melanin KO mice (n=12), renal melanin mRNA was decreased to 2.5% of that in control mice (n=16). Renal Agt staining was markedly diminished, with increase in urinary Agt in KO mice. However, renal Agt levels were similar between KO and control mice (108±11 vs. 101±17 fmol/g). We next tested the effect of melanin KO on intrarenal Agt generation in fructose-fed rats. Rats with abnormally increased filtered load of Agt in mice with podocyte-specific injury, by crossing with NEP25 mice. Control NEP25 mice (n=10) showed markedly intense renal Agt staining and enhanced renal Agt level (450±61). Melanin KO/NEP25 mice (n=12) showed diminished renal Agt staining and significantly attenuated renal Agt level (119±23, p<0.01). KO/NEP25 mice showed similar renin and Agt mRNA, and more presence of cRNA in the kidney.

Conclusions: These indicate that, in podocyte injury, abnormally increased filtered load of Agt is reabsorbed via megalin by proximal tubular cells and induces the inappropriate activation of intrarenal renin-angiotensin system, which may be involved in the progression of tubulointerstitial damage secondary to podocyte injury.

Funding: Government Support - Non-U.S.
Results: At baseline systolic BPs were similar in CNTF-KO and WT mice (119 ± 2 vs. 124 ± 1 mmHg). CNTF deficiency significantly attenuated BP increase under Ang II infusion (week 1: 139 ± 3 vs. 153 ± 3 mmHg; week 2: 151 ± 5 vs. 168 ± 4 mmHg; n = 19; P < 0.01). Strikingly, in the CNTF-KO group significantly less animals died of cardiovascular causes (4.2% (KO) vs. 29.2% (WT) P < 0.05). In accordance, end organ damage (cardiac hypertrophy, renal vascular fibrosis and tubulo-interstitial damage) was attenuated in the CNTF-KO group. In the isolated perfused kidney, pressor response to Ang II was significantly attenuated in CNTF-KO mice. Administration of CNTF (0.5nM) nearly restored the Ang II dependent pressor response. This effect was mediated through a JAK2/STAT3 dependent pathway as renal vascular fibrosis and tubulo-interstitial damage) was attenuated in the CNTF-KO group (3.4 ± 0.6 vs. 29.2% (WT) P < 0.001). Sodium excretion was unchanged (veh: 3.46 ± 0.6 vs. 3.38 ± 0.6 mmol/24h). There were no changes in proximal fractional reabsorption (Veh: 57 ± 2%, Veh: 59 ± 0.6%) and distal fractional reabsorption (Veh: 83 ± 3%, AII: 87 ± 2%). UMOD expression in the renal medulla was 3 fold higher in Ang II treated rats compared to vehicle rats.

Conclusions: Our data demonstrate that AngII increases UMOD expression and excretion independent of blood pressure and alterations in tubular reabsorption. These results suggest that the interaction of AngII with UMOD precedes Na+ transport alterations and therefore can be an important mechanism involved in the development of hypertension.

Funding: Government Support - Non-U.S.

FR-PO127
Angiotensin II AT1 Receptor Potentiates Prostaglandin E2 Vasconstrictor Effects
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Background: Prostaglandin E2 (PGE2) is a vasomodulator that has vasopressor and vasodepressor effects. Our previous results have demonstrated that sub-threshold concentrations of Ang II can synergize with PGE2 to modulate Na transport. The present study was performed to determine the mechanism of elevated blood pressure in ATRAP-KO mice after 5/6 Nx, plasma volume and Na/K measurements. On day 3 proximal and distal reabsorption were measured by metabolic cages for 24 h and urine was collected for UMOD and Na/K measurements. On day 3, proximal and distal reabsorption were measured by methylene blue injection and the renal medulla was harvested for determination of UMOD expression by western blot.

Results: Blood pressure was unchanged after 3 days of AngII (veh: 89 ± 1; AII: 81 ±1 mmHg). AngII treated rats had significantly increased UMOD expression compared with control rats (Veh: 17.6 ± 2.19; AII: 28.9 ± 3.6, mg/24h, p < 0.05). Sodium excretion was unchanged (veh: 3.46 ± 0.6; AII: 3.38 ± 0.6 mmol/24h). There were no changes in proximal fractional reabsorption (Veh: 57 ± 2%; AII: 59 ± 0.6%) and distal fractional reabsorption (Veh: 83 ± 3%, AII: 87 ± 2%). UMOD expression in the renal medulla was 3 fold higher in AngII treated rats compared to vehicle rats.

Conclusions: Our data demonstrate that AngII increases UMOD expression and excretion independent of blood pressure and alterations in tubular reabsorption. These results suggest that the interaction of AngII with UMOD precedes Na+ transport alterations and therefore can be an important mechanism involved in the development of hypertension.

Funding: Government Support - Non-U.S.
increased blood pressure and plasma volume after 5/6 Nx compared with WT mice. Therefore, endogenous ATRAP may exert a protective function against pathological blood pressure elevation in CKD.

FR-PO131
In Vivo Action of Angiotensin II Type 1a Receptor in Renal Injury Induced by Deoxycorticosterone Acetate-Salt Hypertension  
Mikako Hisamichi, Atsuko Romori,1 Takashi Sugaya,1 Daisuke Ichikawa, Kenjiro Kimura, Yugo Shibagaki.1 1Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; 1Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; 1Dept of Internal Medicine, Tokyo Takanawa Hospital, Tokyo, Japan.

Background: The AT1α receptor plays a major role in the renal action of Ang II and is expressed in vascular smooth muscle cells of the afferent arterioles. In this study, we investigated the morphological change in deoxycorticosterone acetate (DOCA)-salt hypertensive nephropathy in L-FABP-+/− mice to confirm the in vivo function of the AT1α receptor against renal damage due to hypertension.

Methods: To examine urinary L-type fatty acid binding protein (L-FABP) as an indicator of tubulointerstitial damage, we used healthy L-FABP transgenic mice in addition to disrupting the AT1α receptor gene (L-FABP−/− AT1α−/−). L-FABP−/− AT1α−/− and L-FABP−/− AT1α+/- mice were administered DOCA tablets plus 1% NaCl water for 28 days.

Results: In the DOCA salt hypertensive model with L-FABP−/− AT1α−/− (L-FABP−/− AT1α−/− DOCA), slight expansion of the glomerular area and tubulointerstitial damage were observed, but not glomerular sclerosis. In the AT1α knockout mice administrated DOCA-salt (L-FABP−/− AT1α−/− DOCA mice), glomerular sclerosis with expansion of the mesangial area was found, and the degree of tubulointerstitial damage was more severe compared with L-FABP−/− AT1α−/− DOCA mice. In L-FABP−/− DOCA mice, L-FABP+/- mice were significantly higher in the L-FABP−/− AT1α−/− DOCA mice than in the L-FABP−/− AT1α−/− DOCA. This renal damage induced in the L-FABP−/− AT1α−/− DOCA mice was significantly attenuated by reduction of blood pressure using Hydralazine. Activation of the AT1α receptor may contribute to myogenic response of the afferent arteriole involved in the renal autoregulatory mechanism.

Conclusions: In conclusion, kidneys without AT1α receptors exhibited an increased vulnerability to hypertension, and therefore activation of the AT1α receptor inhibited the transmission of the elevated systemic pressures to the glomeruli.

FR-PO132
Renal Blood Flow and Oxygenation During Renin-Angiotensin-Aldosterone System Activation – Two Sides of the Same Coin?  
René van der Bel,1 Aart J. Nedernev,2 Bram F. Coolen,2 Wouter V. Potters,1 Hein J. Verberne,1 Lottfert Vogt,1 Erik Stroes,1 C.T.P. (Paul) Krediet.1 1Internal Medicine, AMC, Univ of Amsterdam, Netherlands; 1Radiology, AMC, Univ of Amsterdam, Netherlands; 1Nuclear Medicine, AMC, Univ of Amsterdam, Netherlands.

Background: In chronic kidney disease, renal hypoxia and renin-angiotensin-aldosterone system (RAAS) activation may augment each other. Although renal oxygenation (RO) measured by Blood Oxygen Level Dependent (BOLD) MRI is not correlated to Glomerular Filtration Rate (GFR), recent data suggest that RO relates to inter-individual variability in RAAS. Further explore this we measured the effects of Angiotensin II (Ang-II) on renal blood flow (RBF) and RO in healthy humans.

Methods: After a 30 min baseline phase, 8 healthy volunteers (age 19-22 years) were subjected to continuous Ang-II infusion at 0.3, 0.9 and 3.0 ng/kg/min for 12 minutes per dose. RBF were assessed by BOLD and phase contrast MRI, respectively (Ingenia, 1.5T, 7.1%, p=0.016; 24±4.5%, p<0.001). RBF and RO varied proportionately (R=0.48, p=0.017).

Conclusions: Ang-II causes a dose dependent DRBF. The observed DRO seem to differ between cortex and medulla. Only for the cortex BOLD may provide an index of tissue perfusion.

FR-PO133
Chloride Contributes to Hypertension and Renal Injury in Aldosterone-Salt Treated Rats  
Takahiro Yamauchi, Shigehiro Doi, Toshiaki Doi, Kensuke Sasaki, Toshihito Ueno, Ayumu Nakashima, Takao Masaki. Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.

Background: Aldosterone-salt treatment is known to induce renal inflammation and play a role in the development of hypertension, as well as elevating blood pressure. In addition to sodium, chloride has recently been reported to be involved in renal damage, raising the possibility that sodium-bicarbonate may ameliorate renal injury and hypertension in the rats treated with aldosterone-salt combination.

Methods: Following a left nephrectomy, 8-week-old male Sprague-Dawley rats were implanted with an osmotic infusion pump and then allocated to the following 3 groups: 1) drinking a 1% NaCl solution with aldosterone infusion (NaCl-aldosterone treated group), 2) drinking a 1% NaClO solution with aldosterone infusion (NaClO-aldosterone treated group), and 3) drinking water with vehicle infusion. Blood pressure levels were measured by tail cuff method. After 8 weeks, the rats were sacrificed and their renal tissues examined by immunoblotting and immunohistochemistry.

Results: The NaCl-aldosterone group had higher blood pressure levels than the NaClO-aldosterone group. Protein expression of eNOS and Pendrin in the membrane fractions of the aldosterone increased in NaCl-aldosterone group compared with the NaClO-aldosterone group. In addition, the NaCl-aldosterone group had high protein levels of NCC and phosphorylated NCC in the whole protein and membrane fractions. On the other hand, the expression of inflammatory (CD3, CD68, IL17A, IL-23 receptor) and fibrotic markers (α-smooth muscle actin, collagen I) were greater in the NaCl-aldosterone group.

Conclusions: These findings suggest that chloride plays an important role in the development of NaCl-aldosterone-induced hypertension and renal injury.

FR-PO134
RAGE-DNA Aptamer Improves Aldosterone-Induced Renal Injury Possibly via Inhibition of Rac1-MR Axis in Mice with Hypertensive Nephropathy  
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Background: Advanced glycation end products (AGEs) stimulate the generation of reactive oxygen species (ROS) and subsequent enhancement various intracellular pathways through the interaction with receptor for AGEs (RAGE). Although AGEs-RAGE axis has been mainly investigated in diabetic nephropathy, its pathophysiological role in hypertensive nephropathy (HN) is unknown. In addition, recent evidence has suggested that aldosterone (ald) mineralocorticoid receptor (MR) system plays a crucial role for the pathogenesis of HN. In this study, we examined whether AGE-RAGE system could interact with ald-MR axis in deoxycorticosterone acetate (DOCA)-induced HN in mice. Further, we explored the inhibitory effects of DNA-aptamer directed against RAGE (RAGE-aptamer).

Methods: Uninephrectomized 8-week-old C57Bl/6J male mice were divided into three groups; 4% salt diet (control), 4% salt diet with DOCA (50mg/kg), and DOCA with hydralazine (Hyd). RAGE-aptamer constructed by SELEX method was continuously administrated with osmotic mini pump.

Results: DOCA elicited-UAE was independent of blood pressure. Renal ROS generation, RAGE protein expression and plasma carboxymethyl lysine (CML) levels were elevated in DOCA/salt mice. RAGE was colocalized MR in podocytes by immunohistochemical analysis. Further, GTP-bound Rac1 activation and MR overexpression were observed in DOCA/salt mice. DOCA-elicited increase in UAE, renal ROS generation and RAGE expression, plasma CML levels were improved by RAGE-aptamer independent of blood pressure. Interestingly, RAGE-aptamer suppressed GTP-bound Rac1 activity and MR activation in DOCA/salt mice.

Conclusions: AGES-RAGE axis and Rac1-MR pathway could be correlated with each other, which could lead to podocyte injury in HN. RAGE-aptamer may be a novel therapeutic strategy for the progression of HN.

FR-PO135
Dipeptidyl Peptidase-4 Inhibitor Ameliorates the Aldosterone-Induced Renal Fibrosis  
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Background: Renal fibrosis is considered a common outcome of a wide variety of chronic kidney diseases with diverse causes. However, no antifibrotic agent has been approved in clinical practice yet. In this study, we examined the effect of dipeptidyl peptidase-4 (DPP-4) inhibitor on aldosterone-induced fibrosis by aldosterone.

Methods: Human proximal tubular epithelial cells (HK2) were used to examine the inhibitory effect of DPP-4 inhibitor on aldosterone induced epithelial-mesenchymal transition (EMT). Besides, aldosterone infusion mice were used to evaluate the effect of DPP-4 inhibitor, linagliptin, on aldosterone induced renal fibrosis. Expression of TGF-β, OPN and molecules involved in EMT were examined using western blot and immunohistochemistry. Although AGEs-RAGE axis has been mainly investigated in diabetic nephropathy, its pathophysiological role in hypertensive nephropathy (HN) is unknown. In addition, recent evidence has suggested that aldosterone (ald)-mineralocorticoid receptor (MR) system plays a crucial role for the pathogenesis of HN.

Results: In vitro studies showed that aldosterone significantly increases the expression of TGF-β, OPN, and markers of the epithelial-mesenchymal transition in HK2 cells, while these effects were decreased in that treated with DPP-4 inhibitor. Similarly, the aldosterone-infused mice exhibited severe kidney fibrosis. The expression of TGF-β, OPN, vimentin and α-SMA were induced by aldosterone, and oral DPP-4 inhibitor ameliorated the kidney fibrosis and lessened the increase in fibrotic proteins without significant changes in blood pressures.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  Underline represents presenting author.
Mitochondrial Oxidative Stress-Activated Renal Local RCS Promotes the Expression and Function of NCC in Proteinuric Kidney Disease

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Background: The fluid retention and hypertension are common complications of kidney diseases, whose pathogenic mechanisms remain elusive.

Methods: Kidney tissues from mice subjected to albumin overload via i.p injection for 12 days and renal biopsy specimens were analyzed.

Results: Following albumin overload, we found a striking increase of Na+ -Cl cotransporter (NCC) expression by 2.3-fold in mouse kidneys determined by Western blotting and qRT-PCR. To evaluate NCC function in these mice, we examined key components of RCS and found a striking elevation of angiotensinogen (AGT) and angiotensin converting enzyme (ACE) by 2-3 folds in line with enhanced urinary AngII excretion. In proteomic mice, we also observed 4-fold upregulation of NCC and remarkable stimulation of ACE detected by immunohistochemistry in accord with significantly increased urinary Ang II output. To further investigate the role of RCS in NCC upregulation, we did primary culture of renal tubular cells and observed that albumin directly increased NCC paralleled with significant induction of AGT, ACE, and Ang II. Strikingly, administration of specific ACE inhibitor captopril to the cells remarkably abolished albumin-induced enhancement of NCC and RCS components. Additionally, albumin overload significantly reduced mitochondrial superoxide dismutase (SOD2) by 60%, and administration of a SOD2 mimic (MnTBAP) entirely abolished the stimulation of NCC, ACE, and AGT in mice with albumin overload.

Conclusions: The findings demonstrated an important role of albuminuria in upregulating RCS expression via a renal mitochondrial oxidative stress-initiated stimulation of renal local AGT/ACE/Ang II, which may contribute to the fluid retention and hypertension in proteinic kidney disease to some extent.

Funding: Government Support - Non-U.S.

FR-PO138

Prophylactic and Therapeutic Tenapanor Are Vascular Protective in a Rat Model of CKD

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Background: Tenapanor (AZD1722), an inhibitor of the Na+ /H+ exchanger NHE3, reduces absorption of gut sodium and phosphate. It is being developed for renal and constipation-related indications.

Methods: 5/6 nephrectomized Sprague Dawley rats were fed 4% NaCl chow to induce salt-sensitive arterial hypertension. Oral tenapanor (1 mg/kg/day) was initiated either at the start of NaCl intake (prophylactic; Px) or 2 weeks later (therapeutic; Tx), and was administered for up to 6 weeks. Disease controls (DCs; vehicle-treated) and healthy controls (HCs; sham operated, normal chow) were included to enable assessment of disease progression. Systemic hemodynamics and urinary and plasma biomarkers were assessed every 2 weeks. Ex vivo vascular function (isometric tension recording) or arterial stiffness (pulse wave velocity) was evaluated to include assessment of disease progression. Systemic hemodynamics and urinary and plasma biomarkers were assessed every 2 weeks. Ex vivo vascular function (isometric tension recording) or arterial stiffness (pulse wave velocity) was evaluated to include assessment of disease progression.

Results: Compared with DCs, rats in the Px and Tx groups had reduced urinary albumin, sodium and phosphorus excretion (p<0.05), and looser stools. Systolic, diastolic and mean BP increased in DCs but were normalized in the Tx group. Arterial stiffness was reduced by Px and Tx tenapanor (p<0.05). Compared with HCs, DCs had impaired aortic vasoconstrictor and vasodilator function at 2 weeks (p<0.05) and significant endothelial dysfunction at 6 weeks. Px tenapanor normalized, and Tx tenapanor attenuated arterial hypertension, vascular stiffness, vasoconstrictor and endothelium-dependent and independent vasodilator function (Table).

Funding: Government Support - Non-U.S.

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Underline represents presenting author.
Conclusions: Tenapanor prevented most of the maladaptive consequences in a rat model of renal insufficiency-induced salt-sensitive arterial hypertension and CKD. The benefit of Tx treatment was similar to that elicited by PxB use, suggesting disease modification. Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO140

Urinary Exosome Profiling in Thiazide Induced Hyponatremia

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Background: Thiazides are one of the most widely used and cost-effective class of anti-hypertensive medication. Thiazide-Induced Hyponatremia (TIH) is one of their major adverse effects and the leading cause of drug-induced hyponatremia requiring hospitalization. A priori TIH must result from excessive saliuresis and/or water reabsorption. The water and electrolyte transporter composition of urinary exosomes (UE) reflects their cellular origin and are a promising way to study renal dysfunction. This study assessed the expression of AQP2 and NCC in the UE of TIH patients.

Methods: 100 patients admitted to hospital with severe TIH donated urine samples during acute TIH and at two months post TIH cessation. Matched normotensive controls were recruited both on and off thiazides (groups 1 & 2 respectively). UE from a representative sample of each patient group were isolated and AQP2 and NCC were evaluated by Western blotting and Nanoparticle Tracking Analysis (NTA). AQP2 and NCC expression was normalized by urinary creatinine. Immunoblots were also corrected for total protein and results expressed as units of optical density/µg.

Results: Westerns showed that UE expression of AQP2 was higher in cases during acute TIH compared to convalescent (32.93 vs 28.71, P<0.01) and compared to both control groups 1 and 2 (15.61 and 15.09 respectively, P<0.001). NCC expression was lower in TIH patients acutely compared to convalescent (17.72 vs 31.86, P<0.05) and compared to both control groups (30.32 and 31.17, P<0.05). NTA also demonstrated increased AQP2 expression in acute & convalescent TIH.

Conclusions: This study highlights the utility of UE analysis to probe the molecular pathophysiology of TIH. Increased AQP2 and reduced NCC expression suggests that TIH results from increased water reabsorption and sodium wasting in the distal nephron. TIH studies may further understand of renal physiology and inform the design of new thiazide medicines less prone to cause hyponatremia. Funding: Government Support - Non-U.S.

FR-PO141

Epigenetic Modulation of Renal Arterioles Induced by DOCA-Salt Loading in Mice

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Background: The relationship between salt intake and development of hypertension is familiar; however, the mechanism for the onset has not been fully revealed. Our previous report showed that the medial hypertrophy of renal arterioles after transient salt loading in spontaneous hypertensive rat caused lasting elevation in blood pressure. The present study investigated the significance of epigenetic modulation of the gene expressions which are relevant to the medial hypertrophy after transient salt loading.

Methods: Male 6 week old C57Bl6 mice were implanted deoxycorticosterone acetate (DOCA) pellets and given drinking water containing 1% NaCl for 2 weeks for generation of MetS+RAS. Sham served as controls (n=7 each). Single-kidney renal blood flow (RBF) and glomerular filtration rate (GFR) were studied in-vivo, and microvascular architecture (micro-CT) and interstitial fibrosis ex-vivo.

Results: EVs were detected in the stenotic-kidney 4 weeks after injection. RBF and GFR did not increase and BP did not recover reflecting an absence of increase in reflex SNA. Histological examinations of the kidney were performed during and after the salt loading. Gene expressions in the kidney such as matrix metalloproteinases (MMPs), which promote the medial hypertrophy, were quantified. Epigenetic modulation of the genes were analyzed.

Results: Transient salt loading caused elevation in blood pressure during the loading period. Blood pressure after stopping salt-loading was also significantly higher than that before salt loading. Salt loading caused medial hypertrophy of renal arterioles, and it remained after stopping salt loading, as to cause lasting renin elevation. Real time PCR revealed that MMP2 and MMP9 were increased during the salt loading. CGN5, CBF and p300, which are histone acetyltransferases, were elevated. Sir1, Sir3, HDAc1 and HDAc3, which are histone deacetylases, were decreased. Histone H3K9 and H4K16 acetylations in the MMP2 gene were enhanced by the salt loading.

Conclusions: The last medial hypertrophy and renin elevation after transient salt loading were suggested to be caused by the increased expression of MMPs along with augmented histone acetylations by the salt loading. Increased expressions of acetyltransferases along with decreased expressions of Sirs and HDAcS by transient salt loading would be involved in the enhancement of the histone acetylations.

FR-PO142

Radio-Frequency Catheter-Based Renal Denervation in Hypertensive Sheep with Chronic Kidney Disease Impairs Responses to Hemorrhage

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Background: Renal sympathetic nerves medulate kidney function and blood pressure (BP). Trials using catheter-based renal denervation (cDNX) in hypertensive patients yielded results both in support of and, against its efficacy in lowering BP. A critical question is whether cDNX has adverse consequences, in situations of clinical challenge, such as hemorrhage in denervated patients where intact nerves would be required. This study examined consequences of cDNX 1) on BP and renal function and 2) on reflex activation of sympathetic nerve activity (SNA) in hypertensive sheep with chronic kidney disease (CKD).

Methods: Sheep with established hypertension and renal dysfunction (CKD group) with an appropriate control group were used. At 10 months of age, some animals underwent cDNX (CKD-cDNX; control-cDNX) while the remaining underwent sham procedure (CKD-intact; control-intact). Al 2 months post-cDNX, BP, renal function, and plasma renin activity (PRA) were assessed before, during and after hemorrhage (20% blood volume withdrawn over 15 minutes).

Results: CKD sheep had higher BP compared to all groups but CKD-cDNX sheep had similar BP to control sheep. Basal renal function was not further reduced. In response to hemorrhage, BP fell in all groups but the greatest decrease occurred in CKD-cDNX. In Control-intact sheep this fall in BP gradually recovered, associated with increase in PRA reflecting an increase in reflex SNA. In contrast, in Control-cDNX and CKD-cDNX groups, PRA did not increase and BP did not recover reflecting an absence of increase in reflex SNA.

Conclusions: cDNX effectively reduced BP at 2 months post-cDNX in previously hypertensive sheep but had no effect on renal function. However, the lack of reflex activation of neural mechanisms observed during hemorrhage suggest, that cDNX may impair a patient’s ability to adequately respond to physiological challenges. Funding: Government Support - Non-U.S.

Interleukin-10 Mediates the Renoprotective Properties of Mesenchymal Stem Cells-Derived Extracellular Vesicles in Porcine Metabolic Syndrome and Renal Artery Stenosis

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Background: Mesenchymal stem/stromal cells (MSCs) are immunomodulatory and have unique potential to restore the renal microvasculature, but may generate safety concerns. MSC-derived extracellular vesicles (EVs) emerged as a novel non-cellular alternative. Using a swine model of metabolic syndrome (MetS) superimposed on renal artery stenosis (RAS) we tested whether intrarenal injection of EVs attenuates renal injury and if this capacity is mediated by their cargo of the anti-inflammatory cytokine IL-10.

Methods: Mesenchymal stem cells (MSCs) were cultured and if this capacity is mediated by their cargo of the anti-inflammatory cytokine IL-10. Using a swine model of metabolic syndrome (MetS) superimposed on renal artery stenosis (RAS) we tested whether intrarenal injection of EVs attenuates renal injury and if this capacity is mediated by their cargo of the anti-inflammatory cytokine IL-10. Using a swine model of metabolic syndrome (MetS) superimposed on renal artery stenosis (RAS) we tested whether intrarenal injection of EVs attenuates renal injury and if this capacity is mediated by their cargo of the anti-inflammatory cytokine IL-10.

Results: EVs were detected in the stenotic-kidney 4 weeks after injection. RHF and GFR, which increased in Mes cDNX compared to Lean, fell in Mes+RAS. Yet, the lack of reflex activation of neural mechanisms observed during hemorrhage suggest, that cDNX may impair a patient’s ability to adequately respond to physiological challenges. Funding: Government Support - Non-U.S.
FR-PO144

Role of Mitochondrial Dysfunction and ROS Production in Ang II-Induced NLRP3 Inflammasome Activation

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Background: The type 1 angiotensin (AT1) receptor plays an important role in maintaining blood pressure. Previous studies suggested that the activation of immune responses by angiotensin (Ang) II during hypertension may aggravate renal damage. NLRP3 inflammasome activation promotes renal inflammation and contributes to chronic kidney injury. Further investigation should be performed to explore the correlation between the RAS and NLRP3 inflammasome activation, and possible mechanisms.

Methods: C57BL/6 AT1R-/- and NLRP3-/- mice underwent left nephrectomy followed 1 week for recovery. Blood pressure measurements were recorded at baseline and following 4 weeks of chronic Ang II or saline infusion. At the end of the experiment, the kidney were harvested and fixed. AT1R siRNA and mito-TEMPO treatment were performed before the Ang II stimulation in HK2 cells. The expression levels of NLRP3 inflammasome and mitochondrial dysfunction were measured.

Results: Ang II significantly induced kidney injury and NLRP3 inflammasome activation. Mitochondria swelling and fragmentation were observed by transmission electron microscope. AT1R-/- blocked Ang II-induced hypertension, inhibiting the mitochondrial dysfunction and NLRP3 expression. Deficiency of NLRP3 attenuated kidney injury in hypertension with no significant influence to blood pressure. In vitro studies showed that Ang II stimulation increased the mitochondrial damage and NLRP3 activation in dose- and time- dependent manner. AT1R siRNA and mito-TEMPO treatment were performed before the Ang II stimulation in HK2 cells. The expression levels of NLRP3 inflammasome and mitochondrial dysfunction were measured.

Conclusions: Ang II stimulation increases NLRP3 inflammasome activation through AT1a receptor. Ang II-induced NLRP3 activation is mediated by mitochondrial dysfunction, with overproduction and accumulation of ROS. NLRP3 inflammasome activation plays an important role in kidney injury, and blocking it can be a potential therapeutic target for hypertension-associated kidney damage.

Funding: NIHDK Support, Other NIH Support – DK102325-01 & DK100881

FR-PO145

The Endoplasmic Reticulum Stress Inhibitor 4-Phenybutyric Acid Prevents the Development of Essential Hypertension in Young Spontaneously Hypertensive Rats

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Background: Essential Hypertension is the leading global risk factor for premature death. This complex multifactorial disease has no known cause and has been shown to contribute to the progression of chronic kidney disease (CKD). Mechanistically both Endoplasmic Reticulum (ER) stress and the Unfolded Protein Response (UPR) have been implicated in the pathobiology of this disease. A small molecular chaperone, 4-phenylbutyric acid (4-PBA), is known to inhibit ER stress. In our previous studies, we found that 4-PBA is able to lower blood pressure in animal models of hypertension. It remains unclear however if ER stress is a cause of hypertension or a consequence.

Methods: Young spontaneously hypertensive rats (SHR) were used in this study and Wistar Kyoto (WKY) rats were used as its normotensive control. High blood pressure begins to develop in the young SHR at 4-weeks of age. Radio-telemetry transmitters (HE7-X1 transmitter, Data Sciences International) were implanted to monitor blood pressure development, heart rate and ECG activity in both SHR and WKY. SHR and WKY were both randomized into 4-PBA (1 g/kg/d) or vehicle groups at 4-weeks of age to determine

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FR-PO146

Macrophage Endothelin-B Receptors Clear Endothelin-1 and Regulate Blood Pressure

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Background: Hypertension is common. Its cause remains unclear in the majority of those affected. Recent data suggest that macrophages (Mφ) contribute to, and protect from, hypertension. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor with additional pro-inflammatory properties. The effects of ET-1 on Mφ biology are not well studied.

Methods: To examine the interactions between the ET and Mφ systems we administered incremental doses of intravenous ET-1 to C57BL/12-nephrin toxin receptor (CD11b-DTR) mice – given diphtheria toxin (DT) and to target ET-B receptors – on the myeloid lineage. Mφ depletion or loss of function – CD11b-DTR mice given DT and lYsMET-5- mice – were not associated with a difference in baseline BP or endothelial dysfunction. In both, administration of ET-1 resulted in an exaggerated hypertensive response compared to controls. At a dose of ET-1 1nmol/kg the maximal change in BP was –2 fold greater in Mφ deficient mice compared to control groups. In vitro, bone MDM and human Mφ possess both ET-B and ET-A receptors. Whereas stimulation of mouse and human Mφ with exogenous ET-1 did not polarize Mφ to a classical or alternative phenotype, both displayed chemokines to ET-1. This was reduced by selective ET-B receptor mediated antagonism.BMDM stimulation with LPS/INFγ led to an increase in the concentration of ET-1, an effect that was blocked by phosphoramidon, an inhibitor of endothelin converting enzyme. Importantly, using pharmacological and gene targeting studies we show a novel clearance mechanism for ET-1 through ET-B receptor mediated dynamin-dependent endocytosis present in both murine and human Mφ. Finally, patients receiving Mφ depleting therapy we show that BP is higher and the ET system more activated than in those receiving non-depleting therapies.

Conclusions: Overall, these data suggest that Mφ and ET-1 may play an important role in BP control and potentially have a critical role as a therapeutic target in hypertension.

FR-PO147

Role of the Myeloid Endothelin-B Receptor in Angiotensin II Mediated End-Organ Damage


Background: Hypertension is common and in the majority of cases its cause remains unknown. Recent interest has focused on the role of macrophages (Mφ) in blood pressure (BP) regulation. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor mediating its effects through two receptors – the endothelin-A receptor (ET-A) and endothelin-B (ET-B) receptor. The ET-B receptor has a specific role in ET-1 clearance. We investigated the role of the Mφ ET-B receptor in a model of angiotensin (AngII)-mediated end-organ damage.

Methods: Mφ ET-B receptor deficient mice (lYsMET-5-) and controls were exposed to Ang II infusion for 6 weeks under a high salt diet. We assessed BP via telemetry, cardiac structure and function and endothelial function by Doppler ultrasound, end-organ injury and plasma and urine ET-1.

Results: At baseline, components of BP did not differ between groups and increased similarly with Ang II. Whereas after 6 weeks of Ang II lYsMET-5- and controls had similar left ventricular hypertrophy and cardiac insufficiency, endothelial function was better in lYsMET-5- at both baseline and after Ang II (% dilation of basilar artery in response to CO2/CO2 vs. controls: baseline: 20 ± 1%, p<0.01; at 6 weeks: 11 ± 0.2% vs. 0.5 ± 0.1%). Baseline renal function and proteinuria did not differ between groups. After Ang II, lYsMET-5- showed similar renal function compared to controls but less proteinuria (urine albumin/crea, mg/mmol: 20.8±10 vs. 530±25, p<0.01), glomerulosclerosis (34±0.2 vs. 61±0.4%, p<0.01), and fewer renal Mφ compared to controls (F4/80 staining per high power field, lYsMET-5- vs. controls: 1.1±0.7 vs. 3.2±0.5%, p<0.02), although similar levels of CD3+ cells. Plasma ET-1 was no different at baseline but increased more in lYsMET-5- with Ang II vs. controls after 6 weeks Ang II: 3.7±0.7 vs. 1.4±0.2pg/ml, p<0.03). Urine ET-1 was similar baseline and 6 weeks.

Conclusions: Deletion of the Mφ ET-B is associated with a blunting of the effects of systemic Ang II infusion as reflected by less endothelial dysfunction, reduced inflammation and end-organ damage. The mechanisms for these effects are the focus of ongoing research.

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**FR-PO148**

A Novel Reduced Uterine Perfusion Pressure (RUPP) Model of Preeclampsia in Mice

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**Background:** Preeclampsia (PE) is a pregnancy-related hypertension with proteinuria that typically develops after 20 weeks of gestation. PE is caused by a reduction in uterine blood flow due to abnormal trophoblast invasion of the spiral arteries. The ischemic placenta releases anti-angiogenesis factors such as sFlt-1, leading to maternal hypertension and proteinuria. The reduced uterine perfusion pressure (RUPP) model is widely used in rats, but not in mice, hindering the clarification of genetics of PE. The aim of the present study is to establish a novel PE model using an improved RUPP method in mice.

**Methods:** As shown in the Figure, 1 uterine vessels of pregnant ICR mice were ligated at 14.5 dpc, and BP, renal phenotype and pregnancy outcome were analyzed.

**Results:** RUPP in mice increased blood pressure. B.B’ ligation mice showed increased urinary albumin excretion, mesangial expansion and endotheliosis as shown by the reduction of glomerular open capillary area. RUPP increased the risk of miscarriages but not in mice, hindering the clarification of genetics of PE. The aim of the present study is to establish a novel PE model using an improved RUPP method in mice.

**FR-PO149**

Sildenafil Treatment Is Protective against Progression of Renal Injury in the Preeclamptic Dahl Salt Sensitive Rat

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**Background:** Preeclampsia, a hypertensive disorder of pregnancy, is characterized by transient glomerular damage and increased risk for kidney disease later in life. Recent studies in our lab have identified the Dahl salt sensitive (Dahl S) rat on a 0.3% NaCl diet as a spontaneous model of superimposed preeclampsia. We hypothesized that sildenafil treatment would result in an improvement in renal function during the preeclampsia pregnancy exhibited by the Dahl S rat.

**Methods:** Female Dahl S rats (n=4-9) were mated, and rats were randomly divided into control and sildenafil treated groups. Sildenafil was administered to the treated group via food on gestational days 10-20 at a dose of 50 mg/kg/d. Rats were placed in metabolic cages on gestational day 19 for 24-hr urine collection, and blood and tissues were harvested via food on gestational days 10-20 at a dose of 50 mg/kg/d. Rats were placed in metabolic cages on gestational day 19 for 24-hr urine collection, and blood and tissues were harvested via food on gestational days 10-20 at a dose of 50 mg/kg/d.

**Conclusions:** We developed a novel RUPP mouse model that recapitulates the phenotype of PE. This model is expected to be useful for investigating pathogenesis of PE and evaluating its new therapies.

**FR-PO150**

Recessive Mutations of the Interaction Partners, TENC1, DLC1 or MAGI2, Cause Nephrotic Syndrome in Humans

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**Background:** Identification of monogenic causes of nephrotic syndrome (NS) has furthered the understanding of its pathogenesis. However, many genes and disease mechanisms remain unknown.

**Methods:** We performed homozygosity mapping (HOM) and whole exome sequencing (WES) in individuals of consanguinous families with NS to identify the underlying mutations. To identify additional families, we performed microfluidic PCR (Fluidigm Access Array™) and next generation sequencing (NGS) to screen worldwide cohort of ~2000 individuals with severe NS.

**Results:** By WES in consanguineous family A1358, we identified a homozygous missense mutation (p.R292Q) in the TENC1 (Tenascin-J) gene in an amino acid residue conserved since Ciona intestinalis. By microfluidic PCR and NGS, we detected additional mutations in TENC1 in three unrelated families with NS. Later, we also discovered mutations in 2 different families with NS in DLC1 gene, a known binding partner of TENC1. Interestingly, most of the individuals with TENC1 or DLC1 mutations had steroid sensitive NS or histologically showed biopsy of MCNS. Furthermore, in 2 families with NS and neurological impairment, we identified 2 different homozygous truncating mutations in MAGI2 gene. Deficiency of Tenc1 or Magi2 has been previously shown to cause NS in mice. By Co-IP, we now show that TENC1 and DLC1 interact with MAGI2 in HEK293T cells and these interactions are abrogated in one of the MAG2 mutant. Knockdown of TENC1, DLC1 or MAGI2 in cultured podocytes exhibited an altered podocyte migration rate. Immunofluorescence microscopy showed that TENC1 and DLC1 colocalize with phosphotyrosine at the focal adhesions in cultured human podocytes.

**Conclusions:** We, thus, identified mutations of TENC1, DLC1 and MAGI2 as three novel single-gene causes of NS revealing a potential new pathogenic pathway for NS.

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390A
Genes Encoding Nuclear Pore Outer Ring Components NUP85, NUP107, and NUP133 Are Mutated in Patients with Nephrotic Syndrome Svijetlana Lovric,1 Weizhen Tan,2 David Schapiro,2 Shazia Ashraf,3 Daniela A. Braun,1 Jia Rao,1 Richard P. Lifton,4 Heon Yang Gee,1 Friedhelm Hildebrandt,1,3 1Div of Nephrology, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 2Dept of Genetics, Yale Univ School of Medicine, New Haven, CT; 3Howard Hughes Medical Inst, Chevy Chase, MD.

Background: Steroid resistant nephrotic syndrome (SRNS) almost invariably progresses to end-stage kidney disease. Although more than 30 single-gene causes of SRNS are known, a large proportion of SRNS remains unexplained. Recently, mutations in genes encoding proteins of the nuclear complex (NPC) have also been implicated in nephrotic syndrome. Study of these proteins has implicated SMAD signaling in the pathogenesis of nephrosis.

Methods: To identify additional novel causes of nephrotic syndrome, we performed a candidate screen of 17 nuclear pore complex (NPC) genes in an international cohort of >900 individuals with SRNS using microfluidic multiplex PCR (Fluidigm Access Array)1 and next generation sequencing (Illumina MiSeq)2,3.

Results: In two families we identified two homozygous missense mutations, p.A777V and p.R645W, (conserved to S. cerevisiae) in the NPC outer ring protein NUP133. We then sequenced the exons of 1,000 additional families in genes encoding other outer ring proteins and found mutations in NUP107 (3 families, p.Y889C, conserved to C. elegans) and NUP133 (2 families, p.S974R and p.R231G, conserved to D. rerio). Although the structure resolution of the NPC 3D complex is incomplete, we modeled the interacting portions of the Y-subcomplex proteins NUP107 and NUP133. Two of the mutations, p.S974R in NUP133 and p.Y889C in NUP107, are located in the interacting alpha helix between the two proteins. 5 of 6 families demonstrated FSGS on biopsy.

Conclusions: As a novel cause of SRNS we identified mutations in 3 different NPC outer ring proteins NUP85, NUP107, and NUP133 that form an integral part of the Y-subcomplex. Further functional studies are needed to illuminate how the defect of NPC contributes to the pathogenesis of nephrotic syndrome.

Funding: Other NIH Support - DK076683

Defining the Genetic Epidemiology of a Phenotypically Well-Characterized Adult-Onset Focal and Segmental Glomerulosclerosis Cohort Moumita Barua,1 Daniel C. Catran,1 Heather N. Reich,1 Michelle A. Hadunezhad,1 Mark Leung,1 Weili Li,1 Andrew D. Paterson,2 York P. Pei,1 Nephrology, Toronto General Hospital, UHN, Toronto, ON, Canada; 1Biology, Univ of Waterloo, Waterloo, ON, Canada; 2The Centre for Applied Genomics, Hospital for Sick Children, Toronto, ON, Canada; 3Dalla Lana School of Public Health, Univ of Toronto, Toronto, ON, Canada; 4Genetics and Genome Biology, Hospital for Sick Children, Toronto, ON, Canada.

Background: The genetic epidemiology underlying adult-onset sporadic FSGS has not been well characterized and rigorous correlation of rare genetic forms of disease with clinical outcomes is also lacking. We defined the genetic epidemiology of the phenotypically well-characterized sporadic and familial Toronto GN FSGS cohort using next-generation sequencing.

Methods: We have ascertained the clinical information and performed whole exome sequencing in adult-onset disease of 90 sporadic FSGS cases, 41 steroid-sensitive nephrotic syndrome (SSNS) cases, and next generation sequencing in adult-onset disease of 90 sporadic FSGS cases, 41 steroid-sensitive nephrotic syndrome (SSNS) cases. In contrast, in 4 of 23 autosomal dominant and 4 of 23 autosomal recessive families with FSGS, a disease-causing mutation was identified in the following genes: NIP12, TRPC6, LMX1B and ADCK4. Mutations in the known FSGS genes were found in 7.8 and 17.4% of sporadic and familial cases of adult-onset disease, respectively, but none were discovered in patients with SSNS.

Conclusions: Our results are consistent with extensive genetic heterogeneity in FSGS. We will test the association of rare variants with phenotype. Clinical outcomes will be described.

Funding: Private Foundation Support

A Novel Mouse Mutant with a Point Mutation in Laminin α5 Exhibits Chronic Nephrotic Syndrome Sara Falcone1, Thomas Nicol,1 Cheryl Scudamore,2 Frederick W.K. Tam,3 Charles D. Pusey,4 Jeffrey H. Minner,5 Steve Dm Brown,1 Paul K. Potter,1 Mammalian Genetics Unit, MRC Harwell, Harwell, Oxfordshire, United Kingdom; 2Mary Lyon Centre, MRC Harwell, Harwell, Oxfordshire, United Kingdom; 3Renal Sciences, Imperial College, London, United Kingdom; 4Renal Div, Washington Univ, St. Louis, MO.

Background: Diseases associated with ageing pose an increasing social and financial burden on society and represent an imperative for research in the biomedical sciences. We are undertaking the first large-scale project to investigate the interaction between genetic variation and the pleiotropic effects of ageing, employing random mutagenesis and phenotyping to generate new models of late onset or age-related disease.

Methods: Mutant mice are being aged to 18 months and undergo comprehensive phenotyping across a wide range of disease areas at several time points throughout the life of the mice. To date we have identified lines with a variety of late onset phenotypes which are being characterised in detail.

Results: Mutant mice were identified at 6 months of age with elevated creatinine and urea levels, which reached end stage renal failure at approximately 10 months of age. Mapping and whole genome sequencing identified a Lama51562 mutation in the L4a domain of Lama5. Time course studies of Lama51562 homozygotes showed reduced serum albumin (18.0 ± 1.2 vs 24.9 ± 3.1 g, mean SD) and proteinuria from 12 weeks of age with a gradual loss of renal function over time. Affected mice also have significantly elevated cholesterol levels and a progressive nephropathy leading to diffuse glomerular fibrosis, dilated protein filled tubules and pigment deposition suggesting this is a model of nephrotic syndrome. The mutation does not affect expression of the LAMA5 protein within the glomerular basement membrane.

Conclusions: We have identified a novel mouse mutant with a missense mutation Lama5 resulting in nephrotic syndrome. Recent patient sequencing data suggests LAMA5 mutations are associated with focal segmental glomerulosclerosis. Further functional studies are needed to determine how the mutation affects the expression of LAMA5 and whether this mutation predisposes to other glomerular diseases.

Analysis of the remaining 20 families (65%) did not reveal any gene with rare segregating mutations present in multiple independent families.

Conclusions: Mutations in genes known to be associated to FSGS are identified in a small proportion of cases. Mutations with focal segmental glomerulosclerosis in children with kidney disease can result in defects that present as FSGS. These findings can point to a correct genetic diagnosis and the identification of mutations in genes involved in CAKUT suggests that glomerular sclerosis could be the manifestation of a maladaptive reaction to reduced glomerular mass from whatever cause.

Funding: NIDDK Support, Private Foundation Support
Role of CD2AP Mutations in Steroid Resistant Nephrotic Syndrome Revisited – New Insights from Next Generation Sequencing

Fang

FR-PO156

Role of CD2AP Mutations in Steroid Resistant Nephrotic Syndrome Revisited – New Insights from Next Generation Sequencing

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Background: Steroid Resistant Nephrotic Syndrome (SRNS) is a rare disease characterized by glomerular filter malfunction. Analysis of inherited cases has identified mutations in >50 genes. However, clinical data can be limited and the true pattern of inheritance difficult to verify. In light of recent advances in next generation sequencing (NGS) and rare disease genetics, we re-examined CD2AP, a gene considered to cause autosomal dominant SRNS in an in vivo model.

Methods: In-house whole exome sequencing (WES) data on 200 deeply phenotyped SRNS patients was tested to assess the ability of CD2AP mutations to act as autosomal dominant. All protein altering CD2AP variants detected with a MAF < 0.05 were selected for further examination in the Exome Aggregation Consortium (ExAC) database. Samples with likely pertinent variants in CD2AP were also analysed for causal mutations in other SRNS genes.

Results: Variants with a frequency of >1 in 1000 in the ExAC database were considered unlikely to cause autosomal dominant SRNS based on frequency of SRNS in populations. Two rare CD2AP variants remained after filtering but one case also demonstrated a rare heterozygous non-syndromic disease causing variant in SYNPO (allelic frequency 0.0002179 in ExAc, non-homogeneous) and the other a variant in NPHS2 (not seen in ExAc). SYNPO interacts with CD2AP and combined, these genes cause FSIG in mice. The NPHS2 variant neighbourd a mutation linked previously to bighemogenic heterozygosity with CD2AP in SRNS.

Conclusions: Some heterozygous CD2AP variants occurred in normal controls or were detected incidentally during sequencing variants. This indicates that mutations behaving as a dominant negative in a small number of cases may in fact demonstrate more complex inheritance on interrogation of a larger cohort. Computational analysis of WES provides a useful adjunct to rapidly examine and ascertain actual heritability in rare disease populations, especially in seemingly sporadic cases.

Chemical Chaperone 4-PBA Is Not Nephroprotective in Experimental Podocin Nephropathy

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Background: 4-PBA has been demonstrated to improve protein trafficking from ER to plasma membrane and function of mutant AF508-CFTR protein in cystic fibrosis. In hereditary nephrotic syndrome the most common NPHS2 (podocin) mutation, R138Q, leads to retention of podocin in the ER and therefore to defective intracellular protein trafficking. In order to investigate beneficial effect of chemical chaperone in podocin nephropathy, we administered 4-PBA to knock-in mice carrying this mutation. Analogous to human disease, these mice develop heavy proteinuria, podocyte loss, focal segmental glomerulosclerosis and progressive renal failure.

Methods: 12 mice in C57Bl/6 mice with Nphp2 wild type or Nphp2 R138Q were used. After 8 weeks of age, 4-PBA (100 mg/kg) or PBS was administered i.p. for 4 weeks. Weight and proteinuria were monitored weekly. Biochemical and histopathological changes were examined after 4 weeks of treatment.

Results: All animals developed massive proteinuria (116% of untreated controls). Hypoalbuminemia at 4 weeks was slightly ameliorated (21.1 (Co) vs. 24.7 g/dl; n.s.). Serum urea, cholesterol and creatinine levels were deteriorated by 4-PBA treatment. Podocyte loss (podocytes per glom.: 93% (Co), 69% (4-PBA) of healthy animals, n.s) and glomerular sclerosis index (1.75(Co), 1.824-PBA) were unchanged, whereas an increase in tubulointerstitial fibrosis was noted in 4-PBA treated animals (1.36 (Co) vs. 3.82 (4-PBA).

Conclusions: In an in vivo model of hereditary podocin nephropathy, prophylactic 4-PBA treatment showed no beneficial effect on proteinuria and podocyte loss but aggravated tubulointerstitial fibrosis and renal failure. Our findings argue against a nephroprotective action of 4-PBA in this hereditary podocytopathy.

Prominent Renal Complications in the c.80A>G in MMACHC Gene

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Background: MMACHC C defect is a clinically heterogeneous disease caused by mutations in the MMACHC gene. The aim of the present study was to delineate renal phenotype in Chinese children with MMACHC C defect.

Methods: Detailed clinical data were collected and analyzed, and all coding exons of MMACHC gene were PCR-amplified and sequenced from genomic DNA.

Results: Four unrelated Chinese children (1 female, 3 male) with unexplained microscopic hematuria and proteinuria were included. The onset age of renal symptoms ranged from 9 months to 4 years. Two patients had nephrotic-level proteinuria in their initial visit, and renal dysfunction was detected in 2 patients in 3 months and 6 months after onset, respectively. Only 1 patient had hypertension in 6 years after onset. All patients had metabolic acidemia, and megaloblastic anemia was present in 2 patients. None of 4 patients had thymoglobulinemia or pancytopenia. One of 4 patients had mild development backward. Four patients had hyperhomocysteinemia, and 2 of 4 patients presented with remarkable elevated urinary methylnalamic acid. Renal biopsy in 3 patients showed thronoblastocromatinic acid. Mutations in MMACHC gene was found in four patients. Two patients were a compound heterozygote for c. 658_660delAAG and c.80A>G, and one patient was a compound heterozygote for c.80A-G. Three patients were in follow up. After vitamin B12 [in the form of hydroxycobalamin (OHCbl), folic acid and L-carnitine betaine supplementation, urine protein became negative in 2 patients and reduced in 1 patient, and renal function in 1 patient was improved. In all 3 patients, hemoglobin increased to normal, plasma homocysteine decreased and still was abnormal. In 2 patients with remarkable elevated urinary methylnalamic acid was normal in 1 patient and decreased in another patient. Blood pressure of the patient with hypertension was well-controlled using calcium channel blocker.

Conclusions: Prominent renal complications can be found in c.80A-G in MMACHC gene, and treatment resulted in improvement of renal and hematological signs.

Funding: Government Support - Non-U.S.

The Susceptible Human Leukocyte Antigen Class II Genes and the Encoding Amino Acid Residues on Major Histocompatibility Complex Molecules to Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) is an organ-specific autoimmune disease. M-type phospholipase A2 receptor (PLA2R) appears to be the specific target antigen, which needs to be presented by major histocompatibility complex (MHC) Class II to activate immune system. In genome wide association studies, risk alleles at PLA2R loci and single nucleotide polymorphism (SNP) (rs2187668) within HLA-DQA1 closely associate with the disease. However, the full association of HLA class II genes and MHC molecule amino acids has not been investigated in MN.

Methods: We genotyped 860 Chinese individuals, including 261 primary MN patients and 599 healthy controls, for DRB1, DQAI, DQBI and DPBI, 4 digits resolution HLA alleles, and extracted the encoding amino acid sequences from IMGT/HLA database. Circulating anti-PLA2R antibody was detected in all patients.

Results: We found that DRB1*1501 (OR=3.49, P=1.77×10^-13) and DRB1*0301 (OR=3.34, P=3.46×10^-10) were both significantly higher risk alleles for MN. In patients with positive anti-PLA2R antibodies, DRB1*1501 (OR=6.06) and DRB1*0301 (OR=92) showed even higher risk for the disease. The SNP (rs2187668) is the tag SNP of DRB1*0301. After conditioning on DRB1*1501 and DRB1*0301, no other HLA allele showed significant association with MN. At amino acid level, the most significant and independent associations were mapped to amino acid position 13 (P=5.78×10^-12) and position 71 (P=7.99×10^-12) on MHC DRB1 chain. After conditioning on these positions, no other amino acid position showed significant association with MN. Alamine on position 71 and Arginine on position 13 were encoded by DRB1*1501; lysine on position 13 was encoded by DRB1*0301. These amino acids were susceptible to MN and showed positive association with the presence of anti-PLA2R antibodies (P<0.001).

Conclusions: We concluded that two alleles of HLA class II genes, and the encoding three amino acid residues on two positions at the epitope-binding pockets of MHC DRB1 chain, were responsible for higher risk to MN.

Funding: Government Support - Non-U.S.

Somatic Mosaicism and Variant Frequency Detected by Next Generation Sequencing in X Linked Alport Syndrome

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Background: Alport syndrome is a hereditary disorder of type IV collagen, characterized by chronic kidney disease progressing to end-stage renal disease, sensorineural hearing loss, and urinary abnormalities. Approximately 85% of Alport syndrome patients show X-linked inheritance (XLAS) and variants in the type V collagen, a5 gene (COLA5), which encodes the type IV collagen α5 chain. Although male patients with XLAS usually develop end-stage renal disease before 30 years of age, some male patients with a milder phenotype and develop end-stage renal disease later in life. However, the molecular mechanisms associated with this milder phenotype have not been fully identified.

Methods: We genetically diagnosed 186 male patients with suspected XLAS between January 2009 and August 2014. Genetic examination involved: 1) extraction and analysis of genomic DNA using polymerase chain reaction and direct sequencing using Sanger’s method for all patients; and (2) next-generation sequencing to detect variant allele frequencies for four patients who suspected somatic mosaic variants.

Results: We identified somatic mosaic variants in the COLA5 in four patients. Interestingly, two of these four patients with variant frequencies in kidney biopsies or urinary sediment cells of ≥50% showed hematuria and moderate proteinuria, while the other two with variant frequencies of <50% were asymptomatic or only had hematuria.
FR-PO161

A New Non-Invasive Method to Examine Collagen α5(IV) Expression Using Plucked Hair Follicles: Analysis of an X-Linked Alport Family with a Novel COL4A5 Splice Region Variant Andrew E. Maloney, Steven Daniel Funk, Jeffrey H. Miner. Renal Div; Dept of Medicine, Washington Univ, St. Louis, MO.

Background: Alport syndrome is a hereditary disease caused by mutations in COL4A5 in 85% of cases. Many different mutation types in this gene have been described. Levels and patterns of type IV collagen deposition are variable in the glomerular basement membranes of Alport kidneys. As COL4A5 is also expressed in the skin, we sought to characterize COL4A5 deposition in the basement membrane of plucked hair follicles from a family with a novel COL4A5 variant as a way of confirming the functional significance.

Methods: Whole-exome sequencing was done on the proband of a family with biopsy proven Alport syndrome. Sanger sequencing was performed on all affected family members and a married-in unaffected individual. Immunofluorescence microscopy was performed on whole mount and sectioned hair follicles co-stained with monoclonal antibodies to collagen α2 and α5(IV). Staining intensity between males and females, affected and unaffected, was analyzed.

Results: Family WU1 is a 3 generational family with chronic kidney disease secondary to Alport syndrome. Affected are in each generation, and both males and females are asymptomatic. Whole-exome sequencing of affected individual 3227 revealed a novel splice region variant c.1780-6G>C in COL4A5. There were no other potentially pathogenic variants found in COL4 or other podocyte genes. This variant was confirmed by Sanger sequencing and segregated with disease. Reduced and abnormal expression of COL4A5 protein was confirmed in affected family members by immunofluorescence microscopy of hair follicles.

Conclusions: We confirmed linkage of a novel splice region variant in COL4A5 to Alport syndrome in a family with a typical X-linked inheritance pattern; this variant may be pathogenic. We developed and validated a new approach to characterize the expression of COL4A5 protein using immunofluorescence microscopy of plucked hair follicles. Furthermore, we demonstrated variability of COL4A5 expression between patients in this family, suggesting intermittent failure of splicing and/or variable lyonization in females.

Funding: NIDDK Support

FR-PO162

X-Linked Alport Dogs Demonstrate Mesangial Filipodial Invasion of the Capillary Tuft as an Early Event in Glomerular Damage Sabrina D. Clark,1 Mary B. Nabity,1 Rachel Bianzio,1 Brianna M. Dufek,1 Dominic E. Cosgrove,2 Veterinary Pathobiology, Texas A&M Univ, College Station, TX; 2Veterinary Biosciences, The Ohio State Univ, Columbus, OH; 1Genetics, Boys Town National Research Hospital, Omaha, NE.

Background: X-linked Alport syndrome (XLAS), caused by a mutation in the type IV collagen COL4A5 gene, accounts for approximately 80% of the cases of human Alport syndrome. Dogs with XLAS have a similar clinical progression. Prior studies in autosomal Alport mice demonstrated early mesangial cell invasion as the source of laminit 211 in the glomerular basement membrane (GBM), leading to podofibril loss. Thus far, these findings have not been confirmed in a large animal model.

Methods: XLAS dogs and unaffected littermates were monitored with serial clinicoopathologic data and renal biopsies. Biopsies were obtained at the onset of microalbuminuria (MA), overt proteinuria (urine protein:creatinine (UPC) > 2), onset of azotemia, moderate proteinuria, and at euthanasia. Glomeruli were analyzed by immunohistochemistry.

Results: With disease progression, XLAS dogs showed a progressive decrease in renal function (based on serum creatinine, symmetric dimethylarginine (SDMA), UPC, and oxohedrin clearance) and increased in interstitial fibrosis and glomerulosclerosis (based on light microscopy and/or immunostaining for ASMA and fibronectin). The only identifiable structural abnormality at the time of MA was segmental multilamination of the GBM observed on transmission electron microscopy (TEM), which was more extensive when overt proteinuria developed. Co-localization studies showed that mesangial laminin 211 and integrin α6β1 accumulate in the GBM, which was identified with laminin 212. This was first observed when overt proteinuria developed and coincided with evidence of mild cellular interpositioning on TEM, consistent with invasion of the capillary loops by mesangial cell processes.

Conclusions: These findings confirm, in a large animal model, the induction of mesangial filipodial invasion of the glomerular capillary tuft leading to the irregular deposition of mesangial laminin 211 as an early initiating event in Alport glomerular pathology.

Funding: Pharmaceutical Company Support - IDEXX Laboratories, Inc

FR-PO163

Drug Repurposing for the Treatment of Experimental Alport Syndrome Vanessa R. Williams,1 Ana Konvalinka,2 Xuewen Song,2 Eun Hui Bae,2 Fei Fang,1 Rohan John,3 York P. Pei,1 James W. Scholroy,1,2 1Inst of Medical Science, Univ of Toronto, Canada; 2Diy of Nephrology, Univ of Toronto, Canada; 3Internal Medicine, Chonnam National Univ Medical School, Korea; 2Pathology, Univ of Toronto, Canada.

Background: Alport Syndrome (AS) is a hereditary nephropathy caused by mutations in genes that encode type IV collagen, leading to progressive injury and eventually end-stage renal disease. Currently there are few effective therapies for AS. Therefore we applied a drug repurposing strategy, utilizing data on drugs currently approved for use in humans, to identify a novel AS treatment.

Methods: 129/SvCola3(F0) and wild-type (WT) mice were studied at 4 and 7 weeks (N=8/group). Histological analyses of formalin-fixed mouse kidney sections were performed. Plasma and 24-hour urine samples were collected. Global gene expression profiling of RNA from renal cortex was performed with the Affymetrix Mouse Gene 2.0 ST Array. Significance Analysis of Microarrays (SAM) was used to identify differentially expressed genes. In silico drug repurposing with the Connectivity Map (CMap) was used to identify drugs expected to effectively treat murine AS.

Results: Mice with AS developed a progressive rise in albuminuria and serum creatinine. These changes were associated with glomerulosclerosis and tubulointerstitial fibrosis. SAM was used to generate a disease signature of differentially expressed genes, comparing 7-week-old KO versus WT mice. The disease signature was used to query the CMAP. Vorinostat, a lysine deacetylase inhibitor, was the top drug predicted to reverse the signature. KO mice were treated with vehicle or vorinostat daily from 4 to 7 weeks of age. Vorinostat treatment induced hyperacetylation of kidney lysine residues. This was associated with reduced albuminuria, decreased α5α4 protein expression, and reduced gene expression of inflammatory cytokines.

Conclusions: In silico drug repurposing identified a novel therapeutic approach to AS. Further testing of the putative therapy showed that vorinostat exerted a renoprotective effect. Further studies will better define the mechanisms underlying the protective effect of this novel therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO164

KCTD1 Mutations in Scalp-Ear-Nipple (‘Finlay-Marks’) Syndrome: A Further Cause of Thin Basement Membrane Nephropathy Dongmo Wang,1,2 Peter Diakumis,3 Melanie Bahlo,3 Deb J. Colville,3 Judith A. Savige.1 1Medicine, The University of Melbourne (Menzies Health), Melbourne, VIC, Australia; 2Bioinformatics, WEHI, Melbourne, VIC, Australia.

Background: Scalp-Ear-Nipple syndrome is a ectodermal dysplasia, with a scalp defect, thinning of ears and absent breasts. It results from mutations in KCTD1, an inhibitor of the transcription factor, AP2. AP2 regulates the expression of the collagen IV α3 and α4 chains, which are major components of the glomerular, corneal and retinal basement membranes. This study characterised the clinical phenotype in Scalp-Ear-Nipple syndrome and how mutations caused disease.

Methods: Two unrelated families with Scalp-Ear-Nipple syndrome were examined by a renal physician and an ophthalmologist. One family member provided a skin biopsy that was used to derive a fibroblast cell line. Urine specimens from two family members were used to study the expression of the collagen IV α3 and α4, and laminin α5 and b1 transcripts. The ER size was measured using immunohistochemistry before and after treatment with PBA, a chemical chaperone.

Results: Seven family members had developed renal cysts and impaired renal function by late adulthood, and all 14 who were examined had astigmatism. A renal biopsy demonstrated a thickened glomerular membrane. One individual had a thinned cornea and the two who were examined with optical coherence tomography had a small optic disc, and thinned retinal nerve fibre layer.

Discussion: Reduced transcription of the collagen IV α3 and α4 chains in the urine. The fibroblast cell cultures confirmed reduced laminin transcripts. ER size was increased in the fibroblast cells in vitro but PBA chaperone treatment reduced ER size. However no KCTD1 mutations were identified in 20 individuals with Thin membrane nephropathy and no 141A1 COL4A4 mutations nor in 20 individuals with familial astigmatism.

Conclusions: The clinical features of Scalp-Ear-Nipple syndrome are due to KCTD1 mutations that affect basement membrane collagen IV and laminin expression. Chemical chaperones represent a potential treatment to delay renal failure.

FR-PO165

Podocyte Globotriaosylceramide (GL3) Accumulation in Fabry Disease Is Influenced by Age and Genotype Behzad Najafi,1 Camilla Tondel,2 Einar Svarstad,2 Michael L. West,1 Michael Mauer,1 1Univ of Washington; 2Univ of Bergen; 2Dalhousie Univ; 1Univ of Washington.

Background: Podocyte injury plays a key role in Fabry nephropathy, a major complication of Fabry disease. Identification of factors affecting podocyte injury may help to understand the pathophysiology of Fabry nephropathy. We studied effects of age and genotype on podocyte GL3 accumulation in Fabry patients.

Methods: Kidney biopsies from 55 male Fabry disease patients, age 25 [4-65] (median [range]) years were studied using electron microscopic stereology. Podocyte GL3 volume

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
A Founder Haplotype of APOE-Kyoto Mutation Associated with Lipoprotein Glomerulopathy

Background: The Canadian Fabry Disease Initiative (CFDI) is a multicentre prospective study of outcomes with enzyme replacement therapy (ERT) in Fabry disease. ERT has been shown to be of benefit in reducing Fabry cardiac and renal disease. There is uncertainty as to the benefits of ERT in older patients. We compared outcomes of ERT in patients over 65 years of age with the overall CFDI population.

Methods: Patients are reviewed every 6-12 months as to clinical status. ERT is provided every 2 weeks according to national guidelines with intravenous dose agalsidase alfa (0.2 mg/kg), with a maximum dose of 1.0 mg/kg. Cardiovascular risk factor modification is promoted with use of ASA, statins and ACEi/ARB. Clinical outcomes are defined as stage 5 CKD, stroke/TIA, acute deafness, cardiac arrest, CHF, arrhythmia, unstable angina, MI, PTCA, pacemaker/ICD, AVR/CABG and death.

Results: As of Jan 2015, 429 subjects were enrolled. There were 51 patients over 65 yr, 68.6% female, and 60.8% on ERT with mean age 71.8 y. There were no differences in mean age, cardiac variant genotype, or time in the CFDI between those on ERT and those not. Compared with patients not on ERT, those on ERT had lower GFR, greater proteinuria and higher LVM at both baseline and 6 y later. Three patients not on ERT had 5 clinical events, prevalence 15%, no deaths with clinical event rate of 1/34.5 patient years. Twenty patients on ERT had 5 deaths, 38 clinical events, prevalence 64.5% and clinical event rate of 1/9.3 patient years.

Conclusions: Older patients with Fabry disease continue to have clinical events, mainly cardiac, despite ERT but appear to be living longer. Use of the Canadian Fabry Disease guidelines appears to successfully target high-risk older patients. ERT use in this subgroup appears to be of benefit.

Funding: Pharmaceutical Company Support - Genzyme, a Sanofi Company; Shire Inc, Government Support - Non-U.S.

FR-PO166

Outcomes of Patients Over 65 in the Canadian Fabry Disease Initiative Study

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Results: We report 11 pregnancies in 4 women (table 1). Two had an established diagnosis of aHUS prior to the first pregnancy (case 2 and 3). Case 1 presented with end-stage renal disease due to TMA (biopsy-proven) 12 months after her first delivery and case 4 presented postpartum after her uncomplicated first delivery. In 8 pregnancies females received preventive plasma infusions (PI, 200-1600 mL) 2 to 4 weeks apart. After kidney transplantation case 1 received a maintenance therapy (PIs once a month), which was intensified during the II pregnancy to every other week. Two pregnancies (case 2, case 4) are currently ongoing without evidence of a disease flare so far. Nine pregnancies went without any complication and the offspring are healthy. One pregnancy (c.3, II) without PIs resulted in an intrauterine fetal death at gestation week 36, without signs of TMA in the mother.

Funding: NIDDK Support, Pharmaceutical Company Support - Sanofi, Genzyme, a Sanofi Company, Pharmaceutical Company Support - Genzyme, a Sanofi Company, Genetics, Univ of Calgary, Calgary, AB, Canada, Emeritus, Univ of Toronto, Toronto, Canada, Medicine, Univ of British Columbia, Vancouver, BC, Canada, Pediatrics, Univ of Sherbrooke, Sherbrooke, QC, Canada, Nursing, Nova Scotia Health Authority, Halifax, NS, Canada.

Background: Pregnancy activates the maternal alternative pathway of the complement system due to presentation of paternal antigens. In females with atypical Hemolytic Uremic Syndrome (aHUS) – a disease of the complement regulatory proteins and C3 – each pregnancy can trigger life-threatening disease episodes.

Methods: Data were collected from patients with aHUS, enrolled in the Viennese TMA Cohort. Pregnancies occurred between 2002 and 2015.

Results: We report 11 pregnancies in 4 women (table 1). Two had an established diagnosis of aHUS prior to the first pregnancy (case 2 and 3). Case 1 presented with end-stage renal disease due to TMA (biopsy-proven) 12 months after her first delivery and case 4 presented postpartum after her uncomplicated first delivery. In 8 pregnancies females received preventive plasma infusions (PI, 200-1600 mL) 2 to 4 weeks apart. After kidney transplantation case 1 received a maintenance therapy (PIs once a month), which was intensified during the II pregnancy to every other week. Two pregnancies (case 2, case 4) are currently ongoing without evidence of a disease flare so far. Nine pregnancies went without any complication and the offspring are healthy. One pregnancy (c.3, II) without PIs resulted in an intrauterine fetal death at gestation week 36, without signs of TMA in the mother.

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Background: Pregnancy activates the maternal alternative pathway of the complement system due to presentation of paternal antigens. In females with atypical Hemolytic Uremic Syndrome (aHUS) – a disease of the complement regulatory proteins and C3 – each pregnancy can trigger life-threatening disease episodes.

Methods: Data were collected from patients with aHUS, enrolled in the Viennese TMA Cohort. Pregnancies occurred between 2002 and 2015.

Results: We report 11 pregnancies in 4 women (table 1). Two had an established diagnosis of aHUS prior to the first pregnancy (case 2 and 3). Case 1 presented with end-stage renal disease due to TMA (biopsy-proven) 12 months after her first delivery and case 4 presented postpartum after her uncomplicated first delivery. In 8 pregnancies females received preventive plasma infusions (PI, 200-1600 mL) 2 to 4 weeks apart. After kidney transplantation case 1 received a maintenance therapy (PIs once a month), which was intensified during the II pregnancy to every other week. Two pregnancies (case 2, case 4) are currently ongoing without evidence of a disease flare so far. Nine pregnancies went without any complication and the offspring are healthy. One pregnancy (c.3, II) without PIs resulted in an intrauterine fetal death at gestation week 36, without signs of TMA in the mother.

Funding: NIDDK Support, Pharmaceutical Company Support - Sanofi, Genzyme, a Sanofi Company, Pharmaceutical Company Support - Genzyme, a Sanofi Company, Genetics, Univ of Calgary, Calgary, AB, Canada, Emeritus, Univ of Toronto, Toronto, Canada, Medicine, Univ of British Columbia, Vancouver, BC, Canada, Pediatrics, Univ of Sherbrooke, Sherbrooke, QC, Canada, Nursing, Nova Scotia Health Authority, Halifax, NS, Canada.

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Whole Exome Sequencing Identifies Mutations in TUBAL3 as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)\textsuperscript{1}\textsuperscript{,} Shirlee Shirl,\textsuperscript{1,} Asaf Vivante,\textsuperscript{1,} Jan Halbritter,\textsuperscript{1} Jing Chen,\textsuperscript{1} Julian Jakob Schulz,\textsuperscript{2} Stefan Kohl,\textsuperscript{2} DAW-yang Hwang,\textsuperscript{2} Eljah O. Kehinde,\textsuperscript{3} Richard P. Lifton,\textsuperscript{4} Martin Zenker,\textsuperscript{4} Friedhelm Hildebrandt,\textsuperscript{4,} 5\textsuperscript{ Dept of Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, MA; 5 Dept of Surgery, Kuwait Univ, Safat, Kuwait; 6 Dept of Genetics, Yale Univ School of Medicine, New Haven, CT; 7 Dept of Human Genetics, Otto von Guericke Univ, Magdeburg, Germany; 8 Howard Hughes Medical Inst, Chevy Chase, MD; 9 These authors contributed equally to this work.\textsuperscript{a} Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of end-stage kidney disease in children. The morphogenesis of kidney and urinary tract is modified by genetic mutations that lead to CAKUT. Identifying these mutations will not only provide deeper insight on disease mechanisms but also aids in improving diagnosis. TUBAL3 was identified as a potential candidate gene for causing CAKUT.\textsuperscript{b} Methods: Homozygosity mapping with whole exome sequencing (WES) was performed in 20 consanguineous families with CAKUT from India. Homozygous recessive mutations within the homoyzogous region were further evaluated as the strongest candidates. Furthermore, we screened an additional cohort of 900 patients with CAKUT for additional mutations with a barcoded array based multiplex exon PCR (48x48 Fluidigm Access Array\textsuperscript{TM}) followed by next generation sequencing (Illumina MiSeq\textsuperscript{TM}). All identified mutations were confirmed by Sanger sequencing.\textsuperscript{c} Results: A homozygous truncating mutation (p.Tyr179*) in the gene TUBAL3 was identified in the consanguineous Indian family A3838 using WES. We then independently detected another mutation homoyzogously (p.Gly10Ser) in the gene TUBAL3 in a family A1347 of Kurdish descent. TUBAL3 (Tubalin, alpha-like 3) is a protein coding gene and is very conserved across species. Tubulin is the major constituent of microtubules.\textsuperscript{c} Conclusions: We identified recessive mutations in TUBAL3 as a novel single-gene cause of CAKUT. Further genetic information and functional studies will help understand disease mechanisms and the role of TUBAL3 in the pathogenesis of CAKUT.

Whole Exome Sequencing Reveals Mutation of PAPLN as a Novel Cause of Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)\textsuperscript{1} Jing Chen,\textsuperscript{1,} Asaf Vivante,\textsuperscript{1} Julian Jakob Schulz,\textsuperscript{2} Shirlee Shirl,\textsuperscript{2} Stefan Kohl,\textsuperscript{2} DAW-yang Hwang,\textsuperscript{2} Eljah O. Kehinde,\textsuperscript{4} Velibor Tasic,\textsuperscript{4} Friedhelm Hildebrandt,\textsuperscript{4,} 5

\section*{Methods:} To identify novel monogenic causes of CAKUT we applied homozygosity mapping with whole exome sequencing (WES) to 36 families with CAKUT. Then we investigated a worldwide cohort of ~1,600 families with CAKUT with a barcoded array based multiplex exon PCR (48x48 Fluidigm Access Array\textsuperscript{TM}) and next generation sequencing (Illumina MiSeq\textsuperscript{TM}).

\section*{Results:} In a consanguineous family with isolated CAKUT we detected a homozygous protein truncating mutation (p.Arg480*) in the PAPLN gene by WES. PAPLN encodes papillin, a component of the extracellular matrix (ECM) that plays a role in ECM development and interacts with ADAMTS metalloproteases. Papillin contains several thrombospondin type 1 domains homologous to ADAMTS-1, in which mutations leads to protein truncating mutation (p.Arg480*) in the PAPLN gene. PAPLN mutations were detected in another patient, of which 19 patients with CAKUT were screened using next-generation sequence analysis, and candidate mutations were confirmed using Sanger sequencing. The correlation between mutations and clinical manifestation was evaluated.

\section*{Methods:} To investigate the incidence and effects of mutations of PAX2 and 25 related genes, 25 patients with CAKUT were screened using next-generation sequence analysis, and candidate mutations were confirmed using Sanger sequencing. The correlation between mutations and clinical manifestation was evaluated.

\section*{Results:} Thirty patients, including two family cohorts (n = 5 and 2), 19 patients with sporadic CAKUT, and 4 coloboma only control cases were evaluated in the present study. Screening the sequences of PAX2 and 25 other genes identified 46 nonsynonymous single nuclear changes and 9 indels. Among these candidate gene abnormalities, eleven PAX2 mutations were detected in another patient, of which KIF26B mutation was novel. Kidney function and proteinuria were more severe in patients with PAX2 mutations than in those without themutation. Moreover, the coloboma score was significantly higher in patients with PAX2 gene mutations. Three out of five patients with PAX2 mutations had focal segmental glomerulosclerosis diagnosed from kidney biopsies.

\section*{Conclusions:} Our data indicate that PAX2 mutation is a key mutation in CAKUT and may make a major contribution to the pathogenesis of kidney and eye abnormalities. However, other factors and gene mutations may play a role, and further human and animal studies will be required to define the mechanism of pathogenesis of CAKUT.

\section*{Funding:} Government Support - Non-U.S.

Whole Exome Sequencing Identifies a Mutation in TCC25 as a Novel Monogenic Cause of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)\textsuperscript{1} Julian Jakob Schulz,\textsuperscript{1} Asaf Vivante,\textsuperscript{1} Jing Chen,\textsuperscript{1} Shirlee Shirl,\textsuperscript{1} Eljah O. Kehinde,\textsuperscript{4} Friedhelm Hildebrandt,\textsuperscript{4,} 5

\section*{Methods:} To identify novel monogenic causes of CAKUT we applied homozygosity mapping with whole exome sequencing (WES) to 36 families with CAKUT. Then we investigated a worldwide cohort of ~1,600 families with CAKUT with a barcoded array based multiplex exon PCR (48x48 Fluidigm Access Array\textsuperscript{TM}) and next generation sequencing (Illumina MiSeq\textsuperscript{TM}). All identified mutations were confirmed by Sanger sequencing.

\section*{Results:} A homozygous truncating mutation (p.Tyr179*) in the gene TUBAL3 was identified in the consanguineous Indian family A3838 using WES. We then independently detected another mutation homoyzogously (p.Gly10Ser) in the gene TUBAL3 in a family A1347 of Kurdish descent. TUBAL3 (Tubalin, alpha-like 3) is a protein coding gene and is very conserved across species. Tubulin is the major constituent of microtubules.

\section*{Conclusions:} We identified recessive mutations in TUBAL3 as a novel single-gene cause of CAKUT. Further genetic information and functional studies will help understand disease mechanisms and the role of TUBAL3 in the pathogenesis of CAKUT.
Methods: To identify causative genes for CAKUT we investigated consanguineous families with CAKUT by applying whole exome sequencing (WES) combined with homozygosity mapping.

Results: In one family we detected a homozygous loss-of-start-mutation in the gene TCT25 (tetratricopeptide repeat-containing 25). This mutation (p.MetThr; c.2T>C) was present in a consanguineous family with a posterior urethral valve, vesicourethral reflux and bilateral hydrourephrosis. TCT25 plays a role in ciliogenesis, pronephric cilia function and signal transduction in the sonic hedgehog pathway (Hayes, J. M. et al., 2007. Dev. Biol. 312: 115; Xu Y et al., 2015. PLOS ONE 10(4): e0124378). The latter has been shown to coordinate bladder as well as urethra formation in mice (Haraguchi R et al., 2007. Development 134(3):525; Haraguchi E et al., 2012. PLOS ONE 7(1): e42245).

Conclusions: By WES and homozygosity mapping we identified TCT25 as a novel monogenic CAKUT-causing gene if mutated.

Funding: NIDDK Support

FR-PO174

Phenotypic Analysis of a Cohort of Patients with Hepatocyte Nuclear Factor 1 Beta (HNF1β) Mutations and Correlation with Established Scoring Systems

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Background: Hepatocyte nuclear factor 1 beta (HNF1β) mutations may lead to a wide spectrum of clinical phenotypes including developmental defects of the kidney, pancreas, liver, and Mullerian duct. HNF1β mutations account for Renal Cysts and Diabetes (RCAD) syndrome. We reviewed patients with known HNF1β mutations to determine the range of phenotypes encountered and identified if these patients would have been detected based on established scoring systems.

Methods: We selected patients who had been screened for HNF1β mutations from 2009 to 2014 within our hospital. Serum magnesium, potassium, urate and creatinine levels were noted along with renal morphology based on imaging. All positive and negative patients for HNF1β mutations had their phenotypes quantified and correlated with published HNF1β scoring systems and screening criteria.

Results: 135 patients were screened over 5 years. The cohort included 17 patients from 10 families with confirmed HNF1β mutations. The majority of these patients had CKD stage 3, with a mean creatinine of 144 umol/L. Only 35% of mutation positive patients had both renal cysts and diabetes. 57% of patients had hypomagnesaemia, 50% of the patients had hyperuricaemia and 4 patients had clinical symptoms of gout with 75% of these patients having hyperuricaemia and 4 patients had clinical symptoms of gout with 75% of these patients presenting with gouty symptoms before the age of 30. Using a published HNF1β scoring system, 16 patients reached a threshold score of ≥8, sufficient for a presumed diagnosis, validating the sensitivity of the scoring system in our cohort. Based on alternative screening criteria, all 17 patients would have been identified for screening.

Conclusions: The majority of patients with HNF1β mutations demonstrated hypomagnesaemia (50%), hyperuricaemia (53%) and deranged liver function tests (59%). RCAD remains a misnomer and patients with HNF1β mutations have a wide phenotypic spectrum, with only one third having renal cysts and diabetes. The use of a HNF1β scoring/screening system will help to improve detection rates.

FR-PO175

CTNS Gene Mutations and Variants in Adult Hemodialysis Patients

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Background: Nephropathic Cystinosis (NC), a rare, systemic, autosomal recessive disease due to CTNS gene mutations causes end-stage renal disease (ESRD). While most cases of NC are recognized in infancy (95%), late-onset NC with ESRD is rare but might be under-diagnosed. NC is rarely diagnosed in African-Americans (AA). Objective: To identify CTNS mutations and possible pathogenic variants (A) in a representative sample of adult patients (pts) in the US.

Methods: Genomic DNA was extracted from whole blood from 4007 adult hemodialysis pts from the Davita biorepository. Fluidigm’s Access Array IFC was used for the CTNS target enrichment. Enriched DNA was sequenced on the Hiseq 2500 using 2 x 100bp read length.Reads were mapped to the human genome version hg19 using the BWA aligner. Mutations and Δ were called using both GATK and Samtools and confirmed by Sanger sequencing.

Results: 16 pts had homozygous (HoZ) and 52 pts had compound heterozygous (HTZ) CTNS sequence Δ. 168 pts had a known diagnosis of NC (W138X). In HoZ pts, 6 had known mutations in CTNS (V42I/G66 were AA) consistent with NC. 9 had upstream promoter mutations (UPM) (7 with -294C>T and 2 with -295G>C, a mutation locus with known disease association), and 3 of these pts were AA. In 52 HTZ CTNS sequence Δ, 2 AA pts had UPM. The other 50 had combinations of changes in the CTNS coding sequence & promoter region.

Conclusions: The unexpected frequency of CTNS gene mutations & Δ suggest that late-onset NC may be underrecognized in ESRD. These CTNS alterations need further study to determine pathogenicity and association with NC. In addition, CTNS mutations & Δ in AA subpopulation signals a need for evaluation for a diagnosis of late onset nephropathic cystinosis in ESRD.

Funding: Pharmaceutical Company Support - Raptor Pharmaceuticals

FR-PO176

Sixteen Monogenic Genes Cause 20% of Early-Onset Urinary Stone Disease

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Background: Urinary stone disease (USD) is a prevalent condition that affects 10-15% of adults in their lifetime. It is associated with high morbidity due to colicky pain, the necessity for surgical intervention, and sometimes progression to chronic kidney disease. In recent years, multiple monogenic causes of USD have been identified. However, the prevalence of each monogenic gene has yet to be systematically studied in a pediatric urinary stone cohort.

Methods: To determine the proportion of cases that can be explained molecularly by mutations in 1 of 30 known urinary stone genes, we conducted a high throughput exonic sequencing analysis in an international cohort of consecutively recruited individuals from three renal stone clinics. The cohort consisted of 143 individuals under 18 year of age, with nephrolithiasis (n=123) or isolated nephrocalcinosis (n=20).

Results: We detected likely causative mutations in 16 of 30 analyzed genes, leading to a molecular diagnosis in 20% (29 of 143) of affected individuals; 14 of the 32 detected mutations were not previously described as disease causing (43.8%). We show that mutations in recessive genes are more likely to cause infantile onset disease, whereas mutations in dominant genes are more likely to manifest later.

Conclusions: We present the first exclusively pediatric cohort examined for monogenic causes of urinary stone disease, and our data demonstrates that important therapeutic and preventative measures may result from mutational analysis in individuals with early-onset USD.

Funding: Other NHII Support - DK1069274, DK1068306, and DK064614

FR-PO177

Mild Inhibition of Alanine-Glyoxylate Aminotransferase Translation as a Possible Treatment of Primary Hyperoxaluria Type I

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Background: Primary hyperoxaluria type I (PH1) is a kidney stone disease, often leading to ESRD, caused by absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT), encoded by AGT. The most frequent mutation G170R, responsible for 30% of PH1 cases in Caucasians, results in aberrant mitochondrial localization rather than catalytic inactivity. Modulating AGT maturation and folding has long been perceived as a therapeutic approach. Yet, numerous attempts over the years failed to rescue AGT mutants. We propose mild translational inhibition as a novel approach to rescue AGT mutants. We propose mild translational inhibition as a novel approach to modulate AGT translation in a dose-response fashion. Mild inhibition of AGT translation would allow AGT partial resurfacing in the mitochondrial (major) versus peroxisomal (minor) subpopulations of mutated AGT.

Methods: Using a short-term treatment with low concentrations of emetine showed statistically significant increase of the peroxisomal (minor) subpopulations of mutated AGT we developed the self-assembly split-GFP-based assay for detecting peroxisomal subpopulation of AGT. To ensure selective and specific discrimination between the mitochondrial (major) and peroxisomal (minor) subpopulations of mutated AGT we developed the GlowAGT,WT-AGT but not G170R-AGT was detectable by GFP fluorescence, although both variants were visible by indirect immunofluorescence. Long-term treatment with low concentrations of emetine showed statistically significant increase of fluorescent subpopulation of G170R-AGT. GFP fluorescence was exclusively co-distributed with the peroxisomal staining in all cases.

Conclusions: We have developed and applied successfully GlowAGT as a unique self-assembly split-GFP-based assay for detecting peroxisomal subpopulation of AGT. Using GlowAGT we show that mild translation inhibition by emetine is a novel therapeutic approach for PH1 caused by AGT misfolding/mislocalization.
FR-PO178

Functional Analysis of CLCNKB Mutations Causing Bartter Syndrome Type III
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Background: Bartter Syndrome type III is a human autosomal recessive disease characterized by salt wasting, hypokalemic metabolic alkalosis and secondary hyperaldosteronism. Therefore, patients affected by Bartter syndrome type III display the clinical triad characterized by salt wasting, hypokalemic metabolic alkalosis and secondary hyperaldosteronism. Therefore, patients affected by Bartter syndrome type III display the clinical triad.

Methods: We characterized the electrical activity, total protein expression, surface expression and subcellular localization of mutated forms of ClC-Kb in X. laevis oocytes and mammalian cell lines.

Results: Currents produced by G424R and G437R CIC-Kb channels were reduced by 50%, in proportion to membrane targeting without any change in total protein abundance. A204T mutants did not produce any current but their membrane insertion was only partially reduced (50-80%). Protein abundance of A210V was decreased by half. Conversely, that of P216L was comparable to WT CIC-Kb, suggesting that the P216L mutation might alter channel gating. Finally, A204T seems to be electrically functional, well rather inserted into the plasma membrane and protein level is comparable to that of wild-type CIC-Kb.

Methods: a. Fetal kidneys were exposed to maternal hyperglycemia using Streptozotocin (STZ). Posteriorly these sections were immunostained to detect apoptosis (active caspase3) in the CM (Six2 and NCAM) and nascent neprons (Lefl and NCAM). b. Glycoseis inhibihet ex vivo in E12.5 kidneys by pharmacetical inhibition of PFKFB3 (YN1 5-25nM). c. Glycoseis and oxidative phosphorylation were measured in NIDDK Support, Other NIH Support - NIH-NIGMS newborn kidneys of Six2-GFP-gfp3/2, a genetic model of impaired cap mesenchyme renewal.

Results: a. CM of P0 kidneys of STZ-treated females showed increased apoptosis and reduction in nascent nephron number (Lefl+ and NCAM+). b. Glycoseis inhibition resulted in a smaller dispersed CM, accelerated but not ectopic differentiation of the NPC with up to a 50% increase in Lhex+ nascent nephrons 24-48h post-treatment, and decreased Citedl expression by QPCR in isolated NPC. UB tip and branch numbers were unchanged. Thus, increased nephrogenesis was independent of UB branching. Expression of Wnt4 was unchanged. c. Conditional deletion of p53 in NPC resulted in dispersed CM, depletion of the Citedl+V2+ NPC dependent of apoptosis, and hypoplastic kidneys with fewer nascent nephrons. Isolated mutant cells showed reduced basal oxygen consumption rate and decreased maximal respiratory capacity. Accordingly, the mutant cells exhibit a significant, nearly two-fold decrease in ATP (p<0.005, n=3).

Conclusions: Our data are consistent with the idea that the metabolic status of the NPC is a critical determinant of NPC renewal and differentiation.

Funding: NIDDK Support, Other NIH Support - NIH-NIGMS

FR-PO182

Prorenin Receptor Signaling Promotes Nephron Induction During Mouse Kidney Development
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Background: Deficient nephrogenesis is the major factor contributing to congenital renal hypoplasia (RHD), one of the leading causes of childhood end-stage kidney disease. Nephron induction is driven by reciprocal interactions between progenitor cells of the cap mesenchyme and the ureteric bud (UB).

Methods: To determine the potential role of the prorenin receptor (PRR) in nephrogenesis, we generated mice with a conditional deletion of the PRR in nephron progenitors using Six2-Cre;ROSA-RFP.

Results: Inactivation of PRR in nephron progenitors caused a marked decrease in the number of developing nephrons, severe congenital RHD with collapsed glomeruli and an enlarged Bowman’s space (such as those seen with a collapsing FSGS), podocyte foot process effacement and early postnatal death within 48 hours from birth. UB branching was greatly reduced, likely secondary to decreased nephrogenesis. Reduced congenital nephrogen endowment resulted from premature depletion of nephron progenitor cell population due to impaired progenitor cell proliferation and loss of normal molecular inductive response to canonical Wnt/β-catenin signaling within the metanephric mesenchyme. At 2 months of age, heterozygous Six2+RFP+ mice exhibited focal glomerulosclerosis, decreased kidney function and massive proteinuria.

Conclusions: Collectively, these results are consistent with a cell-autonomous requirement for the PRR within nephron progenitors for progenitor maintenance, induction of nephrogenesis, normal kidney development and function. Thus, PRR is a potential candidate for future genetic screening studies in patients with congenital RHD and proteinuric kidney disease.

FR-PO183

Functional Dissection of Enhancers for Bmp7 in Kidney Development
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Background: Bmp7 is a critical player in the kidney development, as shown by its severe retardation in the KO mice of the gene and their subsequent perinatal lethality due to the malfunction. Previous studies identified two potential enhancers for the Bmp7 expression in the developing kidney around the lona: one residing inside the 1st intron of Bmp7 for expression in the developing ureteric bud; the other located downstream of the 3’nd end of Bmp7, which is rather active in the metanephric mesenchymal cells. Consistently, Bmp7 is also expressed in these two distinct domains. However, neither the requirement of these elements nor the influence of Bmp7 secreted from these different cell types for the kidney development has been uncovered so far. In this study, we aimed to characterize the roles of the two enhancers to better understand the cis-regulation of Bmp7 and the kidney development.

Methods: We established and analyzed homozygous mice carrying a large genomic deletion of the downstream region of Bmp7 including the mesenchymal enhancer.

Results: We found that they have significantly smaller body size than their wild type littermates, although they are viable unlike the KO mouse of Bmp7. We previously showed that the above deletion also disrupts the topological partition of the chromatin conformation between the Bmp7 domain and the neighboring one of another developmental gene, Tjp2/c, resulting in a merger between them (Tsujimura et al. PLAS Genetics 2015). Interestingly, upon this deletion, we scored significant up-regulation of Tjp2/c in the kidney probably by the effect of the intron enhancer.

Conclusions: These results suggest that the endogenous genomic context guarantees robustness in the regulation of the kidney development by linking the more important ureteric bud enhancer to Bmp7 tightly. The differential roles of the two enhancers will be further discussed based on the histological and functional analysis of the kidney in the homozygous deletion mice.

Funding: Government Support - Non-U.S.

FR-PO184

BMP7 Regulates Expansion of the Postnatal Nephron
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Background: The factors that regulate the expansion of nephrons after their initial induction and differentiation are largely unknown. Bone morphogenetic protein 7 (BMP7) is a crucial factor driving proliferation and self-renewal of nephron progenitor cells during the development of the embryonic kidney. In this study we investigated a potential role for BMP7 as a regulator of post-induction nephron growth and differentiation.

Methods: The Bmp7 gene was conditionally mutated in progenitor cells using Six2-GFP-Cre. Kidneys from mutant and control mice were analyzed using a novel approach to quantitatively proximal tubule expansion as an indicator of nephron growth in the postnatal mouse.

Results: Kidneys of Bmp7 conditional mutant mice were smaller with reduced numbers of nephrons. Bmp7 was expressed in developing nephron tubules of control kidneys and was absent from mutant kidneys. Proximal tubule growth, as determined by computationally measuring the area of lectin-stained proximal tubules in postnatal kidneys, was reduced in mutant kidneys. However, the proximal tubule area per glomerulus was increased in mutant kidneys, indicating that those nephrons that were induced underwent hypertrophy. Hypertrophy, as defined by Kdo2×Glomerular size, increased in both mutant and control mice but was greater in mutants than in control by P10.

Conclusions: Loss of Bmp7 in progenitors leads to low nephron number. Bmp7 appears to be an important driver of postnatal nephron expansion. This phenotype is similar to hypogonadism and may be used to understand the basis for nephron hypotrophy in low nephron number situations.

Funding: NIDDK Support

FR-PO185

Grainyhead-Like 2 (Grhl2) Regulates Collecting Duct Barrier Function, Aquaporin 2 Expression and Urinary Concentration
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Background: Osmotic homeostasis is tightly regulated by the kidney and its collecting ducts which form tight barriers, thereby maintaining steep concentration gradients and allowing transcellular reabsorption of water via aquaporins. The transcription factor grainyhead-like 2 (Grhl2) is highly expressed in renal collecting ducts. Using cultured collecting ducts, we recently showed that Grhl2 regulates epithelial barrier formation and lumen expansion via a target gene set comprising the transcription factor Ovo-like 2 (Ovol2), the small GTPase Rab 25 (Rab25) and the tight junction component claudin 4 (Cldn4). The role of Grhl2 in the collecting duct in vivo is unknown.

Methods: To investigate the role of Grhl2 in the renal collecting duct, we generated a collecting duct-specific knockout with Hoxb7-Cre;Grhl2+-/lox mice, which exhibit a deletion of Grhl2 protein in most of the collecting ducts. The molecular and cellular alterations in their kidneys and their response to water deprivation were analyzed.

Results: Transcriptional profiling of Hoxb7-Cre; Grhl2+-/lox mice kidneys and control littermates showed deregulation of Ovol2, Rab25 and Cldn4, but also differential expression of Aquaporin 2 (Aqp2). Following water deprivation, Grhl2-deficient mice displayed significantly lower urinary osmolality at 6 hours (P<0.001) and 24 hours (P<0.04) when compared to control mice. Moreover, Grhl2-deficient mice had more than 35% more urine volume during the first 24 hours in response to water deprivation when compared to controls (P<0.005).

Conclusions: Our data indicate that Grhl2 critically participates in water homeostasis, epithelial barrier function and Aqp2 expression. This might be of relevance to diseases involving defective renal responses to water deprivation.

Funding: NIDDK Support

FR-PO186

Loss of the Transcription Factor Te2f2 in the Renal Struma Leads to Polyuria and Defects in Tubular Development
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Background: Renal stromal cells serve as a supportive framework for nephrons and the collecting duct network, produce erythropoietin, and contribute to renal fibrosis when they undergo myofibroblast-like transformation. Te2f2/Pod1 is a BHLH transcription factor

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

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strongly but not restrictively expressed in the developing renal stroma. Conventional Tcfl1 knockouts (KO) mice survive and have maldifferentiated renal stromal and pericytes without signs of the renal interstitium. However, the precise function of Tcfl1 within renal stromal cells has yet to be clarified as Tcfl1 is also expressed within the condensing metanephric mesenchyme during development.

Methods: In order to characterize the role of Tcfl1 in stromal development and function, we bred floxed Tcfl1 mice with Foxd1-Cre mice allowing specific inactivation of Tcfl1 within the developing renal stroma and its derivatives.

Results: Mice lacking Tcfl1 in the renal stroma (Tcfl1<sup>fl/fl</sup>) do not have an overt phenotype at birth, but renal stromal arterioles branching in embryonic kidney explant cultures. However, by 4 weeks postnatal, Tcfl1<sup>fl/fl</sup> mutant mice develop polycyria similar to diabetes insipidus. Polyuric mutant mice produce urine with significantly reduced osmolarity and creatinine levels but with higher levels of sodium and chloride relative to control littersmates. Mutant kidneys are smaller, have a disorganized interstitium, and shriveling of the medullary rays due to a reduction in the loops of Henle and collecting ducts, whereas proximal tubule densities appear undisturbed.

Conclusions: Specific inactivation of Tcfl1 in the stroma causes polycyria underscoring an important role of the renal interstitium in regulating postnatal development of tubules critical for urine concentration.

Funding: Government Support - Non-U.S.

FR-PO187

Genetic Deletion of Cyclooxygenase-2 Impairs Glomerular Silt Diaphragm Formation During Late Stages of Kidney Development

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Background: Renal cyclooxygenase-2 (COX-2) expression is necessary for normal glomerular development. Impaired COX-2 activity has been associated with decreased expression of VEGF, a vascular growth factor of significant importance for glomerular capillary development. Therefore experiments were designed to test the hypothesis that COX-2 expression supports glomerular development through stimulation of capillary loop formation.

Methods: Kidney tissue was collected from a developmental series of COX-2 knockout (KO) mice and wild-type littersmates (WT).

Results: Renal COX-2 expression showed developmental regulation with significantly higher COX-2 expression at postnatal (P) days 1 and P7 than at any later time points (P14, P21 and P40). Quantitative unbiased stereology at P2 showed significantly reduced glomerular number in COX-2 KO mice compared to WT littersmates (8188 ± 781 and 12251 ± 454 glomeruli/kidney respectively, P=0.0001). Subcapsular accumulation of small and immature glomeruli was seen in COX-2 KO mice whereas glomeruli deeper in the cortex towards the medullary junction appeared normal. Tissue abundance of VEGF, angiopoietin-1 and -2 mRNAs was significantly reduced in COX-2 KO mice compared to WT at P7. By electron microscopy at P28, immature subcapsular glomeruli showed normal appearance of fenestrated endothelial cells but severe podocyte foot process effacement and absence of mesangial cells. Normal morphology was confirmed in glomeruli deeper in the cortex. At P7, COX-2 KO mice showed reduced expression of silt diaphragm proteins nephrin and podocin but not syndecanopin compared to WT. In summary, deletion of COX-2 leads to decreased renal expression of VEGF, a key growth factor for renal stromal and mesangial cells, with severe podocyte foot process effacement and absence of mesangial cells.

Conclusions: In summary, deletion of COX-2 leads to decreased renal expression of VEGF, a key growth factor for renal stromal and mesangial cells, with severe podocyte foot process effacement and absence of mesangial cells.

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FR-PO188

Functional Cross Talk Between Tyrosine Phosphorylation of Crumbs Homolog 2 and Mechanistic Target of Rapamycin Complex 1 in Developing Podocyte

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Background: Mutation of crumbs homolog 2 (CRB2) is a novel cause of congenital nephrotic syndrome (cNS). We have previously characterized transplantation of kidney and liver tissues from CRB2 deficient mice. However, how CRB2 functions in podocyte development is unknown.

Methods: MKC cells expressing mouse full-length CRB2 or mutated-CRB2 lacking tyrosine phosphorylation site were established. Specific antibodies against CRB2 intracellular domain (CRB2-Ab) or tyrosine phosphorylation site (pY-CRB2-Ab) were generated. The samples from cultured cells and rat kidneys were subjected to Western blot and immunofluorescence microscopy.

Results: Int-CRB2Ab determined CRB2 to locate at the apicobasolateral membrane in wild-CRB2 cells. Specificity of pY-CRB2Ab was confirmed by using samples from mutated-CRB2 cells and wild-CRB2 cells treated with protein tyrosine phosphatase inhibitor. Int-CRB2Ab identified that CRB2 expression commenced at the comma-shaped body stage, observed in the apical side of glomerular epithelium. CRB2 in the S-shaped body was still visible at the apical side of immature podocytes, then translocated along the lateral side of mature podocytes. At the mature stage, CRB2 was observed in the podocyte foot processes. In contrast, phosphorylation of CRB2 was determined faintly in immature podocyte at the S-shaped body stage, intensely at the mature stage and then decreased in the proximal distal convoluted tubule (P.05). CRB2 tyrosine phosphorylation may regulate energy system of developing podocytes through suppressing excessive mTORC1 activation.

Conclusions: CRB2 tyrosine phosphorylation may regulate energy system of developing podocytes through suppressing excessive mTORC1 activation.

Funding: NIDDK Support

FR-PO190

Epithelial Cell Fate in the Nephron Tubule Is Mediated by the Etv5a Transcription Factor During Zebrafish Kidney Development

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Background: Kidney development requires the differentiation and organization of discrete nephron epithelial lineages, however the genetic and molecular pathways involved in these events remain poorly understood. The embryonic zebrafish kidney, or pronephros, provides a simple and useful model to study nephrogenesis.

Methods: The pronephros is comprised of two types of epithelial cells: transportive and multi-ciliated cells (MCCs). Transportive cells occupy distinct tubule segments and are characterized by expression of solute transporters, while MCCs function in fluid propulsion and are dispersed in a “salt-and-pepper” pattern in the tubule. Epithelial cell identity is related by a pathway between Notch signaling pathway and retinoic acid (RA) signaling, where RA promotes MCC fate by inhibiting Notch signaling in renal progenitors, while Notch activity acts downstream to trigger transportive cell formation and restrict MCC identity. Previous research has shown that etv5a and its ETS family members are required for ciliogenesis in other zebrafish tissues.

Results: Here, we mapped etv5a expression to renal progenitors that occupy domains where MCCs later emerge. Thus, we hypothesized that etv5a is required for ciliogenesis of MCCs in the nephron. etv5a loss of function produced a decline of MCC number and reduced expression of the MCC markers odf3b and centrin, where rescue experiments partially restored wild-type MCC number. In epistatic studies, exogenous RA treatment expanded the etv5a domain, indicating that etv5a acts downstream of RA. Additionally, treatment with exogenous RA partially rescues the reduced MCC phenotype after loss of etv5a. Further, abrogation of Notch with the small molecule inhibitor DAPT increased etv5a expression, while overexpression of Notch using a transgenic line reduced the etv5a domain, suggesting Notch acts upstream to inhibit etv5a.

Conclusions: Taken together, these findings provide novel insights about the mechanisms of epithelial cell development during nephrogenesis.

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FR-PO191

Emx1 Is Essential for Distal Segment Development During Nephrogenesis

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Background: Vertebrate kidneys are comprised of functional subunits called nephrons that typically have three basic parts: a renal corpuscle, a tubule with proximal and distal segments, and a duct. The developmental pathways that establish nephron segment identities from renal progenitors remain poorly understood.

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Methods: The zebrafish embryo forms a simple two-nephron pronephric kidney that provides an ideal model system with which to study cell-fate decisions with high anatomical and genetic resolution. emx1 is a homeobox gene that, along with its paralog emx2, is known for playing essential roles in brain development. While both genes are expressed in the pronephros, their roles in nephrogenesis have not been established. Using whole mount in situ hybridization, we found that emx1 and emx2 were dynamically expressed in renal progenitors, and became localized to the distal and proximal renal segments, respectively.

Results: In knockdown studies, emx1 morphants formed a normal distal domain, marked by cranx, but within it formed an expanded distal early (DE) segment, marked by slc2a12a. These data suggest that emx1 is essential to promote the DL, and may restrict the DE and/or negotiate the site of the DE/DL boundary. Furthermore, emx2/2 expression is responsive to changes in retinoic acid (RA), which is essential to induce proximal segments and repress distal segments during nephrogenesis. RA treated embryos had a restricted emx1/1 domain and expanded emx2 domain, while exposure to the RA biosynthesis inhibitor DEAB conversely expanded emx1 and restricted emx2 expression. These data suggest that RA signaling acts upstream of both genes in renal progenitors, positively regulating emx1 and negatively regulating emx2.

Conclusions: Future studies will define the role of emx2, independently explore emx1/2 nephron patterning functions with CRISPR-Cas lines, and assess the relationship of these emx genes to other factors, such as irx3, that have been shown recently identified to be components of the gene regulatory networks that direct nephron segmentation. Preliminary data looking at factor interactions suggest that emx genes may be located downsteam of others who regulate independent pathways.

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FR-PO192
Prostaglandins as Regulators of Nephron Proximo-Distal Cell Fate Decisions Shahram Jevin Pourcetzecht, Christina N. Cheng, Rebecca A. Wingert. Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: To date, there have been a number of important discoveries furthering our understanding of nephron segmentation. Despite this, the factors that direct nephron cell-fate decisions remain largely unknown. Danio rerio, the zebrafish, possess an embryonic kidney composed of two nephrons and a blood filter that share a remarkable degree of genetic, structural, and functional homology with the human nephron and when coupled with genetic tractability, ex utero development, and optically transparent embryos make it a cutting-edge model to study nephrogenesis.

Methods: The zebrafish embryonic kidney, the pronephros, is organized in a proximal-distal pattern of contiguous segments much like the human kidney. The proximal segments, the proximal convoluted tubule (PCT) and the proximal straight tubule, share a name with their mammalian counterpart counts; the distal segments, the distal early (DE) and the distal late (DL) – are homologous to the mammalian thick ascending limb (TAL) and distal convoluted tubule (DCT) respectively. We performed a chemical genetic screen using zebrafish embryos during nephrogenesis and analyzed the effects on segmental patterning.

Results: Interestingly, a large number of prostaglandin (Pg) pathway components were identified among our hits. Prostaglandins (Pgs) are fast-acting lipids necessary for an array of physiological functions. We discovered that treatment with bioactive Pg agonists restrict the PCT and DL, while inducing an expansion of the PST. Genetic knockdown and small molecule inhibition of the Pg producing Cox1/2 enzymes or the Pg Ep G-protein receptors triggered an expansion of the DE segment at the expense of the DL. Further, we saw that modest levels of Pj pathway with higher vertebrates. emx1 is a homeobox gene that, along with its paralog emx2, is known for playing essential roles in brain development. While both genes are expressed in the pronephros, their roles in nephrogenesis have not been established. Using whole mount in situ hybridization, we found that emx1 and emx2 were dynamically expressed in renal progenitors, and became localized to the distal and proximal renal segments, respectively.

Conclusions: Thus, we show here for the first time that Pg signaling has an impactful role in nephron cell-fate decisions, suggesting that Pgs may have considerable implications for kidney development and disease.

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FR-PO193
Cloning of the Zebrafish Kidney Mutant Zeppelin Reveals That Bra2/Fancl1 Is Essential for Renal Development Paul T. Kroeger, Rebecca A. Wingert. Biological Sciences, Univ of Notre Dame, Notre Dame, IN.

Background: Zebrafish kidneys are conserved with other vertebrates, making them an excellent genetic model to study renal development. The kidney collects metabolic waste using a blood filter with specialized epithelial cells known as podocytes. Podocyte formation is poorly understood but relevant to many kidney diseases, as podocyte injury leads to proteinuria, which is characteristic of renal disease.

Methods: zeppelin (zep) was isolated in a forward screen for kidney mutants and identified as a homoygous recessive lethal allele, which has a loss of podocyte numbers, deficient filtration, and fluid imbalance. Addition of retinoic acid did not rescue the zep mutant phenotype. Although mutants had normal formation and cell death, the interrenal gland was increased in size, suggesting a possible cell fate switch between these related lineages. This data was corroborated by interrenal gland volume identified by FISH analysis. 3β-HSD staining indicated the interrenal gland produced more hormones in the zep mutants, potentially suggesting an alternate mechanism of an endocrine feedback loop leading to proliferation of interrenal cells.

Results: Meiotic mapping and whole genome sequencing of zep identified a splicing mutation in breast cancer 2, early onset (bra2)/fancl1, which was confirmed by sequencing of bra2/fancl1. Several independent bra2 morpholino phenocopy zep, causing edema and podocyte reductions, as well as an increase in the size of the interrenal gland. Additionally, 3β-HSD staining suggests that morphants have an increased number of cells that generate hormones, similar to zep. Histological analyses of the adult kidney in zep heterozygotes, bra2+/−, 3β-HSD+ juveniles and adults showed renal pathologies associated with glomerular defects. Taken together, these data suggest for the first time that bra2/fancl1 is essential for kidney development and homeostasis.

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FR-PO194
Development of the Vasculature in the Bladder Julia K. Schaffer,1 Kenneth A. Walker,2 Caitlin M. Schaefer,2 Daniel S. Bushnell,3 Elna Mukherjee,1 Sunder Simis-Lucas,2 Carlton M. Bates,2 1Div of Newborn Medicine, Univ of Pittsburgh; 2Div of Nephrology, Univ of Pittsburgh, Pittsburgh, PA.

Background: Developing bladder consists of differentiating outer muscle, middle stromal, and inner epithelial layers. To date, formation of the bladder vascular network has not been determined. Aim: To determine vascular patterning through bladder development.

Methods: We examined developing bladder vasculature from embryonic day (E) 11.5 through postnatal day (P) 30 by genecis histology and immunohistochemistry (including morphometry with GSL1 lectin staining). We performed quantitative realtime PCR (qPCR) for genes associated with vascular formation (e.g. Angiopoietin 1 and Vegfa ligands and Tie2 and Vegf2 receptors) and hypoxia inducible factors (Hifs).

Results: In early bladder development (E11.5-13.5) vascular branches from the umbilical arteries grow towards a network of developing vessels within the primitive bladder mesenchyme. However, by E15.5, connections between the umbilical arteries and primitive bladder vasculature network are diminished and a vascular remodeling. Perfusion (presence of red blood cells) of most bladder vessels was identified even at early developmental time points. Morphometric assessment revealed a peak in relative vascular tissue content in the bladder at E15.5, which regressed with further maturation. This reduction in vascular content after E15.5 suggests vascular pruning and further remodeling. qPCR revealed that Angiel1 and Vegf2 expression peaked during early embryonic development, whereas expression of the Angiel receptor, Tie2, peaked in early postnatal mice. The Vegf2 ligand Vegfa displayed consistent expression at all ages. Interestingly, Hif1a and Hif2a demonstrate inverse mRNA expression profiles with Hif1a highest in embryonic bladders and Hif2a expression peaked in adult bladders.

Conclusions: Unexpectedly, bladder vasculature appears to arise from angiogenic vessels that arise from the umbilical artery. Subsequently, early bladder vessels undergo pruning with age. Key molecules that regulate vascular development, including hypoxia inducible factors, have differential expression patterns.

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FR-PO195
Exploring the Relation Between Cells and Extracellular Matrix in the Developing Human Fetal Kidney Astrik Petrovska,1 Estefanie Rodriguez,1 Ruby Kim,1 Hasmik Soloyan,1 Brendan Grubbs,2 Matthew Edward Thornton,2 Roger E. De Filippo,1 Laura Perin,1 Stefano Da Sacco,3 1Urology, Children's Hospital Los Angeles, Los Angeles, CA; 2Div of Developmental Biology, University of Pittsburgh, Pittsburgh, PA.

Background: It is widely accepted that, during development, the renal compartment undergoes dramatic changes in regards to cell specification and differentiation, matrix deposition and spatial organization. However, despite the growing number of studies focusing on kidney mouse development, very little is known of changes, including cell differentiation and extracellular matrix (ECM) deposition, occurring during human development. To fill this gap, we have characterized human embryonic kidneys (hEK) at different weeks of gestation to better understand renal progenitor biology and cell-matrix interactions.

Methods: Histological analysis were carried out on hEK between 11-22 weeks of gestation for ECM components (such as collagen IV a1-6 chains, collagen I, fibronectin) and progenitor/mature renal cells markers such as WT1, Pax-2, Six-2, Cited1, VE-Cadherin, a-SMA.

Results: We observed dynamic changes in the ECM throughout the progression of the gestational ages. In particular, decrease in nephrogenic zone size along with a higher presence of C- and S-shaped structures and fully developed glomeruli and tubules was observed. Interestingly, Hif1a and Hif2a demonstrate inverse mRNA expression profiles with Hif1a highest in embryonic bladders and Hif2a expression peaked in adult bladders.

Conclusions: Our data suggest that, during hEK development, cell specification is accompanied by marked changes in ECM composition. This characterization might increase our knowledge of reparative processes enabling investigations focused on matrix remodeling and progenitor cell activation, thus ultimately enhancing the chances to treat renal damage.

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FR-PO196
Enalapril Treatment Modulates Lymphangiogenesis and Fibrogenic Machinery in the Developing Rat Kidney
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Background: The renin angiotensin system plays a pivotal role in both renal development and progressive renal disease. Lymphangiogenesis occurs during normal organ development and pathological processes. In this study, we aimed to investigate the effect of angiotensin II inhibition on the expression of fibrogenesis-related molecules and lymphatic vessels in the developing rat kidney.

Methods: Newborn rat pups were treated with enalapril (30 mg/kg) or vehicle for 7 days after birth. We investigated the intrarenal expression of fibroblast growth factor (FGF)-1, FGF-2, FGF receptor (R)–1, Fibroblast-specific protein (FSP)-1, intercellular adhesion molecule-1, toll-like receptor (TLR)-2, and TLR-4 with Western blotting and immunohistochemistry at postnatal day 8. For the determination of lymphatics, the lymphatic vessel markers of vascular endothelial growth factor (VEGF)-C, VEGFR-3, and podoplanin were assessed. For the detection of cell proliferation and collagen fibers, Ki-67 and Sirius red stainings were performed.

Results: In the enalapril-treated group, intrarenal FGF-1, FGF-2, FGF-1 and VEGF-C protein expression were decreased, compared to the controls (P < 0.05). Immunohistochemistry for the lymphatic vessel markers of VEGF-C, VEGFR-3, and podoplanin showed reduced lymphatic immunostainings in the enalapril-treated kidneys. However, FSP-1 expression was prominent in the interstitium and glomeruli in enalapril-treated kidneys. While cell proliferation was reduced in the enalapril-treated group, collagen deposition was enhanced in the enalapril-treated kidneys (P < 0.05). Intercellular adhesion molecule-1, TLR-2, and TLR-4 protein expression showed no differences between the two groups.

Conclusions: Enalapril treatment during postnatal 7 days may induce perturbations in FGF/FGF signals, cell proliferation, and lymphangiogenesis required for renal development and maturation and activate in part the fibrogenic machinery in the developing rat kidney.

FR-PO197
The Effect of Prenatal Hypoxia and a Postnatal High Salt Diet on Renal Structure in the Aged Mouse
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Background: Chronic fetal hypoxia leads to growth restriction and increased risk of adult disease. This study examined the long-term renal outcomes of offspring prenatally exposed to hypoxia, and whether a postnatal high salt diet could exacerbate impairments.

Methods: Pregnant CD1 mice were housed in a hypoxic chamber (12.0% O2; N=8, HYP). For control (21% O2; N=8, CON) environment from embryonic day (E) 14.5 to birth (E) 20.5. A subset of male pups was randomly allocated to a control diet (0.2% NaCl, NS) or high-salt diet (5% NaCl; HS) from 10 weeks of age. Blood pressure was measured at 12 months of age and kidneys were collected. Kidney sections were examined for nephron number, glomerulosclerosis, interstitial fibrosis, renal vascular remodeling, and alpha-smooth muscle actin (α-SMA) expression by a researcher blinded to treatment groups.

Results: Prenatal hypoxia led to a decrease in nephron number and elevated blood pressure. Kidneys of HYP offspring showed expansion of the mesangial matrix, thickening of glomerular basement membranes and increased glomerulosclerosis compared to CON. These changes were exacerbated by the HS diet. Interstitial fibrosis and renal vascular remodeling scores were increased in CON and HYP offspring fed the HS diet, with the effect greatest in HYP offspring. α-SMA staining of CON kidneys was confined to vascular structures, whereas in HYP kidneys α-SMA expression was prominent in the interstitium and glomeruli in enalapril-treated kidneys. Since ureteric branching, and global DNA methylation. Also, blockade of DNA methyltransferase inhibited ureteric branching in organ culture. Since ureteric branching, and global DNA methylation. Also, blockade of DNA methyltransfarase (FR-PO199)
A Perinatal Switch in Iron Utilization Determines Postnatal Chronic Kidney Disease
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Background: Iron deficiency affects 2 billion people world-wide and is a threat to embryonic and early postnatal development. Periconceptual maternal iron deficiency (PM-ID) results in hydropic postnatal kidneys but it is not clear whether PM-ID causes cell-lineage or cell-stage specific hypoplasia, nor which species of iron is involved.

Methods: We investigated a mouse model of dietary iron deficiency and a series of deletions of the transferrin receptor, TIR1 (cell autonomous transferrin iron deficiency, ATF-ID) in different cellular lineages using a novel TIR1-flox/lox construct.

Results: Severe PM-ID depleted both T1 iron and NTBI (non-transferrin bound iron) resulting in severely hypoplastic proximal tubules and even anephric during gestation, whereas the overall structure of uretic bud was maintained. Milder PM-ID resulted in surviving but severe postnatal kidney hypoplasia, disruption of the growth of the proximal tubule and TALH and increased mortality before weaning. To determine the mechanism of hypoplasia we examined mesenchymal, ureteral and stromal ATF-ID with different Cre drivers. Mesenchymal ATF-ID (SisCre or KspCre) demonstrated increasing demand for transferrin by the time of birth, resulting in worsening proximal tubule hypoplasia, remarkable cystic transformation and interstitial fibrosis, and even anephria (ProPax3Cre) after birth, the timing of which coincided with accelerated segment-specific growth. The combination of ATF-ID and PM-ID further worsened nephropen development. In contrast, the collecting ducts (HoxB7Cre) and stroma (Foxd1Cre) did not depend on transferrin.

Conclusions: In sum, NTBI supported prenatal and postnatal stromal and ureteric development and the initial stages of metanephric development, whereas T1 iron was required for perinatal maturation of the nephron. T1 iron depletion resulted in hypoplasia, cysts, and fibrosis, the timing and specificity of which was the result of a sequence of utilization of NTBI followed by T1 iron. We propose that a peri-natal switch in the mechanism of iron utilization during the compaction and segmentation of the kidney is reflected changing cellular control of iron delivery. Iron deficiency is a cause of CKD.

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FR-PO200
Troy/TNFRSF19 Marks a Progenitor/Stem Cell Population in the Kidney
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Background: Segment committed stem cells play a crucial role in renal development and regeneration. Identification of these stem cells is an important step towards the development of new diagnostic and therapeutic strategies for renal diseases. In this study, we evaluated Troy, an adult stem cell marker in other organs, as a marker for segment committed stem cells in the developing and adult kidney.

Methods: Renal Troy expression was assessed during embryonic development and adult turnover using Troy-GFP mice. The contribution of Troy+ cells to renal development and turnover was investigated using in vivo lineage tracing with Troy-GFP-CreERT2;Rosa-LacZ reporter mice. Troy+ cells were labeled with tdTomato and their clonal expansion in Troy+ cells were assessed.

Results: During embryonic development Troy+ cells were present in the ureteric bud [1A], whereas in adult kidney Troy+ cells were present in the papilla. After p1 induction, Troy+ cells gave rise to tubular structures by clonal expansion that persisted up to 2 years after induction [1B-1E]. Immunohistochemistry revealed predominant co-staining with the kidney marker AQP2 [1C]. Troy+ cells were co-localized to collecting ducts formation after cessation of nephrogenesis. Finally, Troy+ cells had a higher in vitro sphere forming capacity than Troy+ and Troy- cells [1F-1H].

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Results: A pulse of BrdU was administered at different periods during E11.5-20.5, respectively, covering the whole process of the kidney development. The adult kidney were incubated with small molecule fluorescent probes to monitor transport into lumens, or with nephrotoxic chemicals to assess upregulation of kidney injury molecule-1 (KIM-1). When treated with the nephrotoxic compounds gentamicin or cisplatin, ~ 70 % of hPSC-derived proximal tubules expressed KIM-1 at the apical/luminal surface. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA, significantly reduced cargo fluorescein methotrexate (MTX) transport cargoes. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA,

Methods: A pulse of BrdU was administered at different periods during E11.5-20.5, respectively, covering the whole process of the kidney development. The adult kidney were incubated with small molecule fluorescent probes to monitor transport into lumens, or with nephrotoxic chemicals to assess upregulation of kidney injury molecule-1 (KIM-1). When treated with the nephrotoxic compounds gentamicin or cisplatin, ~ 70 % of hPSC-derived proximal tubules expressed KIM-1 at the apical/luminal surface. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA, significantly reduced cargo fluorescein methotrexate (MTX) transport cargoes. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA,

Conclusions: These data show that Troy marks a stem/progenitor population for the collecting duct in the developing kidney. Moreover, our data also suggest a role for Troy+ progenitor cells in the adult kidney.

Preserved Nephrogenesis following Partial Nephrectomy in Early Neonates
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Background: For a long time, although the appendage regeneration has been limited to non-mammalian vertebrates, the rodent neonates demonstrated the capability to regenerate the resected cardiac apex. In this study, we hypothesized that neonatal kidney could maintain the capability of neoprogenesis.

Methods: One sixth-partial resection at the inferior pole of right kidney was performed on neonatal rats at postnatal day 1 (P1) and day 4 (P4) under the hypothermic anesthesia. The animals were sacrificed with time to examine by pathology and quantitative PCR, including limited tissue availability, phenotypic alterations due to immortalisation and a lack of genetic diversity. With the dawn of induced pluripotent stem cell (iPSC) technology,

Conclusions: The locations of LRCs were different if BrdU was administered in different periods of kidney development. Most of BrdU-retaining cells were quiescent, few of them in the proximal tubule and papilla may be the renal progenitor cells.

Tissue-Specific Transport and Injury Response in Kidney Tubules Derived from Human Pluripotent Stem Cells
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Background: Human pluripotent stem cells (hPSCs) can differentiate into cells expressing markers of kidney proximal tubules, but the functional capacity of these structures remains poorly understood. We developed a new, adherent, 3D culture system to evaluate transport and injury characteristics in hPSC-derived kidney tubules, compared to undifferentiated hPSCs.

Methods: hPSCs sandwiched in extracellular matrix were maintained in pluri-potency-sustaining media to form undifferentiated cavitated spheroids (SOX2+ OCT4+), or differentiated with growth factors into nephron progenitor cells (PAX2+SIX2+) and subsequently proximal tubules (LTL+LRP2+). hPSC spheroids or differentiated tubules were incubated with small molecule fluorescent probes to monitor transport into lumens, or with nephrotoxic chemicals to assess upregulation of kidney injury molecule-1 (KIM-1).

Results: Kidney tubule lumens selectively accumulated rhodamine-dextran (RD) and fluorescein methotrexate (MTX) transport cargoes. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA, significantly reduced cargo fluorescein methotrexate (MTX) transport cargoes. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA, significantly reduced cargo fluorescein methotrexate (MTX) transport cargoes. Inhibition of actin polymerization with Latrunculin B, or permeabilization of tight junctions with EDTA,
many of these disadvantages could potentially be overcome. To this end we have been attempting to develop a protocol to produce proximal tubule-like cells from human iPSCs with xenobiotic transport capabilities.

Methods: Human iPSCs were differentiated into the intermediate mesoderm (IM) using Wnt and retinoic acid activation (CHIR99021 and TNNBP). Cells were further differentiated using combinations of different growth factors.

Results: The derived cells exhibit cobble stone morphology and express certain proximal tubule proteins such as claudin-2. Additionally, the cells can be maintained for up to 4 weeks in culture. Preliminary results demonstrate the ability of the differentiated cells to form tubule-like structures (DI-10-ASP) and organic anions (6-CF) and to extrude p-glycoprotein substrates (calcein-AM).

Conclusions: While further characterization will be needed, the initial results are promising, indicating that proximal tubule-like cells derived from iPSCs could be a new tool for screening the nephrotoxic potential of compounds.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO205

The Direct Differentiation Method of Renal Tubular Cells by Synthetic mRNA of Transcription Factors Identified from TF-Inducible Human ES Bank

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Background: To find transcription factors which promote differentiation towards renal tubular cells, we utilize the human ES line with doxycycline-controllable transcription factors (TF-inducible hES bank). To establish the differentiation method of renal tubular cells, we transfect the synthetic human mRNA of the target transcription factors into human ES cells.

Methods: We performed exhaustive search for DNA microarray data after TF induction in the hES bank, and analyzed them in silico to find the specific transcription factors, which expressed in kidney epithelial cells. We synthesized the synthetic human mRNA of the target transcription factors. By using the lipofection method, we transfecated the synthetic mRNA of target transcription factors to human ES cells, and cultured them. The morphological changes, mRNA expressions, and protein expressions were analyzed.

Results: Transcription factors, which expressed in human kidney epithelial cells, were identified by in silico analysis. We successfully made synthetic mRNA of candidates of transcription factors. Five days after the transfection of the synthetic mRNA to human ES cells, we were able to observe characteristic morphological changes in the differentiated cells. The mRNA expression of OSR1, ITGA8, AQP1, and MEGALIN were increased. Moreover, the protein expression of AQP1 and LTL were also detected in the differentiated cells.

Conclusions: We identified specific transcription factors for differentiation toward kidney (especially, proximal tubular cells), and demonstrated that the differentiation of proximal tubular cell phenotype from human ES cells by a novel method using synthetic mRNA.

FR-PO206

Differentiation of Human iPSC into Functional Podocytes

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Background: Podocyte injury and subsequent loss of glomerular integrity is a major cause for chronic kidney disease (CKD). Two-thirds of patients with CKD suffer from disorders that arise from the glomerulus, mainly due to podocyte injury. Podocytes are highly specialized cells with a complex cytoarchitecture composed of foot processes that form the glomerular filtration barrier. The study of the molecular processes of glomerular transition and senescence. In a 3D MPS, hPSC-derived RTECs formed tubular structures comparable to primary RTECs. Immunofluorescence staining demonstrated positive signals for the tubule transporters SGLT2 and OAT3 as well as the epithelial markers CD113 and E-cadherin.

Conclusions: We have shown that hPSC-RTECs can propagate in vitro and maintain their differentiated characteristics, with morphology and markers similar to primary RTECs. hPSC-RTECs are grown in a 3D MPS, they maintain an epithelial phenotype and express membrane transporters essential for functions including glucose reabsorption and organic anion secretion. This system establishes a platform in which to optimize hPSC-RTEC expansion and function in a 3D, microfluidic context, with relevance for human disease modeling in vitro and for the generation of regenerative medicine.

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FR-PO207

Sourcing of Renal Tubular Epithelial Cells from Human Stem Cell-Derived Kidney Organoids

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Background: Human pluripotent stem cells (hPSCs) provide a self-renewing, reproducible source of kidney cells for laboratory investigation and regenerative medicine approaches. While we tested the potential of hPSC-derived renal tubular epithelial cells (RTECs) to grow and maintain differentiation in 2D and 3D cultures, compared to primary RTECs from adult kidneys.

Methods: hPSCs were treated with growth factors to promote differentiation into nephron progenitor cells (PAZ2-SIX2) and subsequently proximal tubules (LTL-ZO1-LRP2). RTECs purified from tubular organoids were re-plated on tissue culture plates with or without extracellular matrix. RTECs were analyzed for proliferation, kidney-specific marker expression, and their capacity to seed a ‘kidney on a chip’ 3D microphysiological system (MPS).

Results: RTECs purified from hPSC organoids grew to confluent monolayers in minimal RTEC growth media on extracellular matrix. hPSC-derived RTECs resembled primary RTECs morphologically. Marker immunofluorescence analysis revealed that purified hPSC-RTECs possessed ZO1 tight junctions and reacted with LTL. Sub-cultivation was limited to 2-3 passages, after which hPSC-RTECs underwent epithelial-to-mesenchymal transition and senescence. In a 3D MPS, hPSC-derived RTECs formed tubular structures comparable to primary RTECs. Immunofluorescence staining demonstrated positive signals for the tubule transporters SGLT2 and OAT3 as well as the epithelial markers CD113 and E-cadherin.

Conclusions: While further characterization will be needed, the initial results are promising, indicating that proximal tubule-like cells derived from hPSCs could be a new tool for screening the nephrotoxic potential of compounds.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO208

Genome-Wide Methylation Analysis of Epigenetic Memory in Human Kidney Derived iPS Cells

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Background: Epigenetic memory such as DNA methylation signature of iPS cells derived from parental cells was reported to determine the differentiation fate of the iPS cells (Nature 2012). Last year, we reported the result of kidney specific induction protocol (Nature Commun, 2013) by using two different kind of human iPS cells established from human fibroblast (F-iPS) and human kidney epithelial cells (K-iPS). Last year, we reported the result of kidney specific induction protocol (Nature 2012). Last year, we reported the result of kidney specific induction protocol (Nature Commun, 2013) by using two different kind of human iPS cells established from human fibroblast (F-iPS) and human kidney epithelial cells (K-iPS), and demonstrated more efficient induction of markers of kidney development (WT1, Pax-1, Sall-1) and differentiation (AQP-1, Nephrin) in K-iPS as compared with F-iPS cells.

Methods: In this study, we performed a genome-wide methylation analysis of i-KIPS and F-iPS cells, and tried to clarify the mechanism of kidney lineage specific induction of human iPS cells.

Results: Among 27,578 sites, we focused on high Cpg promoter methylation (GC<0.55, Cpg>0.75). 56 sites such as Kid1 and SOD2 were strongly methylated in F-iPS than in K-iPS cells such as KCNK12 and GATA4 were strongly methylated in F-iPS. In F-iPS, the markers of kidney development were strongly methylated in F-iPS than in K-iPS cells (Pax-2; 23.6 vs 2.1, Sall-1; 18.7 vs 4.3). However, the marker of differentiation was strongly methylated in K-iPS (AQP-1; 1.7 vs 1.1).

Conclusions: These results demonstrate that epigenetic memory in parental cell determine the induction of human iPS cells toward kidney lineages, and the role of key genes in kidney lineage specific induction will be discussed.

Funding: Government Support - Non-U.S.

FR-PO209

Mechanism of Kidney Repair in the Omentum-Kidney Model – Tubulogenesis and Differentiation of Free-Lying WT-1 Cells to Podocytes Occurring in the Fusion Zone

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Background: When activated omentum was fused to the injured kidney it induced glomerular repair and ameliorated chronic kidney disease (Garcia-Gomez et al JASN 2014). The fusion zone between the omentum and the injured kidney was highly proliferative (high BrdU uptake), with abundant free-lying nephrin precursor WT-1 cells. In this study, we examined the fusion area to further understand the mechanism of repair in this model.

Methods: In 5/6 surgically nephrectomized rats, polyethylene glycol was intraperitoneally injected to activate the omentum and fuse to the injured kidney. Nephrectomized rats with complete omentectomy were used as control. Kidney tissues were examined 1-3 weeks after injury by histology and immunofluorescence (Pax-2, WT-1 and podocalyxin).
E15 embryonic rat kidney served as control for immune-staining. Two-week fusion zone tissue and tissue far from fusion zone, control and normal was quantified for mRNA for selected developmental genes (WT-1, Wnt-4, Podl1, Lim1, HNF-6, BMP-7) by RT-PCR.

Results: We found that the fusion zone tissue showed proliferation and expansion of collecting ducts, as evidenced by intense staining for Pax2, in a pattern similar to that seen in E15 embryonic rat kidney. Further, several islands of WT-1 cells in the fusion zone differentiated to podocytes, as judged by co-expression of podocalyxin. mRNA for Wnt-4 and WT-1 increased by 10-20 folds and mRNAs for other developmental genes increased by 2-5 folds in the fusion zone. Control tissue did not show the above changes.

Conclusions: The fusion zone tissue between the injured kidney and omentum appears to be a highly active tissue with proliferation and differentiation of kidney progenitor cells (WT-1, Pax-2, podocalyxin) taking place, and thus providing a healing environment to the injured kidney.

Funding: Private Foundation Support

FR-PO211

Functional Alterations of Adipose-Derived Mesenchymal Stem Cells from Human with Atherosclerotic Renovascular Disease Under Hypoxic Conditions


Background: Atherosclerotic renal vascular disease (ARVD) induces microvascular loss and interstitial inflammation, ultimately leading to ischemic injury. Mesenchymal stem cells (MSCs) can induce angiogenesis, decrease inflammation, and limit apoptosis in experimental animals. Aging and co-morbid conditions may blunt these properties in older human subjects. This study tested the hypothesis that hypoxic preconditioning of adipose tissue-derived MSCs would modify expression of MicroRNAs (miR) associated with MSCs survival, angiogenic, and anti-inflammatory properties.

Methods: MSCs obtained from subcutaneous tissue of 7 patients with ARVd (Age 75±3±4) were cultured under normoxic or hypoxic conditions (%50±10) for 4 days. Hypoxic MSCs were returned to normoxia thereafter. Levels of the pro-survival and pro-angiogenic factors vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) were measured in the supernatant by ELISA. Expression of MiRs-210, 21 and 145 in MSCs was measured by quantitative rt-PCR and apoptosis by flow cytometry for Annexin V.

Results: Hypoxic conditions increased VEGF and IGF (p<0.05) in MSC supernatant, but had no effect on apoptosis.

Conclusion: Hypoxic conditions induced VEGF and IGF (p<0.05) in MSC supernatant while apoptosis was not affected.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
**Conclusions:** Intra-arterial autologous aMSCs were tolerated with no adverse effects. This low dose, delivered without renal revascularization, was associated with increased tissue oxygenation and cortical RBF, consistent with improved renal microcirculation. Our results provide first-in-humans evidence to support a role for aMSC to restore local blood flow and oxygenation in ARVD.

**Funding:** NIDDK Support

**FR-PO213**

**Cell Therapy with Serelaxin Promotes Angiogenesis and Anastomosis which Is Critical for the Preservation of Vascular Integrity After Kidney Injury**

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**Background:** We previously reported that the combination of mesenchymal stem cells (MSCs) and serelaxin (Rln) attenuates ureteral obstruction (UO)-induced fibrosis. However the affect on endothelial cell regeneration is yet to be elucidated. Here we tested the hypothesis that a mechanism of repair after fibrosis is induced via endothelial angiogenesis and sprouting in the presence of MSCs and Rln.

**Methods:** Live cell imaging of human bladder endothelial cells (HBECs) and human umbilical vein endothelial cells (HUVECs) in tube forming assays were conducted with MSC-conditioned media and Rln (1-100ng/mL) to observe their affects on angiogenesis. Spheroid assays determined the effects of MSC and Rln on HBECs and HUVECs sprouting in vivo. Proliferation of HBECs and HUVECs in the presence of MSCs and Rln was investigated. AqPCR for angiogenic genes was performed on MSCs cultured with or without Rln (10ng/mL). Endothelial integrity was visualized using CD31 protein localization in kidneys from mice 3, 5 and 7days post-UUO, with or without MSCs Rln (n=4-6/group).

**Results:** Angiogenesis of HBECs was modulated in the presence of MSC-conditioned media and Rln with tube number and branch length increased compared to control. HUVECs readily formed sprouts in culture, which was enhanced when both Rln and MSCs were present. The migration capacity of MSCs towards injured HBECs was significantly increased when Rln was added. Rln induced the expression of angiogenic genes from the MSCs. Immunofluorescence microscopy of CD31 determined a decrease of endothelial integrity in a time-dependent manner in vivo. However the administration of MSCs and Rln preserved the vascular integrity.

**Conclusions:** These results suggest that both angiogenesis and sprouting is enhanced only when both MSCs and Rln are used in combination. This may be in part due to Rln-induced release of angiogenic factors from MSCs which may aid in revascularization of the fibrotic kidney.

**Funding:** Private Foundation Support, Government Support - Non-U.S.

**FR-PO214**

**Effects of Adipose Derived Stem Cells in a Model of Chronic Renal Hypoxia**

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**Background:** Chronic renal artery stenosis causing chronic hypoxia may lead to irreversible damage of the kidney with progressive deterioration of renal function. Due to reduced regenerative abilities of the kidney, mesenchymal stem cells (MSC) emerge as an alternative therapy. The aim of this study was to investigate the effects of MSC, isolated from adipose tissue (ASC) on renal fibrogenesis induced by chronic renal artery stenosis.

**Methods:** Left renal artery of male Wistar rats was partially occluded and ASC were injected through caudal vein. ASC were characterized by their immunophenotype/multipotentiality. To analyze the migration and retention time, labeled ASC were injected 6 weeks after renal occlusion (RO) and analyzed 24, 48, 72 hours or 15 days after injection by flow cytometry. Caudal systolic blood pressure (SBP) was weekly estimated. Renal function and mRNA expression levels of collagen I (Col I), Fibronectin (FN) and TGF-β were determined by qPCR, 6 weeks after renal artery occlusion in the following groups: Sham; Stenotic control (StC), receiving PBS i.v.; Stenotic + ASC (S+ASC). ASC were injected 3 and 5 weeks after RO i.v.

**Results:** After 48 hours cells were retained in both kidneys, stenotic and contralateral followed by heart and lung. After 15 days the presence of ASC decreased significantly in the lungs and heart but they were still present in the kidneys. SIC animals showed progressive increase in SBP while the S+ASC rats had a stabilization of SBP with no further increase after 15 days. Plasma renin concentration was similar among groups and developed proteinuria which was reduced by ASC treatment. There was an increase in the expression of Coll, FN and TGFβ in the stenotic kidney (cortex and medulla) which was reversed by ASC treatment.

**Conclusions:** In conclusion ASC prevented further increase in SBP and reduced the expression of molecules induced-fibrosis. ASC migration and retention in the clipped and contralateral kidneys can be potentially beneficial to restore damaged tissue and to preserve the function of the contralateral kidney.

**Funding:** Government Support - Non-U.S.

**FR-PO215**

**Therapeutic Effects of Erythropoietin Producing Kidney Mesenchymal Stem Cell Derived Microparticles on Anemia in Chronic Kidney Disease Mice**

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**Background:** Progression of chronic kidney disease (CKD) results in aggravation of erythropoietin (EPO)-dependent anemia. Microparticles (MPs) shed from kidney mesenchymal stem cells (KMSC) have been demonstrated to confer protective effects against acute kidney injury and kidney fibrosis via transfer of messenger RNA. Previous studies have demonstrated improvement of renal anemia by EPO transfected MSC. We investigated whether MPs derived from EPO producing KMSC can exert therapeutic effects on anemia in CKD mice.

**Methods:** Mouse model of CKD and renal anemia was induced by the electrocoagulation of right renal cortex and sequential left nephrectomy. Six weeks post-nephrectomy, CKD and anemia was confirmed via blood urea nitrogen (BUN) and hemoglobin measurements as well as renal histology. Stable human EPO-producing KMSC (EPO-KMSC) and their MPs isolated by differential ultracentrifugation were injected intraperitoneally into established CKD mice and followed for 2 weeks (EPO-KMSC: 1×10^9 per mouse, MP: 2×10^8 per mouse). BUN and hemoglobin were evaluated and degree of renal tubulointerstitial damage was examined for 2 weeks after CKD.

**Results:** EPO secretion from EPO-KMSC was confirmed to sustain over 4 weeks in vitro and RT PCR reviewed the presence of EPO mRNA within MPs. Injected EPO-KMSC-derived MPs were demonstrated within tubulointerstitial area. Animals that received EPO-KMSC and MPs demonstrated significantly lower BUN levels compared to CKD control mice (60±2, 62.7±2.7 vs.83.7±7.5 mg/dL, P<0.05, respectively). Importantly, hemoglobin levels were significantly higher in CKD mice treated with EPO-KMSC and MPs compared to CKD control mice (11.7±0.1, 11.3±0.5 vs.9.7±1.0 mg/dL, P<0.05, respectively).

**Conclusions:** The use of EPO secreting MSC is a viable strategy for cell therapy in renal anemia. Our results suggest that EPO-KMSC derived MPs as well as EPO-KMSC can improve renal function and renal anemia in CKD mice.

**FR-PO216**

**Transplantation of Human Embryonic Mesenchymal Stem Alleviates Lupus Nephritis in MRL/lpr Mice**

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**Background:** Com pared with bone marrow derived MSC, embryo-derived MSC have greater expansion and differentiation potentials. T helper cell 17(Th17) and interleukin 17(IL-17) is closely related to the occurrence and development of Lupus. The glial cell-derived neurotrophic factor (GDNF) which is closely related to the kidney development and is produced by the kidney injury and chronic hypoxia. We investigated the effects of human embryonic MSC (iMSCM) in lupus nephritis in MRL/lpr mice.

**Methods:** The MRL/lpr mice were divided into 2 groups: Control, iMSCM group. iMSCM were injected at one dose of 1×10^9/200ul twice (at the 16th, 19th weeks of age) through tail vein. Mice were sacrificed at 24 weeks of age.

**Results:** Multi-treatment of iMSCM was able to increase the survival, decrease the levels of 24-h proteinuria, and anti-double-stranded DNA (dsDNA) antibody. iMSCM treatment decreased the content of renal Th17 and interleukin 17(IL-17) is closely related to the occurrence and development of Lupus. The glial cell-derived neurotrophic factor (GDNF) which is closely related to the kidney development and is produced by the kidney injury and chronic hypoxia. We investigated the effects of human embryonic MSC (iMSCM) in lupus nephritis in MRL/lpr mice.

**Funding:** Private Foundation Support, Government Support - Non-U.S.
Ctns−/− mice. However, while PTC rescue andare reported to be effective in treatment of various diseases. The aim of this study is to investigate the therapeutic potential of T-MSCs in the treatment of AKI induced by GM.

**Methods:** Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, ip for 10 days), GM-T-MSCs (1x10^5 cells, intravenous injection at 1 day after the 1st GM injection) and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a transwell co-culture system of NRK cells and T-MSC. Intracellular reactive oxygen species measured by measuring NOX activity, H2O2, generation, NOx mRNA expressions with DCF-DA staining.

**Results:** PKH-26-labeled T-MSCs were observed in renal tubular cells in GM-T-MSCs group. The infusion of T-MSCs preserved renal function with a decrease in proteinuria. T-MSCs also alleviated renal tubular dilatation and reduced apoptosis of renal tubular cells in the rats with GM-induced AKI. The infusion of T-MSCs downregulated the expression of Bax, Cytochrome c, Cleaved caspase-9 and -3 and upregulated Bcl-2 of renal cortical tissue. In-vitro study revealed an amelioration of GM-induced oxidative stress and apoptosis of NRK cells by T-MSC.

**Conclusions:** Our results suggest that T-MSCs protect the kidney from GM-induced AKI, possibly via the mechanism of modulation of oxidative stress and apoptosis.

**Funding:** Government Support - Non-U.S.

**FR-PO219**

Exosomes Secreted by Human Urine-Derived Stem Cells Could Prevent Kidney Complications from Type I Diabetes in Rats

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**Background:** Stem cells are currently the main candidates for the development of new treatments for diabetic nephropathy, as they may exert their therapeutic effects mainly through endocrine mechanisms. Therefore, exosome-derived from stem cells have been reported to play an important role in kidney injury.

**Methods:** Exosomes from conditioned medium of human urine-derived stem cells (USCs-Exo) were isolated using ultra-filtration and purification methods. USCs-Exo was then verified by morphology characteristics and specific biomarkers. After the establishment of the streptozotocin (STZ) induced Sprague - Dawley (SD) rats' model, the effects of USCs-Exo on kidney injury were observed via tail intravenous injection of USCs-Exo or control weekly until 12 weeks. In vitro, podocytes cultured in high glucose medium were treated with USCs-Exo to test the protective effect of USCs-Exo on podocyte apoptosis.

**Results:** USCs were cultured and were verified by positive markers of CD29, CD73, CD90 and CD44 antigens, and negative markers of CD34 and HLA-DR. Intravenous injections of USCs-Exo could potentially reduce the urine volume and urinary microalbumin excretion, prevent podocytes and tubular epithelial cells apoptosis, suppress the caspase-3 overexpression and increase glomerular endothelial cells proliferation in diabetic rats. In addition, USCs-Exo could reduce podocyte apoptosis induced by high glucose in vitro.

**Conclusions:** USCs-Exo may have the potential effect to prevent kidney injury from diabetes by inhibiting podocytes apoptosis and promoting vascular regeneration.

**Funding:** Government Support - Non-U.S.
Conclusions: In conclusion, HSC transplantation can repair and preserve near-normal kidney function. Understanding mechanisms underlying kidney repair could spur the development of novel stem cell-based therapies for degenerative renal disorders.

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FR-PO221
Towards the Clinical Application of Gene-Modified Hematopoietic Stem Cell Transplantation for Cystinosis
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Background: Cystinosis is an autosomal metabolic disease caused by mutations in the CTNS gene, encoding a lysosomal cystine transporter, leading to cystine accumulation and multi-organ failure. Affected individuals present before 2 years of age with a Fanconi syndrome and eventually progress to end-stage renal failure. Treatment with cysteamine does not prevent these complications. We showed previously that wild-type HSC transplantation could treat cystinosis in the Ctns-/- mice. Thus, we developed an autologous transplantation strategy of HSCs genetically modified ex vivo to express a functional CTNS gene. Preclinical studies using a SIN-lentivirus vector containing CTNS to transduce Ctns-/- HSCs and transplanted in Ctns-/- mice led to cystine reduction in all tissues and kidney function improvement.

Methods: Pharmacological and toxicological studies are in progress. We established the optimal conditions to transduce human CD34+ HSCs with our lentiviral vector to obtain a Vector Copy Number (VCN) included between 1 and 3. We performed Colony Forming Unit (CFU) assays to ensure normal proliferation and differentiation of transduced human CD34+ HSCs from healthy donors and cystinotic patients and the In Vitro Immunomobilization (IVIM) assay, a genotoxicity test. Serial transplantations in the Ctns-/- mice will assess the safety of our vector in vivo.

Results: While we obtained VCN within the range for healthy donors CD34+ HSCs, the VCN for the CTNS-/- CD34+ HSCs is below 1, requiring further optimization. CFU assays did not show aberrant differentiation of the transduced CD34+ cells from the healthy donors and cystinotic patients. Finally, no immortalized clones were observed with the IVIM assay suggesting a good safety profile of our vector. These results will be included in our IND for a phase 1 clinical trial for cystinosis. The in vivo serial transplantations are in progress.

Conclusions: This work represents the first stem cell and gene therapy treatment strategy for cystinosis and should lead to a phase 1 clinical trial.

Funding: NIDDK Support, Private Foundation Support

FR-PO222
Mesenchymal Precursor Cell Therapy for Diabetic Nephropathy: 24 Week Results from a Phase 2A Randomized Controlled Trial
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Background: Renal inflammation and endothelial dysfunction contribute to the etiology of diabetic nephropathy (DN). Bone marrow derived mesenchymal precursor cells (MPC) can modulate both inflammatory cells and microvasculature. We conducted a randomized, placebo (PBO) controlled, dose-escalating trial of allogeneic MPC in 30 subjects with type 2 DN.

Methods: Patients (24 men, 6 women) with an estimated glomerular filtration rate (eGFR) of 20-50 ml/min/1.73m2 and on a stable regimen of renin-angiotensin inhibition were randomized to a single IV infusion of PBO (saline) or 150 million (M) or 300M MPCs (N=10 per group). Patients have been followed-up for 24 weeks. Baseline mean age was 70 years mean eGFR was 34.6, 35.7 and 34.6 ml/min/1.73 m2 for PBO, 150M and 300M, and 19/30 patients had eGFR<30.

Results: There were no treatment-related adverse events. For eGFR change from baseline at 24 weeks, the least square mean (LSM) differences from PBO were 3.2±2.3 (8.1%) in both 150M and 300M groups. PBO-adjusted treatment differences were greater in pooled MPC with baseline eGFR<30: 4.9±2.3 (+12%) at 24w. The LSM differences from PBO for mean individual annualized slopes of eGFR change over 24w was 6.8±4.8 in both treatment groups. Baseline IL-6 levels correlated with SCR and eGFR improvement at 12 w in the MPC groups (r=0.57 and 0.50; both p<0.05) but not in PBO. The LSM differences from PBO for mean individual annualized slopes of eGFR change over 24w was 7.8±4.8 ml/ min/1.73 m2 in pooled MPC, understanding baseline IL-6=3.5 pg/dl and 5.6±0.5 in PBO in patients with baseline IL-6≤3.5 pg/dl, suggesting greater preservation or improvement in eGFR relative to PBO in the presence of elevated IL-6.

Conclusions: In this first in humans study, a single MPC infusion improved or stabilized GFR over 24w. Baseline eGFR<30 and high IL-6 levels suggest two biomarkers that may predict efficacy with MPC treatment. Positive response to MPC therapy may be enhanced by the presence of non-fibrotic, but at-risk, renal tissue and aberrant pro-inflammatory milieu.

Funding: Pharmaceutical Company Support - Mesoblast PLC

FR-PO223
Long-Term Effect of Methylprednisolone Pulse and Autologous SFV (Stromal Vascular Fraction) Therapy in Severe IgA Nephropathy with CKD Stage III
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Background: Up to date there is no specific method of treatment in severe IgA nephropathy with CKD, but giving ACE inhibitor, angiotensin II receptor blocker(ARB), omega-3 etc. and eventually almost all cases fall into CKD V and need KTP or dialysis. Cell-based therapy is an emerging field in nephrology field especially aspose derived stem cells(ASCs). The beneficial effects of mesenchymal stem cell occur through differentiation-independent pathways include increased cell survival and proliferation, decreased inflammation, immune modulation, tissue regeneration etc.

Methods: We tried methylprednisolone(MP) pulse therapy followed by autologous SFV(stromal vascular fraction), which contained ASCs in severe IgA nephropathy with CKD stage III. This case was 44years old female patient, Renal biopsy finding showed Grade IV(Lee’s classification) with CKD stage 3. MP pulse was tried 6 cycles followed by autologous SFV were injected through intravenously 4 times at 3 weeks interval.

Results: Initial renal biopsy findings before treatment(Tx) showed 61% sclerotic glomeruli, however follow up renal biopsy 18 months after Tx showed 41% sclerotic glomeruli and disappeared immune deposits, The serum creatinine level before Tx was 1.77mg/dl with GFR 35/ml/min, however 18 months after Tx serum creatinine was 1.03mg/dl with GFR 61/ml/min.

Conclusions: In conclusion MP pulse therapy with autologous SFV treatment in intractable IgA nephropathy might be a promising therapeutic means without any notable side-effect or complications especially in early stage CKD, although the efficacy and safety, of SFV infusion therapy needs long term studies.

Funding:

FR-PO224
Extracellular Vesicles in Glomerular VEGF Homeostasis
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Background: Strict regulation of VEGF signaling between podocytes and glomerular endothelial cells (GEC) is critical for GEC survival and function, therefore, loss of glomerular VEGF homeostasis during disease progression can impact GEC integrity leading to decline in glomerular function. Importantly, recent studies have described extracellular vesicles (EVs) to play important role in stem cell mediated paracrine modulation, including in kidney. We have already established that amniotic fluid stem cells (AFSC) are reproactive, and we hypothesize that EVs released within damaged glomeruli are involved in VEGF regulation. Herein, we investigate the impact of AFSC derived EVs in the maintenance of glomerular VEGF homeostasis.

Methods: Using qPCR and ELISA we measured VEGF expression along the course of disease progression in isolated glomeruli of mice affected by Alport Syndrome (AS). Endothelium morphology was evaluated by HIS and TEM. GEC were FACS sorted from a GEC specific Tek reporter mice and studied by gene and protein arrays for VEGF/VEGF-R, oxidative stress, and apoptotic pathways. Co-cultured GEC and ASFV were loaded with EVs. Delivery of ASFC derived EVs normalized VEGF expression and ameliorated endothelial damage. Importantly, the soluble receptor of VEGF, sFlt1—involved in regulating VEGF signaling—was also modulated upon treatment, indicating a VEGF/sFlt1 mechanism of regulation by EVs. In vitro experiments further confirmed the direct role of EVs in VEGF/sFlt1 regulatory mechanism.

Conclusions: In conclusion, our data demonstrate for the first time the alteration of VEGF signaling within AS glomeruli. We further showed that ASFC derived EVs play an important role in maintaining glomerular homeostasis of VEGF signaling, so critical to maintain GEC integrity and function, presenting with a potent for new targeted therapies in CKD.

Funding: Other U.S. Government Support

FR-PO225
Renal Exosomes Store and Transfer the Ischemia Preconditioning State and Protect Rats with Severe Renal Ischemia
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Background: Acute Kidney Injury (AKI) is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD). We have reported that intravenous renal cell transplants (IRCT) improve outcomes in rats with AKI (APJ 303:F357, 2012). IRCT action was mediated by relatively small number of anchored and retained cells, and we have hypothesized that cells amplified renal protection by releasing exosomes (EX) acting at a distance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: We tested if renal EX from cultured cells used for hRCT improved AKI. Nontransgenic male Sprague Dawley rats (SD, n = 4–7) were subjected to 45 minutes of bilateral ischemia/reperfusion (IRI). Renal exosomes (600 µg/protein/rat) were then given intravenously.

Results: There were 5 groups of rats: 1) sham, no IR; 2) renal ischemia (IR) untreated (NO-EX); 3) IR treated with heat inactivated EX (HI-EX); 4) IR treated with normal EX (NL-EX) and 5) IR treated with EX prepared by kidney cells subjected to ischemia/reperfusion injury (IPC-EX). In sham, serum creatinine was 0.3±0.03 at 24 hrs and 0.3±0.02 at 48 post-surgery. In NO-EX it was 2.1±0.6 and 1.7, post IR, respectively. In HI it was 2.2±0.1 and 1.6±0.3. However, in NL-EX it was 2.4±0.4 and 0.78±0.1. The most striking effect was found in IPC-EX: 0.7±0.2, and 0.50±0.1, p<0.05 vs. all including NL-EX. Kidney weight (mg/gm body weight) 6 days post IR was also improved by EX: 3.8±0.1 in sham; 6.7±0.6 in NO-EX; 6.7±0.6 in HI; 5.2±0.2 in NL-EX 5.2±0.2, and 4.8±0.2 in IPC-EX, which was significantly lower than all IR groups, including NL-EX. Neutrophils (PMN) in IPC-EX were also reduced by 65 % (p<0.05) when compared to NL-EX. IPC-EX reduced renal C3 expression in glomeruli and tubules by 73 % and 82 % respectively (p < 0.05 for both). IPC-EX also protected 76 % of renal tubules when compared to NO-EX.

Conclusions: IPC is effective but impractical. However, given IV can communicate the IPC state, reach the kidneys, modulate inflammation and protect function and structure following severe IR.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

FR-P0226
The Impact of Preexisting Chronic Kidney Disease on the Severity and Recovery of Acute Kidney Injury
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Background: Recent observational studies have shown that a substantial proportion of patients with acute kidney injury (AKI) have often progression to chronic kidney disease (CKD). Among several risk factors for the development of CKD after AKI, decreased baseline glomerular filtration rate (GFR) represents an important risk factor. However, precise mechanisms involved in the development of fibrosis after AKI with preexisting CKD have not been completely ascertained. Here in this study, we assessed the impact of preexisting CKD on the severity and recovery of AKI in mouse model of 5/6 nephrectomy.

Methods: Male CD-1 mice underwent 5/6 nephrectomy or sham operation, and 6 weeks later ischemia reperfusion injury (IRI) was performed. On day 1, 7 and 28 after IR, functional, histological, and molecular parameters were compared between them.

Results: Twenty minutes clamping of renal pedicle in 5/6 nephrectomized mice did not provoke more severe functional, histological deterioration compared to normal mice on day 1 and 7. Similar elevations in SCR were observed in both groups until day 7 after IR; however, SCR remained higher on day 28 in 5/6 nephrectomized mice compared to normal mice, suggesting that preexisting CKD does not modify severity of AKI but adversely affect the recovery process. From day 7 to 28, mRNA expression of p21, and protein level of pH3, both representing cell cycle arrest were significantly increased in 5/6 nephrectomized mice compared to sham (AKI) mice. Treatment with p53 inhibitor after IRI resulted in not only decreased p21 and pH3 protein level, but also fibrosis in CKD+AKI mice, suggesting that epithelial cell cycle arrest is partially responsible for impaired recovery from AKI in 5/6 nephrectomized mice.

Conclusions: Taken together, reduced nephron mass do not seem to increase severity of AKI, but have negative effect on repair process, leading to development of fibrosis.

Funding: NIDDK Support

FR-P0227
Impaired Functional Recovery from Acute Kidney Injury in Rats with Preexisting Chronic Kidney Disease Predicts the Severity of De Novo Hypertension
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Background: The mechanisms by which AKI accelerates the progression of CKD remain poorly understood. We have recently demonstrated that preexisting CKD predisposes to impaired recovery from AKI as evidenced by exaggerated levels of tubulointerstitial fibrosis and modest elevations in blood pressure at 4 weeks post injury. However, a rigorous examination of the relationship between impaired functional recovery from AKI and the development of hypertension has not been examined.

Methods: Male SD rats underwent normotensive 3/4 nephrectomy (3/4 NX) and were chronically instrumented with a BP radiotelemeter. Two weeks later, rats were subjected to 40 min IR (n=20) or sham IR (n=8). BP was assessed every 10 min, 24 hr/day for 4 weeks and glomerular filtration rate (GFR) was then assessed in the conscious state (FITC-imulin).

Results: As compared to baseline values, systolic BP was significantly elevated (P<0.05) in rats at 4 weeks post IR (134±2 vs. 149±5 mmHg, respectively) but not sham IR (139±4 vs. 140±2 mmHg, respectively). GFR was significantly less (P<0.05) in rats subjected to IR vs. sham IR (1.1±1 vs. 1.4±1 ml/min, respectively). As shown in Figure 1, a very strong negative correlation was observed between GFR and the increase in systolic BP over the 4 week protocol. Systolic values 48 hours post AKI did not correlate with either GFR or the change in systolic BP at 4 weeks post AKI, indicating that the development of hypertension following IR was due to impaired recovery from AKI as opposed to a greater severity of AKI.

Conclusions: The development of hypertension following AKI in the presence of preexisting CKD is likely to significantly contribute to the subsequent progression of CKD.

Funding: NIDDK Support, Veterans Administration Support

FR-P0228
Exocytosis of Endothelial Lysosome-Related Organelles Hair-Triggers a Patho-Loss of Glycocalyx at the Onset of Sepsis
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Background: Endothelial surface glycocalyx (ESG) is a well-known regulator of leukocyte surveillance, vascular permeability, and a sensor of shear stress. ESG is degraded during sepsis, thus contributing to systemic multiorgan involvement. Our previous demonstration of a very early post-stress exocytosis of lysosome-related organelles (LRO) with their lytic enzymes led us to hypothesize that exocytosis of LRO may catapult a synchronized deregulation of ESG.

Methods: To test this hypothesis we first analyzed the time-course of exocytosis of Weibel-Palade bodies and secretory lysosomes after application of lipopolysaccharides (LPS) to endothelial cells.

Results: Time-lapse video microscopy revealed that LROs undergo agitation and vectorial movement with a time course of a few minutes after LPS. In addition, spectrophotometry measurements illustrated an increase of lysosomal cargo, cathepsin B, within the media after 10min of LPS exposure. Two therapeutic maneuvers, a nitric oxide intermediate, NG-hydroxy-L-arginine (NOHA), and culture media conditioned by endothelial progenitor cells (ECM-CM) reduced the directionality and motility of LRO. The patch loss of ESG occurring with the similar fast kinetics was confirmed using confocal fluorescence microscopy and Stochastic Optical Reconstruction Microscopy. The loss of ESG was blunted by pretreatment with NOHA or ECM-CM. Moreover, these treatments resulted in a significant reduction of mortality of septic mice.

Conclusions: In summary, above studies provide the first demonstration of the very early patchy disintegration of ESG which can be prevented by pretreatment with NOHA and ECM-CM, maneuvers that reduced exocytosis of LRO. Data support the hypothesis assigning to stress-induced exocytosis of these organelles the role of a hair-trigger for local degradation of ESG that in turn initiates leukocyte infiltration, increase vascular permeability, and partially accounts for the later morbidity and mortality.

Funding: NIDDK Support

FR-P0229
Vitamin D Deficiency Contributes to Vascular Damage in Sustained Ischemic Acute Kidney Injury
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Background: It has been shown that injury to the renal vasculature may play an important role in the pathogenesis of ischemic acute kidney injury (AKI). Reductions in microvascular density may play a critical part in the progression of chronic kidney disease (CKD) following AKI-induced ischemia/reperfusion injury (IRI). Vitamin D deficiency (VDD) is associated to tubulointerstitial damage and fibrosis progression following IRI-AKI. We evaluated the effect of VDD in sustained IRI-AKI, hypothesizing that VDD contributes to vascular damage.

Methods: Wistar rats were fed 25(OH)D3-free or standard diets for 35 days. On day 28, rats were randomized into four groups: control (sham), VDD, bilateral IRI and VDD. Rats were analyzed 7 days after the surgeries.

Results: VDD rats showed impaired capillary density (by cbin1 staining) and reduced VEGF expression, even in the absence of injury. In addition, VDD IRI rats manifested a remarkable capillary rarefaction and also had increased RW/BW, tissue injury scores, FSP-1.
FR-PO230

Exosomes-Mediated Delivery of Pro-Survival MicroRNA-486-5p in Acute Kidney Injury


Methods: We have previously reported that up-regulation of miR-21 contributed to the protective effect of delayed ischemia preconditioning (IPC) in renal ischemia/reperfusion injury (IR). The role of vascular endothelial cells in the protective effects of miR-21 in renal delayed IPC is less well understood. In the present study, we examined the role of vascular endothelial cells in the protective effects of miR-21 in renal delayed IPC.

Results: We provide evidence that the deficiency of MR in the SMC protects against the development of acute kidney lesions induced by IR, however MR deficiency in SMC did not impact the appearance of CKD induced by IR, suggesting that MR in other cell types is involved.

Funding: Private Foundation Support

FR-PO231

The Role of Vascular Endothelial Cells in the Protective Effect of Delayed Ischemic Preconditioning in Renal Ischemia/Reperfusion Injury

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Background: We have previously reported that up-regulation of miR-21 contributed to the protective effect of delayed ischemia preconditioning (IPC) in renal ischemia/reperfusion injury (IR). The role of vascular endothelial cells in renal IR is not well-understood. In the present study, we examined the role of vascular endothelial cells in the protective effects of miR-21 in renal delayed IPC.

Methods: For the delayed IPC and IR model, 4 d after IPC (15 min ischemia) or sham surgeries, preconditioned mice were subjected to 35 min occlusion of bilateral renal pedicles, followed by 24 h reperfusion. Human umbilical vein endothelial cells (HUVECs) were treated with cobalt chloride for hypoxia model in vitro. Locked nucleic acid (LNA) modified anti-miR-21 or anti-scrambled was transfected into cells or delivered into the mice via tail vein injection less than 1 hour prior to IPC. Vascular permeability was determined by the Evans Blue dye. Cell apoptosis was estimated by Annexin V/FITC apoptosis detection. Expression of programmed cell death 4 (PDCD4) protein and miR-21 was examined by western blot and real-time PCR, respectively.

Results: Compared with the Sham+IR group, mice in the IPC+IR group showed significant improvement of renal function and histology injury (P<0.01). MiR-21 was up-regulated in the IPC+IR group with concomitant decline of PDCD4 (P<0.05) and improvement of vascular permeability (P<0.05). In vitro, miR-21 in HUVEC was increased in hypoxia, but PDCD4 expression was decreased. Knockdown of miR-21 by LNA anti-miR-21 abrogated the protective effect of IPC with concomitant up-regulation of PDCD4 (P<0.05) and exacerbated renal vascular permeability (P<0.05). Cell apoptosis significantly decreased after knockdown of miR-21 in vitro.

Conclusions: Up-regulation of miR-21 in renal delayed IPC improved the apoptosis of vascular endothelial cell by inhibiting its target PDCD4. This may be another mechanism underlying the protective effect of the delayed IPC.

Funding: Government Support - Non-U.S.

FR-PO232

Role of Vascular Mineralocorticoid Receptor in Renal Ischemia/Reperfusion

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Background: Renal ischemia/reperfusion (IR) is a major cause of acute kidney injury and is associated with chronic kidney disease (CKD) development. Mineralocorticoid receptor (MR) antagonism prevents the acute and chronic consequences of renal IR. Whether the benefit of the MR antagonists is due to the blockade of the MR in the vessels is unclear.

Therefore we want to study the specific contribution of endothelial and smooth muscle cells (SMC) MR in acute and chronic consequences of renal IR.

Methods: To inactivate MR in endothelial cells (MR−/− mice), floxed MR mice (MRflox) were crossed with mice expressing the inducible Cre recombinase under the Vcadence promoter. To allow inactivation MR in smooth muscle cells (MRflox/mice), MR−/− mice were crossed with mice expressing the inducible Cre recombinase under the Sma promoter. Sham surgery or bilateral renal IR for 20 min was performed in MR+/− and KO mice and the animals were studied at short term (24 h) and long term (30 days) after reperfusion.

Results: In MR−/− mice, IR induced renal dysfunction (plasma creatinine from 8.9±0.3 in sham to 33.8±6.8 μmol/L in IR), tubular injury and increased mRNA levels of kin-1 (400-fold) and NGAL (220-fold). The MR−/− mice displayed similar alterations induced by IR as MR−/− mice. In contrast, after 24 h of IR, the MRflox/mice presented normal renal function (plasma creatinine was 9.6±0.7 and 14.0±1.9 μmol/L in sham and IR, respectively), absence of histological alterations and reduced kin-1 and NGAL levels.

After 30 days, the MR−/− mice developed CKD characterized by renal dysfunction (plasma creatinine from 10.5±0.1 in sham to 15±0.8 μmol/L in IR), tubular-interstitial fibrosis and increased mRNA levels of fibronectin and Galexin-3 (2-fold). The MRflox/mice developed similar alterations.

Conclusions: We provide evidence that the deficiency of MR in the SMC protects against the development of acute kidney lesions induced by IR, however MR deficiency in SMC did not impact the appearance of CKD induced by IR, suggesting that MR in other cell types is involved.

Funding: Government Support - Non-U.S.

FR-PO233

Renal Vein Hydrodynamic Fluid Delivery Ameliorates Established Renal Injury following Ischemia/Reperfusion Injury

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Background: Past and current treatment for Acute Kidney Injury (AKI) is mainly supportive in nature; no therapeutic modalities to date have shown efficacy in improving the condition. While numerous experimental approaches can prevent AKI, there are few potentially translatable studies which may influence the course of established AKI. The goal of this study was to target vascular congestion and inflammation, which contribute to impaired renal perfusion and renal damage, following the established injury. We hypothesized that high-pressure retrograde hydrodynamic delivery (HD) of saline will improve established AKI, in part, by improving vascular congestion.

Methods: Male Sprague Dawley rats underwent left unilateral ischemia (35 min) and right unilateral nephrectomy or bilateral IRI (35 min) and reperfusion for 24 hours to induce AKI. 0.5mL of isotonic saline was then injected into either the vena cava (VC) or retrograde to left kidney via the renal vein (RV) under high pressure (~60mHg). Recovery was evaluated via serum creatinine and accumulation of immune cells were evaluated using FACS.

Results: Average serum creatinine at 24hrs was similar between groups (sCre=3.3mg/dl), however, RV-HD treated rats showed a rapid improvement in serum creatinine over the following 24 hours vs VC HD rats (24 to 48 h a serum creatinine ≤0.54 mg/dl vs. ≤0.6375 mg/dl, p=0.0237). To evaluate effects on inflammation, bilateral IRI rats subjected to left-RV HD resulted in a significant reduction in C4d (54%±18; p=0.05), CD68 (60%±8; p<0.05), B cells (56%±3.5; p<0.05) and DC/Macs (71%±13; p<0.05) compared with VC rats.

Conclusions: These results indicate that high pressure retrograde hydrodynamic delivery HD may provide a novel and effective therapeutic strategy for the treatment of AKI and transition of AKI to CKD.

Funding: NIDDK Support, Veterans Administration Support
**FR-PO234**

**Human Adipose Stromal Cells Ameliorate Renal Injury and Attenuate Capillary Rarefaction following Ischemia-Reperfusion**

**Background:** Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of the kidney’s excretory function, resulting in excess in 17 million hospital admissions a year. Although the tubular epithelium is the primary target of ischemic injury, early damage to endothelial cells contribute to AKI by resulting in impaired perfusion. Moreover, renal capillary density is permanently compromised in rats following AKI induced by ischemia reperfusion (IRI), which is hypothesized to promote CKD. Therefore, to preserve capillaries may impact both short-term recovery and long-term function post-AKI. Adipose tissue resident stromal cells (ASCs) have proangiogenic and anti-inflammatory properties. It is hypothesized that ASCs facilitate repair by capillary preservation, revascularization of damaged endothelium and decreased inflammation.

**Methods:** Male Sprague Dawley rats were subject to bilateral IRI (40 min). At the time of reperfusion, ~2×10^4 ASCs (hASCs, n=15) or vehicle (n=14) were injected into the suprapenal abdominal aorta. Recovery was evaluated via serum creatinine and capillary specific staining. Accumulation of immune cells in the kidney were evaluated using FACS.

**Results:** hASC-treated rats had a 90% survival by day 7, compared with 70% for vehicle. Serum creatinine showed a significant reduction in hASC-treated rats vs vehicle at 48 hrs, (35%, p=0.0008). By day 7, vehicle-treated rats showed a reduction in renal capillary density relative to sham (43%), which was significantly attenuated in hASC-treated rats (28%). Additionally, hASCs-treated rats exhibited a significant decrease in C4D (62%, ±16.8) and C5b-9 (72%, ±3.5) Tecil infiltration (p<0.05). Further, IL-17 cytokine secreted by CD4+T cells was reduced by ~40% in hASC-treated rats (185±66) as compared to vehicle (292±83.9). Conversely, the number of regulatory T cells was increased in hASC-treated rats compared with vehicle (35%, p=0.05).

**Conclusions:** These data suggest that ASCs may ameliorate AKI, at least in part, by preserving capillary density, decreasing inflammation and restoring renal function.

**Funding:** NIDDK Support

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**FR-PO235**

**Studying the Effect of Induced Expandable Human Kidney Progenitor Cells on Renal Function Using Transcutaneous Assessment**

**Background:** Mitochondrial dysfunction causes various mitochondrial diseases and mitochondrial repair. The process of creating new mitochondria to replace damaged mitochondria, is a potential therapeutic target for AKI. Our laboratory has demonstrated that LY344864, a selective 5-HT<sub>1F</sub> receptor agonist, promotes recovery from AKI as demonstrated by an increase in MB and reduced BUN and Kimm in a mouse model of ischemia reperfusion. While the 5-HT<sub>1F</sub> receptor is a G<sub>B</sub> coupled GPCR, the mechanism of 5-HT<sub>1F</sub> receptor mediated MB is unknown.

**Methods:** Mechanism of 5-Hydroxytryptamine 1F Receptor Stimulation of Mitochondrial Biogenesis in the Kidney

**Results:** 5-HT<sub>1F</sub> receptor agonist, promotes recovery from AKI as demonstrated by an increase in MB and reduced BUN and Kimm in a mouse model of ischemia reperfusion. While the 5-HT<sub>1F</sub> receptor is a G<sub>B</sub> coupled GPCR, the mechanism of 5-HT<sub>1F</sub> receptor mediated MB is unknown.

**Conclusions:** These studies report the novel finding that G<sub>B</sub> heterodimer initiates MB and does so through a new pathway. Specifically, 5-HT<sub>1F</sub> stimulation of G<sub>B</sub> activates Akt and eNOS, leading to the induction of MB. The identification of this pathway provides additional therapeutic targets for a drug intervention which could treat AKI.

**Funding:** NIDDK Support, Other NIH Support - NIGMS Support, Veterans Administration Support

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**FR-PO236**

**Indole Anagols Have Novel Therapeutic Effects on Mitochondrial Diseases and Kidney Injury**

**Background:** Mitochondrial dysfunction causes various mitochondrial diseases and kidney injuries. Anti-oxidant quinones have been used clinically to prevent the disease progression but the effectiveness is yet to be established. We recently found that an indole-derivative increased ATP levels in Hep3B cells and analyzed 41 newly synthesized indole derivatives. Among these compounds, we focused on the most potent derivative #5A (MA-5). The aim of this study was to clarify the effects of MA-5 in mitochondrial diseases and kidney injury.

**Methods:** Fibroblasts from patients with mitochondrial diseases (Leigh syndrome, MELAS, Leber disease, and Kearns-Sayre-syndrome) were cultured in ROS generating condition with BSO(β-lithionine (S)-retinoxime) and cell viabilities, cellular ROS and glutathione levels were measured. The redox property of MA-5 was examined by cyclic voltammetry. The site of MA-5 distribution was visualized by fluorescence-labeled MA-5 (MA-5FRET). MA-5 was exposed to kidney slices for 3 hr before they were exposed to kidney ischemia (26 min) reperfusion injury (IRI) or cisplatin (20 mg/kg body weight). Plasma creatinine (Cr), blood urea nitrogen (BUN) and renal pathology were assessed.

**Results:** MA-5 improved mitochondrial disorders in cultured human fibroblasts in a dose-dependent manner in mitochondrial disease fibroblasts. MA-5 exhibited irreversible oxidation peaks by cyclic voltammetry, suggesting that MA-5 did not have antioxidant property like anti-oxidant quinones. MA-5 did not affect the cellular ROS or GSH levels. MA-5 FL co-localized with the mitochondrial marker. In IRI mice model, after ischemia (60 min), MA-5 treated group showed a reduction in renal injury and tubular cell injury were significantly reduced in MA-5 treated group. BUN (70.9 + 10.1 vs 101 + 13.0 mg/dl) and tubular injuries, at 96 hr after cisplatin injection, were significantly reduced in Indole #5 treated groups.

**Conclusions:** MA-5 exhibited therapeutic effects in fibroblasts from mitochondrial disease patients as well as renoprotective effects in both IRI and cisplatin nephrotoxicity.

**Funding:** NIDDK Support, Other NIH Support - NIGMS Support, Veterans Administration Support

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**FR-PO236**

**Formoterol Induces Renal Mitochondrial Biogenesis Through G<sub>B</sub>-Dependent Signaling**

**Background:** Acute kidney injury (AKI) carries a high mortality and morbidity with no effective treatments beyond renal replacement therapy. AKI is characterized by mitochondrial dysfunction, particularly in the renal proximal tubule cells (RPTC). The induction of mitochondrial biogenesis (MB) is a therapeutic target for AKI. Our group has shown that formoterol, a β<sub>2</sub> adrenoceptor agonist, can induce MB in vitro and in vivo, and stimulate recovery of mitochondrial and renal function following AKI in mice. However, the signaling events leading to formoterol-induced MB remain unknown.

**Methods:** Formoterol increased Akt phosphorylation in RPTC at 30 min, and this increase was augmented by the G<sub>B</sub> inhibitor gallicin. Gallicin also augmented formoterol-induced increases in FCCP-OER, a biomarker of MB. Formoterol increased the phosphorylation of eNOS, a downstream target of Akt, at 1 hr, and pretreatment with the Akt inhibitor MK2206 blocked Akt and eNOS phosphorylation. Additionally, treatment with the NOS-inhibitor L-NAME attenuated formoterol-induced increases in FCCP-OER.

**Conclusions:** This study demonstrates that formoterol-induced MB occurs via β<sub>2</sub>-adrenoceptor coupling to G<sub>B</sub>, G<sub>B</sub> leads to the activation of Akt and eNOS, promoting MB. Stimulation of these signaling pathways represents an attractive therapeutic target for AKI.

**Funding:** NIDDK Support, Other NIH Support - 5T2DHL007260-38, 5T32GM008716-14, Veterans Administration Support
FR-PO239

Identification of Slow-Cycling Cells in the Kidney Using TetOP-H2B-GFP Mice
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Background: Renal tubular epithelium can regenerate after a variety of insults. During tubular regeneration, survived tubular cells proliferate, migrate and differentiate into mature cells. After several cell divisions, kidneys were removed for analysis. Localization of GFP-positive cells was examined by immunostaining with several nephron markers and their cell number was quantitatively assessed.

Results: 1) After a pulse of doxycyline, GFP-positive cells were found in the kidney of TetOP-H2B-GFP mice. Most GFP-positive cells were AQP-1 positive tubular cells. As pulse periods become longer, the number of GFP-positive tubular cells increased (pulse 8h-0.5%, pulse 24h-10%, pulse 72h-18%, pulse 3 weeks-5%). After a short pulse (8h) of doxycyline with no chase, all GFP-positive cells were present as a single cell, but after 2 weeks or 4 weeks chase periods, GFP-positive cells were found in clusters of two cells or three cells. 2) In TetOP-H2B-GFP mice treated with a long pulse (3 week) of doxycyline, the number of GFP-positive cells decreased according to chase periods (Chase 2h-50%, Chase 4h-40%, Chase 8h-5%).

Conclusions: These data suggest that slow-cycling cells cannot be detected as GFP-positive cells using TetOP-H2B-GFP mice under doxycyline control. This model will be applicable for selective isolation and in vitro characterization of slow-cycling tubular cells.

FR-PO240

Renal ERK1/2 Regulates PGC-1a and Mitochondrial Biogenic Homeostasis Physiologically and During Renal Injury
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Background: Acute kidney injury (AKI) is defined as a sudden decline in kidney function and the outcomes of AKI have not changed in the past few decades. Previous studies demonstrated that persistent disruption of mitochondrial homeostasis (e.g. peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), a master regulator of mitochondrial biogenesis (MB),) is an important contributor to renal ischemia reperfusion (IR) injury and repair. While the MAPK extracellular-regulated kinases 1/2 (ERK1/2) regulates numerous cell signaling pathways, the role of ERK1/2 activation in MB physiologically and as a consequence of renal IR injury remains limited.

Methods: Renal proximal tubule cells (RTCP) were treated with the specific MEK1/2 inhibitor trametinib (10nm) for various time points. Control mice were treated with trametinib (1mg/kg). Trametinib was administered 1 hour before 18 min of bilateral IR. Mitochondrial respiration was measured in primary renal proximal tubules (RPTC) using the Seahorse XF96 Extracellular Flux Analyzer. I/R injury was induced in male C57BL/6 mice aged 8-10 weeks by bilateral clamping of the renal pedicle for 19 minutes. Mice received daily treatment with saline vehicle or BAY 58-2667 (0.1 mg/kg) beginning at 24 h after IR.

Results: Treatment of RPTCs with BAY 58-2667 increased FCCP-uncoupled respiration, a marker of MB. BAY 58-2667 also increased mitochondrial gene and protein expression and mtDNA content in the renal cortex of naïve mice. Beginning 24 h after IR injury, daily treatment with BAY 58-2667 accelerated recovery of renal function evidenced by reduced BUN and renal expression of NGAL and KIM-1 at 6 d. Histological examination demonstrated reduced renal tubular necrosis in BAY 58-2667 treated mice at 6 d. Increased renal expression of growth factors and anti-fibrotic cytokines TGF-α and IL-10, and reduced oxidative DNA damage. These changes were associated with the recovery of renal MB signaling evidenced by increased mRNA expression of PGC-1α, NRF1, D10X, COX1 and ATP5F6, as well as mtDNA content and protein expression of PGC-1α and COX1. In addition, mitochondrial function was recovered as renal ATP returned to sham control levels. Finally, BAY 58-2667 blunted the progression of renal fibrosis evidenced by reduced COL1A2 and aSMA expression.

Conclusions: These data demonstrate that activation of guanylyl cyclase by BAY 58-2667 promotes recovery from AKI by stimulation of MB, reduction of inflammatory and oxidative damage, and inhibition of renal fibrosis.

Funding: NIDDK Support

FR-PO241

The Guanylyl Cyclase Activator BAY 58-2667 Stimulates Mitochondrial Biogenesis and Promotes Recovery from Ischemia-Reperfusion Induced AKI
Rick Whitaker, Rick G. Schneilmann. Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.

Background: Mitochondrial dysfunction is an important pathophysiological component of acute kidney injury (AKI). As reduced mitochondrial function can impair energy-dependent renal repair processes following AKI, stimulation of mitochondrial biogenesis (MB), the generation of new, functional mitochondria, could promote renal energy-dependent repair processes following AKI. This study was utilized the transgenic mouse with doxycyline-inducible expression of an H2B-GFP fusion protein (TetOP-H2B-GFP mice), in which divisions can be labeled with GFP under doxycyline control.

Methods: TetOP-H2B-GFP mice were treated with doxycyline for the indicated periods, kidneys were harvested, and kidneys were harvested for analysis. Localization of GFP-positive cells was examined by immunostaining with several nephron markers and their cell number was quantitatively assessed.

Results: 1) After a pulse of doxycyline, GFP-positive cells were found in the kidney of TetOP-H2B-GFP mice. Most GFP-positive cells were AOP-1 positive tubular cells. As pulse periods become longer, the number of GFP-positive tubular cells increased (pulse 8h-0.5%, pulse 24h-10%, pulse 72h-18%, pulse 3 weeks-5%). 2) After a short pulse (8h) of doxycyline with no chase, all GFP-positive cells were present as a single cell, but after 2 weeks or 4 weeks chase periods, GFP-positive cells were found in clusters of two cells or three cells. 3) In TetOP-H2B-GFP mice treated with a long pulse (3 week) of doxycyline, the number of GFP-positive cells decreased according to chase periods (Chase 2h-50%, Chase 4h-40%, Chase 8h-5%).

Conclusions: These data suggest that slow-cycling cells cannot be detected as GFP-positive cells using TetOP-H2B-GFP mice under doxycyline control. This model will be applicable for selective isolation and in vitro characterization of slow-cycling tubular cells.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Conclusions: MSC administration offers renoprotection from AKI on CKD when given immediately post insult. Early, specific biomarker-guided diagnosis of AKI identifies the optimal time for MSC-based therapy. Another clinical trial in high-risk cardiac surgery patients showed that giving MSCs 24-48 hrs post insult, based on the late and non-specific rise in SCr, abolished their protective effects.

Funding: Veterans Administration Support

FR-PO244
Improved Survival of Graft Bone Marrow-Derived Mesenchymal Stem Cells in the Ischemia-Reperfusion-Induced Injured Kidney with Overexpression of Heme Oxygenase-1
Nanmei Li, Jinn Hospital of Shanghai.

Background: one marrow-derived mesenchymal stem cells (BMSCs) transplantation offers therapeutic potential for acute kidney injury (AKI), but with limited efficacy. This study investigated the effect of HO-1 overexpression on the donor BMSCs’ survival, and its impact on the repair of AKI was also observed.

Methods: Ischemia/reperfusion (IR)-AKI kidney homogenate supernatant (KHS) was prepared. SD BMSCs, eGFP-BMSCs and HO-1-BMSCs were harvested and treated by the AKI-KHS. Cell viability, apoptosis and cell cycle were evaluated. Activities of oxidant stress-related enzymes, expression of p65 and the protein levels of Caspase-3 and Bcl-2 in BMSCs were tested. Survivals of the implanting BMSCs in the AKI rat model as well as the renal function were also assessed.

Results: HO-1-BMSCs showed a higher expression of HO-1 and AKI-HKS treatment further enhanced this level. This increased HO-1 expression promoted BMSCs survival under the AKI microenvironment with decreased apoptotic cells as well as less proportion of G0/G1 cells. AKI-KHS induced reduction of SOD activity and GSH-Px in BMSCs with increased MDA and AOXD levels, however, HO-1 overexpression changed this phenomenon. Activation of NF-xB p65 was inhibited in HO-1-BMSCs. Western blot showed decreased Caspase-3 expression and increased Bcl-2 expression in HO-1-BMSCs. The in vivo study showed increased survival of HO-1-BMSCs in the AKI kidneys, which was associated with improved renal function.

Conclusions: HO-1 overexpression could enhance survival of BMSCs under the IR-AKI microenvironment both in vitro and in vivo as the result of ROS elimination. Activity of NF-xB p65 and Caspase-3/Bcl-2 signal transduction pathways were involved in this process.

Funding: Government Support - Non-U.S.

FR-PO245
Induced Pluripotent Stem Cell-Conditioned Medium Mitigates Renal Ischemia-Reperfusion Injury by Suppressing Oxidative Stress We-Cheng Tseng, Der-Cherng Tang. Div of Nephrology, Dept of Medicine, Taipei City Hospital Heping-Fuxue Branch, Taipei, Taiwan; Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Ischemic acute kidney injury (AKI) carries high mortality and current treatment remains unsatisfying. Induced pluripotent stem cell (iPS) is a promising therapeutic option for AKI; nonetheless, teratoma formation addresses critical safety concerns for iPS cell transplantation. iPS-derived conditioned medium (iPS-CM) is comparable with iPS cells on ameliorating acute lung injury but the beneficial role of iPS-CM on AKI remains unclear.

Methods: Rat model of renal ischemia-reperfusion injury (IRI) and NRK52E cells subjected to hypoxia-reoxygenation (HR) were used to explore the role of iPS-CM on AKI. BUN, creatinine, tubular cell apoptosis, level of reactive oxygen species (ROS), expressions of proinflammatory cytokines and animal survival were investigated.

Results: Administration of iPS-CM intraperitoneally significantly improved renal function and decreased tubular cell apoptosis after renal IRI. Moreover, elevated ROS level in IRI-rat kidneys was markedly attenuated by iPS-CM. Co-culture of NRK52E cells with iPS-CM also significantly diminished HR-induced apoptosis and ROS production. Furthermore, iPS-CM downregulated both H-Ras and IRI-stimulated expressions of p38 MAPK, TNF-α, NF-xB and caspase 3. Additionally, the IRI-related IL-6 and MCP-1 expression were also suppressed by iPS-CM. Finally, after being subjected to renal IRI, the rats treated with iPS-CM demonstrated better survival as compared those treated with phosphate-buffered saline or normal control medium.

Conclusions: iPS-CM decreases renal IRI-related lethality by suppressing ROS, inflammation, and tubular cell apoptosis. iPS-CM may be a potential therapeutic option for kidney repair in ischemia.

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

Underline represents presenting author.

FR-PO246
Vascular Adhesion Protein-1 (VAP-1) Inhibition Ameliorates Cisplatin Induced Acute Kidney Diseases and Disorders (AKD)
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Background: Cisplatin (CP) is a platinum compound that is used as an effective chemotherapeutic agent for many malignancies. Its nephrotoxicity is dose dependent, which often limits its use. Research in the field of acute kidney diseases and disorders (AKD), including acute kidney injury (AKI), is important to prevent their progression to chronic kidney disease (CKD).

Methods: A new clinically relevant animal model using multiple low doses of CP was used to evaluate AKD. Human liver fatty acid-binding protein (L-FABP) transgenic (Tg) mice were administered 10 mg/kg of CP (three times, at 0, 1, 3 weeks) for four weeks. Vascular adhesion protein-1 (VAP-1) inhibitor that was recently reported to prevent fibrosis in organs was studied in this model. For treating group, mice received 2 mg/kg/day of PXS-4728A, a selective VAP-1 inhibitor, starting 3 weeks after the first CP administration.

Results: Moderate renal interstitial fibrosis occurred with multiple CP administration. Urinary L-FABP, one of the promising AKI biomarkers, increased about 10-fold one week after every CP injection. Although no further elevation of L-FABP was observed at 3W, following the omission of CP at 2W, L-FABP did not revert to baseline levels. Treatment of PXS-4728A for one week attenuated interstitial fibrosis in this model. VAP-1 inhibitor treatment remarkably reduced 4-HNE- and 8-OHdG-positive areas. The mRNA expressions of TP53, VEGF, VEGFR2, and MMP2 in the kidney were increased significantly by multiple CP treatments and attenuated by VAP-1 inhibitor treatment. Further, the inhibition of lipid accumulation in the S3 segments, together with L-FABP suppression was confirmed.

Conclusions: Multiple treatments with CP lead to moderate kidney dysfunction with increased AKI biomarkers and renal fibrosis. As a standing point of onco-nephrology, VAP-1 inhibitors are promising candidates for the prevention of CKD in patients using CP for the treatment of malignancy.

Funding: Government Support - Non-U.S.

FR-PO248
Pulsed Focused Ultrasound Improves Mesenchymal Stem Cell Therapy for Acute Kidney Injury by Upregulating Renal Interferon-Gamma to Stimulate Stem Cell Production of Interleukin-10
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Background: Pulsed focused ultrasound (pFUS) to kidneys enhances mesenchymal stem cell (MSC) homing to kidneys and improves outcomes when treating early or established acute kidney injury (AKI) compared to MSC infusions alone. However, mechanisms of improved combination therapy are unclear.

Methods: AKI was induced in C3H or interferon-γ (IFNγ)-deficient mice with cisplatin (15 mg/kg), pFUS (40W, 5%da) was delivered to kidneys –3hr before infusion of 10 human MSC. MSCs were observed by immunostaining for human mitochondria. For some experiments, MSCs were treated in culture with recombinant IFNγ or siRNA against IL-10. Cytokines were analyzed by mouse- and human-specific ELISAs. Serum creatinine and blood urea nitrogen values were measured spectrophotometrically.

Results: Proteomic profiling of AKI kidneys revealed that pFUS upregulated renal IFNγ and after MSC homed to pFUS-treated kidneys, they produced more human IL-10 compared to MSC in kidneys without pFUS. MSCs were observed by immunostaining for human mitochondria. For some experiments, MSCs were treated in culture with recombinant IFNγ or siRNA against IL-10. Cytokines were analyzed by mouse- and human-specific ELISAs. Serum creatinine and blood urea nitrogen values were measured spectrophotometrically.

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The purpose of this study is to clarify the therapeutic effects of SHED on AKI induced by IRI.

Methods: Seven days after heminephrectomy, the renal artery and vein were clamped for 20 min to induce ischemia in male C57BL/6 mice. SHED or PBS as a control was administered subcapsularly after the reperfusion. Blood, urine and tissue samples were collected. In order to confirm renoprotective potential of conditional media of SHED (SHED-CM) in vitro, H2O2 stimulation assay and scratch wound assay using mouse tubular epithelial cells (TECs) were also performed.

Results: Serum creatinine and BUN levels and urinary KIM-1 excretion were significantly decreased in SHED-treated group. In inflammatory cell infiltrations and aSMA was reduced in animals receiving untreated and SAHA pretreated cells. In addition, postischemic renal function declined after renal ischemia and remained unaffected in all groups. A significant increase in GTP-Arf6 and GTP-Rac1 levels when compared to kidney sections from HGF treated IRI mice. Additionally, SecinH3 counteracted the renal reparative effects of HGF.

Conclusions: SHED administration successfully attenuated mouse IRI-induced AKI. Our results indicate that SHED exerted anti-inflammatory activity in early stage of inflammation and promote cell proliferation by paracrine effect, thereby renoprotective effect in a mouse model of ischemic kidney injury. These results suggest that SHED might offer novel stem cell resource, which can be applied for the treatment of ischemic kidney injury.

FR-PO249

Endothelial Autophagy and Endothelial-Mesenchymal Transition (EndoMT) in EPC Treatment of Ischemic AKI

Background: Autophagy potentially prolongs the cellular lifespan. Early Endothelial Progenitor Cells (eEPCs) protect mice from ischemic AKI. The mid-term prognosis in AKI critically depends on vascular remanifaction and interstitial fibrosis with the latter partly induced by mesenchymal transdifferentiation of endothelial cells (EndoMT). Aim of the study was to determine the impact of eEPC preconditioning with different autophagy inducing agents (SAHA / Temsirolimus - Tems) in ischemic AKI.

Methods: Male C57/B16 mice were subjected to bilateral renal ischemia (40 min) followed by 45 min of reperfusion. Mice were analyzed 48 hours and 4 weeks later. In addition, cultured EPCs were treated with TGFB +/- SAHA, autophagy (perinuclear LC3-II) and Stress Induced Premature Senescence (SIPS - SA-b-Gal) were evaluated 96 hours later.

Results: Cultured EPCs showed reduced perinuclear density of LC3-II+ vesicles and elevated levels of SA-b-Gal after treatment with TGFB-alone, indicating impaired autophagy and aggravated SIPS. These effects were completely abrogated by SAHA. Systemic administration of either SAHA or Tems pretreated EPCs resulted in elevated intrarenal endothelial p62 at 48 h and 4 weeks. This effect was most pronounced after injection of SAHA treated EPCs. At 4 weeks endothelial expression of mesenchymal αSMA was reduced in animals receiving untreated and SAHA pretreated cells. In addition, SAHA treated cells reduced fibrosis at week 4. Tens in contrast aggravated EndoMT. Postischemic renal function declined after renal ischemia and remained unaffected in all experimental cell treatment groups.

Conclusions: In ischemic AKI, intrarenal endothelial autophagy may be stabilized by systemic administration of pharmacologically preconditioned eEPCs. Early EPCs can reduce postischemic EndoMT and fibrosis in the mid-term. Autophagy induction in eEPCs may either increase or decrease the mesenchymal properties of intrarenal endothelial cells. Thus, endothelial autophagy induction in ischemic AKI is not a renoprotective event per se.

FR-PO250

Impact of Timing Administration of Mesenchymal Stromal Cells on Serum Creatinine following Renal Ischemia/Reperfusion in Rats

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Background: Experimental models of renal ischemia/reperfusion (IR) have suggested protective effects of mesenchymal stromal cells (MSC) therapy. Still, parameters of MSC, including volume, route and timing of cell administration, remain largely debated. Particularly, MSC infusion in mice has been shown to be beneficial “a priori” but deleterious “a posteriori” of renal I/R injury.

Methods: In order to further investigate the influence of the timing of MSC administration on renal injury, we used 10-week-old Lewis rats categorized in 4 groups. Groups 1 (MSC D-7, n=10) and 2 (MSC D-1, n=7) received caudal i.v. injection of MSC (1.5×10⁶ in 1 mL of saline) 7 days before or 1 day after renal I/R, respectively. Control groups 3 (saline D-7, n=6) and 4 (saline D-1, n=6) received equal volume of saline at similar time points. Left renal ischemia was induced by clamping the renal pedicle below the renal hilus and nephrectomy was simultaneously performed. Blood sample was collected from inferior vena cava at 48 hours post reperfusion. MSC phenotype was confirmed by FACS analysis.

Results: In groups 1 and 3, serum creatinine (Scr) reached 1.4 ± 0.7 versus 2.4 ± 0.8 mg/dL, respectively (p<0.001). In groups 2 and 4, Scr was 4.9 ± 0.7 versus 3.3 ± 0.9 mg/dL, respectively (p<0.001). Furthermore, Scr levels were statistically worse when MSC were administered after renal I/R in comparison to a priori infusion (p<0.0001).

Conclusions: MSC administration 7 days prior to renal I/R may attenuate kidney injury in comparison to (i) saline infusion or (ii) MSC infusion 1 day after renal I/R. Conversely, on the basis of Scr levels, MSC therapy performed after renal I/R worsens kidney injury in rats.

Funding: Government Support - Non-U.S.

FR-PO251

Cytosolic Phospholipase A2 Regulates the G2 to M Transition by Modulating the Activity of Tumor Suppressor Sirtuin 2

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Background: SIRT2, a tumor suppressor gene, contributes to the control of the G2 to M transition checkpoint of the cell cycle under cellular stress. However, the mechanisms underlying both SIRT2 activation and the regulation of the G2 to M transition remain largely unknown. Here, we describe the regulatory function of cPLA2α on SIRT2 activity and G2 to M transition.

Methods: G2 to M transition in vitro was evaluated in LLC-PK1 cells overexpressing SIRT2 or cPLA2α and in mouse embryonic fibroblasts (MEFs) derived from cpla2α-/- mice. G2 to M transition in vivo was assessed in cpla2α-deficient mice during moderate I/R and under severe stress induced by colchicine. G2 and mitotic cells were identified by staining with pH1 and MPM-2 antibodies, respectively. Analysis of the phosphorylation state of SIRT2 was carried out in the presence or absence of cPLA2α in vitro by kinase assay and in vivo using a SIRT2 ser331 phosphospecific antibody.

Results: cPLA2α, SIRT2, and cyclo-CaCd2 form a multiprotein complex at the G2/M transition in vivo and in vitro. cPLA2α acts as a bridge in this complex to promote binding of SIRT2 to cyclo-CaCd2. Cyclo-CaCd2 then phospho-activated SIRT2 at ser331. Phosphorylation of SIRT2 at ser331 diminishes its catalytic activity and reduces its binding affinity to centromeres and mitotic spindles. This detachment of SIRT2 from mitotic spindles in the presence of cPLA2α promotes G2 to M transition. In cpla2α-/- MEFs and kidney tubular cells SIRT2 was hypophosphorylated at the G2/M transition. Lack of cPLA2α in these cells resulted in a reduction in the number of mitotic cells in response to mitotic stress.

Conclusions: cPLA2α is a regulator of the G2 to M transition in vitro and during ischemia/reperfusion injury in kidney epithelial cells. This function of cPLA2α may be further exploited to better understand the important link between cPLA2α and tumorigenesis and between inflammation and the age-related disorders such as Alzheimer’s disease, in which SIRT2 has been implicated.

Funding: NIDDK Support

FR-PO252

The Cytosine Guanosine Exchange Factors Are Required to Promote HGF-Mediated Renal Recovery After Acute Kidney Injury in Mice


Background: The lack of current treatment and preventable measures for acute kidney injury (AKI) in hospitalized patients results in an increased mortality rate of up to 80% and elevated health costs. The molecular aspects of kidney injury and repair are still under investigation, with a focus on inflammation and the age-related disorders such as Alzheimer’s disease, in which the molecular aspects of kidney injury and repair are still under investigation.

Methods: We used an ischemia and reperfusion injury (IRI) mouse model to analyze the role of modulating this signaling pathway on kidney recovery. We treated IRI mice with either HGF, the cytosine inhibitor SecinH3, or a combination of both. Kidney function was assessed by measuring creatinine (Cre) and blood urea nitrogen (BUN) levels. Standard H&E staining was used to detect kidney structure and immunohistochemistry was performed to detect active-Rac1 and active-Arf6.

Results: Simultaneous treatment with SecinH3 and HGF blocks the ability of HGF to promote kidney recovery as evidenced by Cre and BUN levels. Immunohistochemistry showed that HGF treatment promoted recovery of tubule structure, and had enhanced levels of active, GTP-bound Arf6 and GTP-Rac1 levels when compared to kidney sections from HGF treated IRI mice. Additionally, SecinH3 counteracted the renal reparative effects of HGF.

Conclusions: We show that HGF-dependent damaged kidney recovery requires the function of a cytosine-dependent signaling module, and that inhibiting cytosine DNA methylation counters HGF-stimulated recovery. In addition, we demonstrate that HGF treatment of ischemic mice promotes the activation of Arf6 and Rac1 in the recovering kidneys in a cytosine-dependent manner, and that cytosine activity is required to promote epithelial repopulation of kidney tubules and thus kidney recovery.

Funding: NIDDK Support
Regulation of Kidney Injury Molecule-1-Mediated Efferocytosis by Rho GT-Pases

Ola Ismail, Xiaohong Zhang, Lakshman Gunarathnam.

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Background: Kidney injury molecule 1 (KIM-1) is a phagocytic receptor for apoptotic cells that is specifically upregulated on the apical membrane of proximal tubule cells (PTCcs) after acute kidney injury. KIM-1-mediated clearance of apoptotic cells (efferocytosis) protects from interstitial fibrosis during acute kidney injury by down-regulating innate immunity and inflammation. As cytoskeletal remodeling is essential for phagocytosis, we examined the relative importance of Rac1 and RhoA, two key Rho GT-Pases that mediate actin remodeling, in KIM-1-dependent efferocytosis. We also investigated a possible link between KIM-1, which we previously identified as a KIM-1-interacting protein, and these Rho GT-Pases.

Methods: To study the role of Rac1 and RhoA in KIM-1-mediated uptake of apoptotic cells, we utilized chemical inhibitors or plasmids encoding dominant negative forms of Rac1 or RhoA proteins and measured the uptake of apoptotic cells by flow cytometry. Using commercially available GT-Pase pull-down assays, we measured the endogenous Rac1 and RhoA activity in KIM-1-expressing cells after apoptotic cell-stimulation. To decipher whether these Rho GT-Pases are down-stream mediators of Gal2-KIM-1 signaling, we silenced Gal2 using siRNA and measured Rac1 and Rho GT-Pase activity.

Results: Inhibition of Rac1 resulted in a significant decrease in KIM-1-mediated phagocytosis, whereas inhibition of and RhoA increased it. RhoA activity gradually increased during phagocytosis and peaked during the later stages of phagocytosis, whereas Rac1 activity remained constant over the entire course of phagocytosis. Furthermore, silencing a key KIM-1-interacting protein, Gal2, caused a significant decrease in RhoA activity.

Conclusions: We conclude that Rac1 and RhoA play opposing roles during KIM-1-mediated efferocytosis, whereby RhoA serves to mediate signaling by KIM-1 and its interacting partner, Gal2.

Funding: Government Support - Non-U.S.

Periostin Increases Kidney Fibrosis After Ischemia-Reperfusion Injury via Rac1 and RhoA Proteins

Boramae Medical Center; Chung-Ang Univ Hospital, Republic of Korea.

Rac1 and RhoA mediate phagocytosis, whereas inhibition of and RhoA increased it. RhoA activity gradually increased during phagocytosis and peaked during the later stages of phagocytosis, whereas Rac1 activity remained constant over the entire course of phagocytosis. Furthermore, silencing a key KIM-1-interacting protein, Gal2, caused a significant decrease in RhoA activity.

Conclusions: We conclude that Rac1 and RhoA play opposing roles during KIM-1-mediated efferocytosis, whereby RhoA serves to mediate signaling by KIM-1 and its interacting partner, Gal2.

Funding: Government Support - Non-U.S.

Acute Kidney Injury Improves Functional Recovery and Prevents Renal Fibrosis

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Translational Medicine and Therapeutics, The William Harvey Research Inst, Queen Mary Univ of London, London, United Kingdom; ‘Dep of Drug Science and Technology, Univ of Turin, Turin, Italy.

Background: Acute kidney injury (AKI) is a major risk factor for the development of chronic kidney disease (CKD). Renal ischemia may cause post-inflammatoyy scarring leading to loss of nephron function. Development of new therapies targeting key factor (NF-kB) is a family of transcription factors activated post-inflammation, but its role in the progression of chronic kidney disease to CKD is unknown.

Methods: Male Wistar rats were subject to a RH nephrectomy and L1 unilateral renal ischemia for 15 min, or nephrectomy (sham) (n=6) (sham) (n=6) (sham) (n=6) (sham) (n=6). Animals subjected to unilateral ischemia were randomly divided into 5 groups: normal control (control animals), rats subjected to unilateral ischemia for 15 min, rats subjected to unilateral ischemia for 15 min and treated with anti-NF-kB agents (NF-kB) is a family of transcription factors activated post-inflammation, and the level of fibrosis at 2d.

Conclusions: Inhibiton of NF-kB at 24h post AKI (at peak creatinine values) improves renal functional recovery at 48h post AKI, and reduces the degree of fibrosis observed at 2d.

Funding: Government Support - Non-U.S.

The Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) Agonist Pioglitazone Prevents Acute Kidney Injury (AKI) Progression to Chronic Kidney Disease (CKD) via Activation of Foxp3+ Regulatory T Cells (Tregs)

Jung Pyo Lee, Yuhong Tao.

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Postn null mice compared within WT mice. Furthermore, Postn null mice compared to in WT mice.

Conclusions: Periostin is related to the progression via p38 MAPK activation in cisplatin nephrotoxicity by reducing p65 acetylation through AMPK-SIRT1/P300 pathway. Treatment in cisplatin nephrotoxicity were attenuated by the PPAR-γ antagonist GW9662.

Results: Compared to sham-operated rats, rats subjected to unilateral renal ischemia developed AKI (increases in serum creatinine and decreases in the estimated creatinine clearance). The delayed administration of IKK16 at 24h post AKI (at peak creatinine values) significantly improved renal functional recovery and structural injury at 48h post AKI, compared to sham-operated rats, rats culled at 7d post AKI demonstrated significant increases in α smooth muscle actin (α-SMA) and CD68+ staining for myofibroblasts and macrophages, respectively. IKK16 administration significantly decreased α-SMA and CD68+ staining at 7d post AKI. Rats culled at 28d post AKI demonstrated a significant increase in Sirius red staining compared to sham rats, indicating the development of fibrosis. Administration of IKK16 at 24h significantly attenuated Sirius red staining, and therefore the level of fibrosis at 2d.

Conclusions: Inhibition of IKK at 24h post AKI (at peak creatinine values) improves renal functional recovery at 48h post AKI, and reduces the degree of fibrosis observed at 2d.

Funding: Government Support - Non-U.S.

Acute Kidney Injury Improves Functional Recovery and Prevents Renal Fibrosis

FR-PO256

Acute kidney injury (AKI) is a major risk factor for the development of chronic kidney disease (CKD). Renal ischemia may cause post-inflammatoyy scarring leading to loss of nephron function. Development of new therapies targeting key factor (NF-kB) is a family of transcription factors activated post-inflammation, but its role in the progression of chronic kidney disease to CKD is unknown.

Methods: Male Wistar rats were subject to a RH nephrectomy and L1 unilateral renal ischemia for 15 min, or nephrectomy (sham) (n=6) (sham) (n=6) (sham) (n=6) (sham) (n=6). Animals subjected to unilateral ischemia were randomly divided into 5 groups: normal control (control animals), rats subjected to unilateral ischemia for 15 min, rats subjected to unilateral ischemia for 15 min and treated with anti-NF-kB agents (NF-kB) is a family of transcription factors activated post-inflammation, and the level of fibrosis at 2d.

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Postn null mice compared within WT mice. Furthermore, Postn null mice compared to in WT mice.

Conclusions: Periostin is related to the progression via p38 MAPK activation in cisplatin nephrotoxicity by reducing p65 acetylation through AMPK-SIRT1/P300 pathway. Treatment in cisplatin nephrotoxicity were attenuated by the PPAR-γ antagonist GW9662.

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Funding: Government Support - Non-U.S.

The Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) Agonist Pioglitazone Prevents Acute Kidney Injury (AKI) Progression to Chronic Kidney Disease (CKD) via Activation of Foxp3+ Regulatory T Cells (Tregs)

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Conclusions: Inhibition of IKK at 24h post AKI (at peak creatinine values) improves renal functional recovery at 48h post AKI, and reduces the degree of fibrosis observed at 2d.

Funding: Government Support - Non-U.S.
Competitive Inhibition of CD95L Reduces Inflammation, but Only Modestly Improves Outcomes in Experimental Ischemia-Reperfusion Injury
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Background: After previous encouraging results in CD95L (FasL) mutant mice in ischemia-reperfusion injury (IR) models, we sought to investigate the effect of the competitive pharmacologic inhibition of CD95 (FAS) in kidney IR using APG101, an orally administered drug developed for the treatment of recurrent glomeruloma, which has shown a good patient tolerability in phase I and II clinical studies.

Methods: C57BL/6 mice treated with different dosages of APG 101 (10, 30 or 100 μg/kg-body weight, single-dose, 12h before IR) or vehicle (PBS) alone were submitted to a 2h period of ischemia by clamping both renal pedicles. Sham-operated mice treated with the highest dosage of APG101 dose or PBS. The experiment was further divided into two observation periods: day 2 (injury phase) and day 7 (recovery phase). Serum and kidney tissue analyses were performed focusing on function recovery, cell proliferation, macrophage infiltration and renal structure. Results are given as mean±SEM.

Results: Optimal serum CD95L saturation was only achieved in the APG 100μg/kg group (98.4±0.35%) and 96.9±1.3% at day 2 and 7, respectively, so that experiments were further conducted with this dosage. At day 2, serum creatinine was significantly higher in the IR PBS group, but not in the IR APG group compared to sham-op (0.26±0.12 and 0.20±0.07 vs. 0.09±0.03 mg/dl P<0.05), a similar pattern was seen in macrophage infiltration and MCL-1 mRNA expression in the kidney, both persisting until day 7. Apoptosis, however, was similar between the IR groups in both observation periods. APG treatment markedly reduced cell proliferation in both sham and IR animals compared to PBS (0.510.9 vs. 8.4±5.7 Ki67 positive cells/hpf, p=0.0004), which was observed at day 2, but didn’t persist until day 7.

Conclusions: Despite an anti-inflammatory effect, the APG101-induced impairment of the tubular cell proliferation may have hampered the early recovery phase after IR leading to the modest results.

FR-PO259
Oral Treatment with PBI-4050 Reduces Ischemia-Reperfusion-Induced Fibrosis
Jean-Francois Thibodeau, Mikael Tremblay, Brigitte Groux, Lilianne Geerts, Alexandra Felton, Francois Sarra-Bourrew, Pierre Laurin, Lyne Gagnon.
ProMetic BioSciences Inc., Laval, QC, Canada.

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase II/III in CKD patients, displays anti-fibrotic activities via a novel mechanism of action. In a double-blind ascending dose (400 to 2400 mg) clinical phase I trial, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant side effects. Clinically relevant fibrosis is a leading cause of acute kidney injury (AKI), which may result from a variety of conditions, such as decreased cardiac output, renal vascular occlusion or obstruction, and kidney transplantation. The aim of this study was to investigate the anti-fibrotic activity of PBI-4050 in a mouse model of acute ischemic kidney injury.

Methods: Renal ischemia-reperfusion (IR) injury was induced by the clamping of the left renal pedicle for 60 minutes in C57BL/6 mice (6-8 week old). Mice were treated with vehicle or PBI-4050. At day 14, mice suffering from renal IR demonstrated the anti-fibrotic activity of PBI-4050 in a mouse model of acute ischemic kidney injury.

Results: There was a significant increase in BUN, Scr and serum NGAL in mice treated with Cis+U0126 vs. Cis only. Tumor weight and volume was decreased in mice treated with vehicle+U0126 vs vehicle alone demonstrating that U0126 decreases tumor growth. Tumor weight and volume was decreased in mice treated with Cis+U0126 vs Cis alone demonstrating that U0126 significantly increased the therapeutic effect of cisplatin.

Conclusions: U0126 decreased cisplatin-induced AKI. In addition, U0126 decreased tumor growth and improved the therapeutic effect of cisplatin. Discovery of a drug that decreases cisplatin-induced AKI and improves the therapeutic effect of cisplatin would be a significant finding for patients with cancer.

FR-PO260
Cisplatin Acute Kidney Injury and Conversion to Chronic Kidney Disease
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Background: Chronic Kidney Disease (CKD) develops in humans after repeated doses of cisplatin (CP). We report on a new model to investigate the mechanism of this form of CKD.

Methods: 8-week old C57Bl6 mice were given either a single or double dose (2 weeks post dose) of CP (15 mg/kg) and studied 1,2,4,6 and 16-25 weeks after the first dose. GFR was measured by inulin clearance followed by intravascular perfusion-fixation. Immunohistochemistry and Multiphoton Microscopy (MPM) were applied to the fixed tissue.

Results: GFR fell precipitously to below 50% controls 2 weeks after the second dose and progressed without hypertension, loss of glomerular number, or glomerulosclerosis. Kidney weight fell as a result of loss of cortical tissue. Collagen deposition increased but was mainly restricted to peritubular locations along the cortico-medullary region. Influx of macrophages, increased cell cycle activity (Ki67) and apoptosis (TUNEL) were followed by vascular rarefaction. Ki67 failed to increase after the second dose as it did after a single dose. The cyclopin-dependent kinase inhibitor protein p21 increased and paralleled the lack of cell cycle activity. Abnormal glomerulotubular junctions (GTJ) developed only after the second dose, which included loss of megalin positive parietal epithelial cells and the formation of atubular glomeruli. These changes correlated well with the development of progressive renal insufficiency.

Conclusions: MPM uncovered abnormalities of the GTJ that marked the transition from AKI to CKD in CP-induced CKD. Coupled with the failure of the proximal tubule (PT) to re-enter the cell cycle suggests a causal relationship between failed repair of this segment and the conversion of AKI to CKD. The increased expression of the p21 gene seen here and its demonstrated role in progression in the renal ablation model of CKD suggests its sustained activation may cause the conversion of AKI to CKD. Understanding why injured PT cells fail to re-enter the cell cycle following the second dose of CP is likely to yield new means to prevent CP-induced CKD, which may be applicable to other forms of AKI to CKD conversion.

Funding: NIDDK Support, Veterans Administration Support

FR-PO262
Glycogen Synthase Kinase-3 Regulates Fibroblast Activation and Development of Fibrosis following Renal Ischemia/Reperfusion in Mice
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Background: Glycogen synthase kinase-3β (GSK3β) is a serine/threonine protein kinase that plays an important role in renal tubular injury and regeneration in acute kidney injury. However its role in the development of renal fibrosis, often a long-term consequence of acute kidney injury is unknown. Using a mouse model of renal fibrosis induced by ischemia/reperfusion (IR) injury, we demonstrated increased GSK3β expression and activity in fibrotic kidneys.

Methods: Bilateral I/R was carried out on male C57BL6/J mice; both renal pedicles were exposed by flank incision and clamped for 30 minutes at 37°C. GSK3 inhibitor (TBDZ-3) was administered by daily IP injection at 1mg/Kg BW. dose starting 1h before (TBDZ-pre) or 48h after (IR/TBDZ-post). Studies were also carried out in rat fibroblast NRK-49F cells. In vivo: TBDZ-3 was added to cell culture medium. In vitro: GSK3β expression and activity increased significantly starting 48h after IR and remained high in the fibrotic kidneys 12 days after IR. GSK3β was detected in renal myofibroblasts and tubules. GSK3 inhibition suppressed fibrosis, with significantly reduced myofibroblast population, extracellular matrix deposition, inflammatory mediators and TGF-β binding in TDZD-pre and TDZD-post treatment groups compared to vehicle treated group. In vitro: TGF-β treatment increased GSK3β expression in NRK-49F cells and GSK3 inhibition abolished TGF-β induced SMAD-3 activation and α-SMA expression. Importantly, overexpression of constitutively active GSK3β stimulated α-SMA expression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
even in the absence of TGF-β1 treatment. These results suggest that TGF-β1 regulates GSK3β expression, which in turn is important for TGF-β1 SMAD3 signaling and fibroblast-to-myofibroblast differentiation.

**Conclusions:** The study thus demonstrates that GSK3 could promote renal fibrosis by activation of TGF-β signaling and the use of GSK3 inhibitors might represent a novel therapeutic approach for progressive renal fibrosis that develops as a consequence of AKI.

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**FR-PO263**

Regulating Cx43 and TRPC6 Expression Protects Renal Epithelial Damage in a Rat AKI Model

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**Background:** Intracellular Ca$^{2+}$ homeostasis plays an essential role in maintaining normal cell function. Connexin43 (Cx43) and transient receptor potential channel (TRPC6) has been reported to regulate Ca$^{2+}$ entry in some pathologic conditions. The aim of this study was to elucidate whether the modifier protein of glyceraldehyde-3-phosphate dehydrogenase (MP) and ATP-MgCl$_2$, could regulate Cx43 and TRPC6 in a rat model of acute kidney injury (AKI).

**Methods:** Male Sprague-Dawley rats were divided into the following groups: normal control, gentamicin-treated, MP plus gentamicin-treated, ATP-MgCl$_2$ plus gentamicin-treated (n=15 for each), as well as control group for MP and ATP-MgCl$_2$ alone (n=5 for each). Levels of serum creatinine (sCr) for each group were measured on the 14th days of treatment. The “in vivo cryotechnique” was used for preparing kidney specimen as before.

**Immunohistochemistry staining for Cx43 and TRPC6 was performed.** Western blotting of the gentamicin-treated group showed a significant increase in sCr compared to the normal control group. Co-treatment of gentamicin with MP and/or ATP-MgCl$_2$, produced marked decreases preventing the increase of sCr. Under light microscope, the gentamicin-treated group showed tubular epithelium damage indicating AKI. This was attenuated by MP and/or ATP-MgCl$_2$, co-treatment. Immunohistochemistry staining indicated that MP and/or ATP-MgCl$_2$, co-treatment prevented gentamicin-induced down-regulation of Cx43 and TRPC6 in renal epithelial cells using the “in vivo cryotechnique”. Furthermore, the expressions of Cx43 and TRPC6 in gentamicin-treated group showed much weaker intensity using conditional fixation method compared to that using “in vivo cryotechnique” suggesting there might be artificial damage during the conditional fixation procedure.

**Conclusions:** Using a rat model of AKI, MP and ATP-MgCl$_2$, were able to prevent the down-regulation of Cx43 and TRPC6, which might reduce Ca$^{2+}$ entry and its downstream signaling, thus minimizing the damage in the renal epithelial cells.

**FR-PO264**

S-Glutathionylation of TAZ Might Contribute to Acute Kidney Injury and Repair

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**Background:** The clinical syndrome of acute kidney injury (AKI) is one of the most important diseases in nephrology and associated with increased morbidity and mortality. Kidney displays a remarkable potential for repair even after severe acute injury. Recent studies identified the Hippo pathway as a master regulator of organ growth and proliferation and uncovered the importance of the two mammalian Hippo-signaling effector molecules YAP and TAZ as regulators of proliferation and apoptosis during kidney development. The objective of the current study is to demonstrate that TAZ undergoes redox regulation via s-glutathionylation.

**Methods:** Immunoprecipitation, reporter gene assay, XTT assay, cycloheximide assay.

**Results:** Our findings indicate that exposure to hydrogen peroxide (H2O2) increased TAZ/TEAD transcriptional activity without affecting YAP/TEAD. Consistently, TAZ/TEAD interaction was slightly enhanced upon H2O2 exposure. Furthermore, H2O2 exposure increased nuclear localization of TAZ in a stable NIH3T3-Fip-in cell line expressing TAZ-GFP. We confirmed s-glutathionylation using recombinant TAZ protein in vitro and biotinylated glutathione ester in cell culture. To identify cysteine residues undergoing s-glutathionylation we generated TAZ C>A mutants. Reporter assays revealed that TAZ C358A showed increased transactivation of TEAD, the effect on cell proliferation and migration was also enhanced in TAZ C358A mutant. Finally, cycloheximide chase assay revealed that all of the TAZ mutants exhibited increased stability following 6h incubation.

**Conclusions:** Our data indicate a novel mechanism how pro-proliferative TAZ activity is regulated by ROS via s-glutathionylation, which could play an important role in tissue injury and repair. Currently, we are following the hypothesis that ROS derived from constitutively active NOX4 could modulate TAZ activity in the kidneys and we are investigating the importance of s-glutathionylation of TAZ in vivo.

**FR-PO265**

Bud-Like Structure Capable of Developing to Lamellipodia in Wound Healing of Tubular Epithelium – A Scanning Electron Microscopic Approach

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**Background:** Cell migration is essential in wound healing during which filamentous (F)-actin assembly plays a pivotal role. Cell biological approaches, using confocal microscopy, succeeded in identifying molecules regulating the assembly, such as the Arp2/3 complex, N-WASP, cofillin, and profilin. Although cells form filopodia (microspike) and lamellipodia (membrane), and move forward, much remains to be seen in the ultrastructure of these processes.

**Methods:** Rat tubular epithelium (NRK-52E) was cultured, grown to confluency, and scratched. The cells were subjected to scanning electron microscopy (SEM) at various time points. In separate experiments, immunoelectron microscopy was performed using an antibody against Arp3. Lastly, 60% confluent NRK-52E cells were cultured in the presence or absence of si-RNA for Arp3, grown to confluency, and scratched. The cells were observed periodically at the SEM levels, and, the length of time for complete recovery was compared.

**Results:** As shown in the figure, SEM elucidated elaborated network of filopodia containing “bud-like structure” (bud) that may develop to lamellipodia. Arp3 was expressed in filopodia and lamellipodia but not in a bud. The Si-RNA knockdown significantly prolong the length of time for the recovery. It at least partially inhibited the formation of filopodia network and lamellipodia but not the formation of a bud.

**FR-PO266**

Inhibition of Microtubule Dynamics Delays Kidney Recovery After Ischemia/Reperfusion Injury in Mice

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**Background:** Ischemia/reperfusion (I/R) is a major cause of acute kidney injury (AKI). If recovery from AKI is delayed, kidney progresses toward chronic renal failure. Microtubules, a component of the cytoskeleton, contribute to cell damages, cell shape, cell motility, and cell division. Here, we investigate that the role of microtubule network on the kidney injury, recovery and progression of fibrosis after I/R injury.

**Methods:** Mice were subjected to 30 minutes of bilateral renal ischemia, and mice were sacrificed 16 days after ischemia. Some mice were administered either saline (vehicle) or paclitaxel (taxol), a microtubule stabilization agent; 1 day before ischemia (pretreatment) or from 1 day after ischemia until sacrifice every 2 days (post-treatment).

**Results:** Pretreatment of taxol did not affect post-I/R renal function compared with vehicle-treated I/R group. Post-treatment of taxol delayed renal functional and histological recovery with retardation of tubular regeneration, and accelerated proliferation of interstitial cells after ischemia. Post-treatment of taxol from 24 hours after ischemia enhanced cell cycle arrest, progression of fibrosis, and macrophage infiltration into the kidney. Furthermore, post-treatment of taxol suppressed reguloparization of primary cilia in tubular epithelial cells.

**Conclusions:** In conclusion, our results demonstrate that microtubule stabilization or inhibition of cell proliferation delays kidney tubule cell restoration after ischemic injury, whereas interstitial cell proliferation is accelerated, leading to kidney fibrosis. It suggests that regulation of microtubule dynamics is critical to repair from AKI and progression of AKI to chronic kidney disease.

**Funding:** Government Support - Non-U.S.
Tubulin Acetylation in the Kidney Tubular Cells After Ischemia/Reperfusion Injury

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Background: Acetylation of tubulin is known to play an important role in the stabilization of microtubules. Kidney ischemia/reperfusion (I/R) is a major cause of acute renal failure. I/R causes damage to the cytoskeleton in the tubular epithelial cells.

Aim: To study the acetylation of tubulin in kidney tubular epithelial cells after I/R injury using western blotting and immunohistochemical staining. Mice were subjected to either 30 min of ischemia or sham-operation. Kidneys were harvested at various times after ischemia.

Results: Acetylated tubulin expression dramatically decreased 24 hours after ischemia and then gradually increased over time. However, total α-tubulin expression was not significantly changed after I/R. In normal kidney, immune-reactivities of kidney epithelial cell to acetylated α-tubulin antibody were different in tubules; the orders were the descending order: duct distal tubules and the proximal tubule. Twenty-four hours after ischemia, acetylated α-tubulin expression increased in the proximal tubule and the distal tubule with strong expression in the nuclei of the tubular cells. In the glomerulus, acetylated α-tubulin was also observed and the expression was very strong in the podocyte and Bowman's capsule. Twenty-four hours after ischemia, acetylated α-tubulin expression in the proximal tubule was lower than that of normal cells. Nine days after ischemia, acetylated α-tubulin expression in the podocyte and interstitial cell increased. Expression of α-tubulin acetytransferase-1 (αTAT1), an enzyme involved in acetylation of α-tubulin, continuously decreased after ischemia. Histone deacetylase 6 (HDAC6), an enzyme involved in deacetylation of tubulin, also decreased acetylation of α-tubulin.

Conclusions: Ischemia/reperfusion reduced tubulin acetylation in renal tubular cells, suggesting that R/I-induced decrease of tubulin acetylation is associated with reduction of stability of microtubule in cells.

Funding: Government Support - Non-U.S.

Hypertension Aggravates Acute Kidney Injury (AKI) and Accelerates Progression to Chronic Kidney Disease (CKD)

Anja Thorenz, Hypertension Aggravates Acute Kidney Injury (AKI) and Accelerates Progression to Chronic Kidney Disease (CKD)

Background: Hypertension is a major risk factor for AKI and its progression to CKD. However, the mechanisms by which hypertension aggravates AKI and accelerates CKD progression are poorly understood. Injured or dying cells release products, or Danger signals, that activate the NLRP3 inflammasome, process pro-IL1 and pro-IL18 to their active secreted forms and activate TLR2/4 and MyD88 dependent transcription of immune genes in non-immune kidney cells. NLRP3 inflammasome activation in injured non-immune cells can result in pyroptotic cell death.

Aim: To study the role of impaired tubulo-interstitial fibrosis and the interplay between immune cell signaling and tubulo-interstitial fibrosis.

Methods: Mice were randomized into control, CD1, and C57Bl/6 strains. After induction of AKI, CD1 mice had significantly more inflammation and fibrosis compared to C57Bl/6 mice.

Results: CD1 mice show severe blood pressure elevation in ischemia induced AKI. Ischemia-reperfusion mouse models: 1) unilateral ischemia reperfusion injury in the kidney (IRI) and contralateral nephrectomy (DCN) on day 9, fibrosis and injury evaluation on day 28 (UIR DCN). 2) I/R with delayed contralateral nephrectomy (DCN) on day 9, fibrosis and injury evaluation on day 28 (UIR DCN D28).

Conclusions: The up-regulation of Gadd45-gamma protects against acute kidney injury, however, maladaptively increases the expression of pro-fibrotic molecules.
Canonical BMP Signaling via BMPR1A and Smad1/5/8 Mediates the Transition to Fibrosis After Renal Ischemia Reperfusion Injury

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Background: Ischemia reperfusion injury (IRI) of the kidney leads to acute kidney injury (AKI) and frequently precipitates the development of tubulointerstitial fibrosis. Bone morphogenic protein (BMP) signaling has been implicated in the pathogenesis and progression of the disease, but its tubular-specific role is unclear.

Methods: We induced IRI in mice by clamping the left renal pedicle for 25 minutes. The severity of injury was measured by histology scoring, elevated mRNA expression of renal injury markers NGAL and KIM-1 and increased urinary NGAL (uNGAL) excretion 24h post-ischemia. Activation of canonical BMP signaling was detected by nuclear pSmad1/5/8 immunostaining and Western blotting. To achieve a doxycycline-dependent Cre-mediated inactivation of BMP receptor 1a (Bmpr1a) in renal tubules, we generated Pax8Rta;LC1;Bmpr1aCreloxP mice (Bmpr1a cKO).

Results: Canonical BMP activity, as revealed by pSmad1/5/8, was widely detected in healthy wild-type (wt) mouse kidney tubules. IRI caused a sustained injury in wt kidneys as shown by elevated NGAL and KIM-1 expression and increased uNGAL excretion. In a 2.7-fold increase in BMP-7 expression, 42.7% decrease in fibroblast activation, and 63.7% decrease in renal fibrosis. These findings demonstrate that HAC1 and HAC2 are responsible for the loss of BMP-7 expression and its renal protective functions in the injured kidney. Furthermore, our study suggests that Class I HDAC inhibitors have a tremendous therapeutic potential for stimulating kidney repair and inhibiting disease progression following chronic renal injury.

Conclusions: BMP-7 expression and its renal protective functions in the injured kidney. Furthermore, our study suggests that Class I HDAC inhibitors have a tremendous therapeutic potential for stimulating kidney repair and inhibiting disease progression following chronic renal injury.

FR-PO275
Gli2 in Perivascular MSC Is Required for Kidney Fibrosis and Can Be Targeted Pharmacologically

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Background: We recently demonstrated that perivascular mesenchymal stem cell (MSC)-like cells are defined by expression of Gli1 and are critical myofibroblast precursors. We now investigate the role of Gli transcriptional activators in myofibroblast progenitors during kidney fibrosis and value as therapeutic targets.

Methods: We utilized mouse genetics, drug binding, RNAi and retrovirual overexpression to dissect the roles of Gli1 vs. Gli2 in myofibroblast activation and fibrosis. We pharmacologically targeted Gli proteins with Darinaparsin, an arsenical, and GANT61, a small molecule Gli inhibitor. We evaluated them in two separate mouse CKD models. We measured hedgpathway activity and expression of Gli in human kidney fibrosis specimen.

Results: In vitro knockdown of Gli1 had no appreciable effect whereas knockdown of Gli2 induced a G0/G1 cell cycle arrest of mouse fibroblasts. Conversely, Gli2 overexpression rescued this cell-cycle effect and drove proliferation. In vivo, knockout of Gli1 showed no effect on fibrosis severity after UUO whereas either conditional knockout of Gli2 or overexpression of the Gli3 repressor in Gli1−/−pericytes ameliorated fibrosis and induced a G1/G0 cell cycle arrest specifically in myofibroblasts, consistent with our in vitro results. We show that darinaparsin directly binds to Gli2, lowers Gli2 protein levels and induces a G0/G1 cell cycle arrest. This effect of darinaparsin absolutely requires Gli2, and Gli2 overexpression rescued the cell cycle defect. When administered in a therapeutic dosing strategy after UUO or IRI, darinaparsin potently reduced Gli1 and Gli2 expression, myofibroblast specific Gli3 expression, induced cell cycle arrest, and ameliorated fibrosis and reduced tubular injury (GANT61, structurally unrelated to darinaparsin, showed the exact same effects. In human kidneys with fibrosis there is strong upregulation of Gli1 and Gli2 mRNA, suggesting this pathway is conserved in humans.

Conclusions: Gli2 is a critical driver of myofibroblast proliferation and a novel therapeutic target in kidney fibrosis.

Funding: NIDDK Support

FR-PO274
Class Ia HDAC Inhibitors Restore BMP-7 Expression and Inhibit the Pathogenesis of Renal Fibrosis following Chronic Renal Injury

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Background: BMP-7 is a potent anti-fibrotic cytokine that is also required for the repair of renal injuries. However, chronic renal injury leads to the loss of BMP-7 and fibrogenic genes. We utilize a model of unilateral ureteral obstruction (UUO) to examine potential therapeutic strategies for stimulating the innate repair mechanisms of the kidney.

Methods: BMP-7 expression was studied in vivo in inner medullary collecting duct (IMCD) cells and in vivo in a mouse model of unilateral ureteral obstruction (UUO). The therapeutic effects of broad spectrum histone deacetylase (HDAC) inhibition with Trichostatin A (TSA) and Class Ia HDAC inhibition with MS-275 were evaluated by assessing renal pathology.

Results: UUO results in an 83.1% decrease in BMP-7 mRNA expression that is paralleled by a 63.0% decrease in the acetylation of histone proteins in the proximal Bmp7 promoter, a process that results in gene repression. These changes are HDAC-dependent and blocked by treatment with TSA. An in vivo pharmacological screen in IMCD cells revealed that TSA and MS-275 stimulates BMP-7 expression, while inhibitors of other HDAC isoforms have no effects. These results were confirmed by using siRNA-mediated genetic ablation to demonstrate specificity and chromatin immunoprecipitation to show binding of the Class Ia HDAC proteins HDAC1 and HDAC2 to the Bmp7 promoter. MS-275 also stimulates anti-fibrotic functions of BMP-7 in vitro by suppressing the expression of the TGF-β-dependent pro-fibrotic genes COL1A1 and aSMA by 68.2% and 97.6%, respectively. Finally, these results extend to the obstructed kidney in vivo where HDAC inhibition results in a 2.7-fold increase in BMP-7 expression, 42.7% decrease in fibroblast activation, and 63.7% decrease in renal fibrosis.

Conclusions: These findings demonstrate that HDAC1 and HDAC2 are responsible for the loss of BMP-7 expression and its renal protective functions in the injured kidney. Furthermore, our study suggests that Class I HDAC inhibitors have a tremendous therapeutic potential for stimulating kidney repair and inhibiting disease progression following chronic renal injury.

Funding: NIDDK Support, Private Foundation Support

FR-PO275
Klotho Influences the Fate of Fibrosis in Cardio-Renal Protection

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Background: Soluble Klotho is an endogenous hormone produced predominantly by extracellular domain shedding of membrane Klotho in the kidney. Although Klotho is known to provide cardio-renal protection through its regulation of ion transport and growth factor signaling, specific cellular localization and function of Klotho in the normal and diseased kidney are not clearly defined.

Methods: We evaluated Klotho expression and localization in human and mouse kidney via in situ hybridization (ISH), immunohistochemistry (IHC) or RNAseq. Cardio-renal protective effects of soluble human Klotho administration were studied in mouse unilateral ureteral obstruction (UUO; 5 day) and isoproterenol-induced cardiac hypertrophy (ISOP, 5 mg/g/d x 10d) models.

Results: In normal adult human kidney (fresh nephropatony and autopsy, n=9), Klotho was highly expressed in distal tubules (DT) and in both cortical and outer medulla collecting ducts (CD). Proximal tubule and podocyte expression was low but detectable. Following UUO, renal Klotho RNA was decreased 61% and protein content was reduced greatly in the corticomedullary vs Sham group. Klotho treatment (10 µg/kg, QD, IP) attenuated UUO-induced tubulointerstitial fibrosis (picrosirius red stain, n=10) by 67%∗ (p<0.05) and 418A
biodmarkermRNA(40±5% vs.16±4%);16%TGFβvsvsVehiclecontrol.IntheISO
model,vehiclevs0.5,1and10mg/kgOB-IPNinhibitedcardiachypertrophy(HW/BW;6,6):5.4±1.8
(p<0.01)inKlotho-vs5.8±0.08inVehiclecontrol.

Conclusions:Klothoishighlyexpressedinnormalhumandmousedistalneephron.
KlothomRNAandproteinarereducedinpreclinicalmodelsofcardiacandrenaldisease.
Despitecomorbidity,Klothosinhibitstheseverityofpathologyandbiodmarkerexpression
intheUOmodelofrenalfibrosisandISO-inducedcardiachypertrophy.Klothopharmacotherapy
hasthetopotenttostabilizeCKDprogressionaswellastheprogressionofextra-renalKlothodependent
diseases.

FR-PO277
Kidney Interstitial Cell Derived Tenascin C Plays an Important Role in
Promoting Injury-Repairing of the Kidney by Stimulating Cell Proliferation
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Background: Tenascin-C (TNC) is a glycoprotein expressed in extracellular matrix during development and injury repairing. This study explored the role of TNC in acute kidney injury (AKI).

Methods: A TNC promoter driven inducible CreERT2 knock-in mouse line with EGFP reporter (IRE-EGFP) as generated (TNC-CreERT-eGFP). AKI was induced by 40 minutes of ischemia followed by reperfusion in unilateral nephrectomized mice (UN+UIR). Cell lineage tracing was conducted in TNC-CreERT2,R26-mTOMato mice to examine the origin of TNC expressing cells. The effect of TNC on cell proliferation was examined using a cell count kit in cultured HK2 cells. TNC expression was also examined in human biopsies with IRB approval.

Results: In normal kidney, TNC was restricted in renal papilla in both mice and human. Following IR, TNC was markedly induced in renal cortex, particularly in injured areas. TNC reporter showed that induced TNC expression is localized in interstitial cells, but not tubular epithelial cells. TNC induction was also shown in human biopsies with AKI. Co-staining IF showed that TNC was expressed by the PDGFRβ (+) renal interstitial cells, but not NG2 (+) pericyte, F4/80 (+) macrophage and FSP-1 (+) cells. Lineage tracing revealed that TNC expressing cells following IR were not derived from the renal medullary interstitial cells that constitutive express TNC, suggesting new TNC induction. To examine the role of TNC induction following AKI, TNC-/- mice were generated. TNC deletion resulted in significantly increased kidney weight, kidney collagen and alpha-smooth muscle actin staining. Since UUO resulted in a dramatic loss of TAZ and YAP expression in NRK52E cells, we examined if TNC could repress TAZ/YAP expression. In vitro, TNC significantly increased cell proliferation by 50%.

Conclusions: TNC is induced in renal interstitial cells after IR-induced AKI, protecting the kidney from injury. The protective effect of TNC on AKI may be associated with promoting renal recovery by stimulating epithelial cell proliferation.

Funding: Government Support - Non-U.S.

FR-PO278
TAZ and YAP Are Mechanoregulators of TGF-β-Smad Signaling and Renal Fibrogenesis

Background: Fibrosis is a final common injury pathway responsible for the progression of most forms of CKD, for which no specific treatments exist. Driven largely by TGF-β signalling, fibroblast-myoﬁbroblast transdifferentiation is crucial for ﬁbrosis. While it is known that ﬁbroblast activation is mechanosensitive, with soft matrix akin to a healthy kidney, impairing TGF-β responsiveness, the underlying mechanisms remain poorly understood. TAZ and YAP are homologous transcription co-factors with TGF-β regulatory activity, whose nuclear localization and activity are regulated by matrix stiffness. Here, our aim was to examine how stiffness regulates TGF-β signalling via TAZ/YAP, and to test if TAZ/ YAP inhibition can attenuate renal ﬁbrosis.

Methods: The effects of matrix stiffness on TAZ/YAP localization and TGF-β/Smad signalling were examined in rat renal ﬁbroblasts (NRK49Fs) cultured on soft (2 kPa) and stiff (100 kPa) gels. To test the effect of TAZ/YAP inhibition, NRK49F cells and mice were treated with verteporfin (VP), a drug used as a macular degeneration treatment with reduced described TAZ/YAP and matrix properties.

Results: In NRK49F cells, stiff matrix resulted in nuclear TAZ/YAP localization and enhanced TGF-β signalling. Growth on soft matrix, in contrast, lead to reduced TAZ/ YAP nuclear localization, and impaired TGF-β-induced Smad2/3 nuclear accumulation and transcriptional activity. In NRK52E cells, knockdown of stiffer resulted in a dramatic loss of TAZ/YAP, leading to a similar inhibition of TGF-β/Smad signalling. VP-induced TAZ/YAP loss also enhanced pro-fibrotic Smad2/3 degradation following TGF-β stimulation. In vivo, VP similarly reduced renal TAZ/YAP and Smad2/3 levels in UUO mice, leading to diminished myoﬁbroblast accumulation and interstitial collagen deposition.

Conclusions: Our data suggest that renal ﬁbrosis is regulated by a novel mechanical stimulus (stiffness) that, through control of the mechanosensory proteins TAZ and YAP, modulates TGF-β/Smad signalling. Furthermore, we hypothesise that verteporfin is a potential anti-ﬁbrotic treatment that interferes with this pro-fibro-mechano-chemo-synthetic axis.

Funding: Government Support - Non-U.S.

FR-PO279
Targeted Deletion of Numb from Proximal Tubules Attenuates Interstitial Fibrosis by Mitigating G2/M Arrest
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Background: Progressive tubulointerstitial fibrosis (TIF) is the final common pathway leading to end stage renal disease. Tubular epithelial cells (TECs) have a crucial role in the pathogenesis of TIF. Numb is a multifunctional protein involved in diverse cellular processes. However, little is known about the physiologic and pathologic role of Numb in kidney.

Methods: We examined the expression and distribution of Numb in normal adult male mouse kidney as well as in mouse model of renal fibrosis induced by unilateral ureteral obstruction (UUO). We previously showed that Numb’s role in renal fibrosis, we generated a conditional knockout mouse model in which Numb is selectively ablated from proximal tubules (PEPCK-Numb-KO). To confirm the role of Numb in regulating cell cycle, Numb was overexpressed in NUR77 cells by infecting with a Numb adenovirus (Ad-Numb) and endogenous Numb was knocked down by siRNA in HK-2 cells before aristolochic acid (AA) treatment. To examine the role of p53 in Numb-induced G2/M arrest, Ad-Numb infected HK-2 cells were incubated with pifithrin-α, a p53 inhibitor.

Results: Numb is expressed in renal tubules and glomeruli. The expression of Numb in renal tubules was significantly increased after UUO. After UUO, PEPCK-Numb-KO mice exhibited significantly attenuated TIF. Ectopic expression of Numb increased the fraction of cells in G2/M stage and upregulated the expression of TGF-β1 and CTGF in NUR77 cells. Knocking down endogenous Numb attenuated AA-induced G2/M arrest and profibrotic cytokines production. Furthermore, G2/M arrest and expression of profibrotic cytokines were significantly reduced in PEPCK-Numb-KO mice after UO. Inhibiting p53 activity dramatically mitigated Numb-induced G2/M arrest and profibrotic cytokines production.

Conclusions: In summary, our studies demonstrate that Numb has a profound effect on prone to G2/M arrest of TECs through stabilizing p53 protein. Depletion of Numb markedly attenuates G2/M arrest of proximal tubules which in turn reduces TIF. Collectively, these data indicate that targeting Numb might be a novel therapeutic approach for the treatment of fibrotic kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO280
Identification of a New Aldosterone Synthase Inhibitor with Anti-Fibrotic Activity in Animal Models

Background: The renin-angiotensin-aldosterone system (RAAS) plays a critical role in renal physiology. Inhibitors of ACE and ARBs are currently the mainstay in the treatment of management of chronic kidney disease (CKD). Despite initial success in reducing aldosterone, concentrations return to pretreatment levels in 30-40% of patients. This "aldosterone escape" significantly limits the therapeutic effectiveness. Through mineralocorticoid receptor dependent and independent processes, aldosterone is thought to directly accelerate renal damage by sustaining inflammation and fibrosis. An attractive approach to deal with aldosterone escape is to inhibit aldosterone synthase (AS), the enzyme responsible for aldosterone production (encoded by the CYP11B2 gene).

Methods: We have identified a promising series of potent and selective small molecule inhibitors of AS. Lead compound ANG3586 has 7 mM potency against AS and excellent selectivity against other P450 enzymes. It is orally bioavailable in rodents and appears to be well tolerated. ANG3586 was tested in the rat remnant kidney model (25 mg/kg, po, bid) and the mouse unilateral ureteral obstruction (UO/O) model (25 mg/kg, po, bid, ten days). In vivo, the rat remnant kidney model, animals with overt renal dysfunction were treated with vehicle or ANG3586. The elevated blood pressure in 5/6 nephrectomized animals was reduced to normal by compound treatment. ANG3586 also markedly reduced kidney collagen content and improved renal histology. Renal function, as determined by serum BUN and creatinine levels, urine albumin to creatinine ratio and urine NGAL, was found to be markedly improved. In the mouse UO model, ANG3586 reduced the increase in kidney weight, kidney collagen and alpha-smooth muscle actin staining. Since UO does not result in distinctly increased blood pressure, the anti-fibrotic activity appears independent of blood pressure lowering activity of ANG3586.

Conclusions: Taken together, ANG3586 shows promise as a potential novel anti- fibrotic agent.

Funding: NIDDK Support

FR-PO281
Tubulointerstitial Fibrosis Increases Peritubular Capillary Permeability and Induces Subsequent Hypoxia
Jun Zou, Jae Won Yang, Haiyun Yang, Agnes B. Fogo. Dept of Pathology, Microbiology, and Immunology, Vanderbilt Univ, Nashville, TN; Div of Nephrology, Xinhua Hospital, Shanghai, China.

Background: We previously showed that folic acid-induced tubulointerstitial injury significantly increased peritubular capillary permeability. In this study, we utilized kidney slices of different species to study the behavior of peritubular capillaries and oxygen supply changes contribute to this cross-talk of tubular to glomerular injury.

Methods: Co-luciferase mice, which have luciferase inserted in the collagen I promoter were mated with Numb mice, which have a phosphoglycerate dehydrogenase (GAPDH) promoter in podocytes, and develop glomerulosclerosis when immunotin is administered. Mice were treated with folic acid (FA, 240mg/kg BW, i.p.) or vehicle (VEH). At day 42, Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 419A

Funding: NIDDK Support.
mice were sacrificed to assess interstitial fibrosis, peritubular capillary number (CD31 staining) and renal fibrotic factors, which were subjected to unilateral ureteral obstruction (UUO). Renal pathological changes were assessed in tissue sections stained with Masson and Collagen I staining. Kidney tissues were removed. HK-2 cells were cultured in DMEM containing DL-Hcy. The expression of G9a and Collagen I were examined by Western blot and qPCR. Renal fibrosis and collagen type I mRNA transcription, showed higher density in folic acid vs. VEH 5.3±0.6 fold (P=0.05). Renal expression of nephrin influenced morphology, adhesion complex composition and ECM adhesion might ultimately inform therapeutic strategies to correct or repair glomerular barrier function.

Funding: Private Foundation Support

FR-PO284

Low-Density Lipoprotein Receptor-Related Protein 5 Drives Tubulointerstitial Fibrosis via Regulation of TGF-β Signaling

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Background: Low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of the canonical Wnt/beta-catenin pathway, was recently reported to drive idiopathic pulmonary fibrosis through activating beta-catenin. In this study, we examined the potential role of LRP5 in the regulation of TGF-β signaling in tubulointerstitial fibrosis.

Methods: LRP5-deficient (LRP5-/-) mice and age-matched wild-type (WT) mice were subjected to unilateral ureteral obstruction (UUO). Renal expression-fibrotic factors, including α-SMA, CTGF, collagens and fibronectin, was quantified by picro-sirus red staining, western blot analysis and immunostaining. Primary tubular epithelial cells (PTECs) were cultured from LRP5-/- and WT mice. Co-Immunoprecipitation was performed in a human proximal tubular epithelial cell line (HKC-8) over-expressing LRP5 and TGF-β receptors.

Results: LRP5-/- mice with UO showed ameliorated renal fibrosis and alleviated TGF-β signaling compared with WT mice with UO. However, activation of the Wnt/beta-catenin signaling was not different between LRP5-/- mice and WT mice, indicating that attenuated tubulointerstitial fibrosis in LRP5-/- mice was not due to mitigated activation of the fibrotic Wnt-beta-catenin pathway.

Conclusion: LRP5 promotes tubulointerstitial fibrosis via regulation of the TGF-β signaling. This activity is independent of its role in the Wnt/beta-catenin pathway.

Funding: Other NIH Support - GM104934

FR-PO285

Loss of Endothelial Nitric Oxide Augments Smad3 Linker Phosphorylation and Precedes Insulin Resistance in High-Fat Diet Induced Obesity

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Background: Deficiency of endothelial nitric oxide synthase (NOS3/enOS) confers susceptibility to diet-induced obesity and its complications. eNOS-derived nitric oxide (NO) acts as a potent vasodilator, enhances insulin sensitivity and also inhibits inflammation. TGF-βSmad signaling plays an important role in regulating glucose and energy homeostasis. Smad3 deficient mice are protected from diet-induced obesity and obesity-related kidney injury. This study investigated whether the loss of endothelial-derived NO promotes Smad3 activation, which precedes insulin resistance in high-fat diet (HFD) induced obesity.

Methods: C57BL/6J wild type, eNOS deficient (eNOS-/-) with C57BL/6J background mice were given HFD or normal diet (ND) treatment for 1, 5, 7 days and 4, 8 or 16 weeks. Results: Within 7 days of HFD treatment in WT mice, Western blotting showed a marked decrease in total eNOS level and its complications. eNOS-derived nitric oxide (NO) acts as a potent vasodilator, enhances insulin sensitivity and also inhibits inflammation. TGF-βSmad signaling plays an important role in regulating glucose and energy homeostasis. Smad3 deficient mice are protected from diet-induced obesity and obesity-related kidney injury. This study investigated whether the loss of endothelial-derived NO promotes Smad3 activation, which precedes insulin resistance in high-fat diet (HFD) induced obesity.

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FR-PO286
HIF1α and HIF2α Both Mediate Glomerulosclerosis but Differentially Regulate the COL1A2 Promoter

Funding: Other NIH Support - National Natural Science Funds of China (Grant No.81100515)

FR-PO287
MiR302a-3p Modulates Renal Epithelial-Mesenchymal Transition in DKD by Targeting ZEB1

Funding: Other NIH Support - National Natural Science Funds of China (Grant No.81100515)

FR-PO288
Kruppel-Like Factor 15 Works as an Early Anti-Fibrotic Transcriptional Regulator in Angiotensin II-Induced Renal Fibrosis via Down-Regulation of Connective Tissue Growth Factor

Funding: Other NIH Support - National Natural Science Funds of China (Grant No.81100515)

FR-PO290
Hyaluronidase-2 Dependent Regulation of CD44 Variant Expression in Anti-fibrotic versus Pro-Fibrotic Cells

Funding: Other NIH Support - National Natural Science Funds of China (Grant No.81100515)
Methods: Fibroblasts & renal epithelial cells were incubated with TGFβ1 to induce myofibroblast differentiation. In comparison to cells incubated with TGFβ1 alone, Vpr induction led to increased extracellular matrix production and reduced collagen deposition. This effect was mediated by inhibition of AMPKα1 in pericytes/myofibroblasts.

Results: In vitro experiments demonstrated that the presence of doxycycline inhibited Vpr induction. In Vpr mice compared with control mice, renal cortex FGF2 content was significantly reduced compared to untreated Vpr mice. In vivo experiments confirmed that administration of FGF2 antagonist decreased albuminuria in Vpr mice at day 21 (0.47 ± 0.9) versus 2.3 ± 0.6). In contrast, FGF2 treatment in glomeruli, biotinylated FGF2 was administered intravenously and detected with fluorescent streptavidin. Vpr mice and control mice received FGF2 (5 mg/animal/weekly for 4 weeks) or FGF antagonist (PD173074, 50 mg/animal/bi-weekly for 4 weeks).

Conclusions: FGF2 plays a crucial role in inflammatory and fibrotic conditions. Our findings suggest that inhibition of the FGF2 signal pathway in pericytes/myofibroblasts leads to inhibition of Wnt activation and reduced renal fibrosis.

Funding: NIDDK Support, Veterans Administration Support

FR-PO292

Role of AMP-Activated Protein Kinase Signaling in Fibroblast Activation and Renal Fibrosis

Yuyan Wang, Yanlin Wang. Medicine, Baylor College of Medicine, Houston, TX.

Background: Renal fibrosis is a common manifestation of chronic kidney disease resulting in progressive loss of kidney function. Although activated fibroblasts are responsible for the production and deposition of the extracellular matrix, the molecular mechanisms underlying fibroblast activation are not fully understood. In this study, we examined the functional role of AMP-activated protein kinase a1 (AMPKα1) in the activation of fibroblasts and the development of renal fibrosis.

Methods: We investigated the role of AMPKα1 in fibroblasts and renal epithelial cells by examining AMPKα1 expression and activity.

Results: We found that AMPKα1 expression and activity were significantly increased in fibroblasts and renal epithelial cells treated with TGF-β1. Inhibitors of AMPKα1 significantly reduced collagen deposition and suppressed extracellular matrix production, suggesting a potential role for AMPKα1 in the modulation of renal fibrosis.

Conclusions: Our findings suggest that targeting AMPKα1 signaling may be a potential therapeutic strategy for the prevention and treatment of renal fibrosis.

Funding: NIDDK Support

FR-PO293

Increased Expression of Complement C1 from Pericyte/Mycoblasts Contributes to Renal Fibrosis Via Activation of Wnt/β Catenin Signaling

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Background: Pericytes/fibroblasts are progenitors of scar-forming cells known as myofibroblasts. We have characterized the inflammatory nature of pericytes/fibroblasts isolated from UUO mice. We have also shown that Wnt/β-catenin signaling is activated during kidney fibrosis. Role of complement C1 on pericyte function or in Wnt activation remains unknown.

Methods: We used the unilateral ureteral obstruction (UUO) and folic acid nephropathy models. Pericytes were isolated using magnetic beads containing anti-PDGFR receptor. Ab expression of C1 complex was examined by western blotting, immunofluorescence, and real-time PCR in tissue and in cell lysates and supernatants obtained from pericytes cultured from sham, day 3 and day 10 UUO mice kidneys. Topflash reporter assays were used to study Wnt signaling.

Results: Expression of C1q chains a,b,c as well as subunits Clr and C1r were increased during fibrosis along with increased expression of TGF-β, n-SMA and Wnt target genes wisp1 and 2. Immunostain showed C1q localization in the mesangial compartment of UUO but not in sham mice consistent with PCR and western blot data. In cultured pericytes, C1 complex component C1q protein was increased in culture supernatants of Day 3 and Day 10 but not in shams. Expression of C1q proteins was absent in supernatants of UUO pericytes isolated from C1qKO mice. Topflash reporter assays for Wnt signaling showed that pericytes from UUO kidneys had pronounced activation of the reporter following Wnt3a treatment as compared to shams, and this effect was blunted in pericytes isolated from C1qKO mice.

Conclusions: We demonstrate both in vivo and in vitro that increased expression of the C1 complex occurs in response to kidney injury along with activation of Wnt signaling. In vivo/in vitro data, showing that inhibition of C1 complex using C1INH prevented renal fibrosis, we conclude that its inhibition in pericytes/fibroblasts leads to inhibition of Wnt activation and reduced renal fibrosis.

Funding: NIDDK Support, Veterans Administration Support

FR-PO294

The Role and Association of Inflammatory and Apoptotic Caspases in Tubulointerstitial Fibrosis

Chun Zhang, You Ke, Hua Su. Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

Background: Caspases are a family of cysteine proteases with pivotal functions in apoptotic and inflammatory signaling. According to their difference of structures and functions, 14 mammalian Caspases are classified into three categories, which are apoptosis activator, apoptosis executor and inflammatory mediator. Caspase-1 is an inflammatory caspase, and Caspase-7 belongs to apoptosis executor. The roles and association of these two distinct types of Caspases in tubulointerstitial fibrosis (TIF) are not well understood.

Methods: Unilateral Ureteral Obstruction (UUO) animal model was constructed on wild-type(WT) and caspase-1 knockout (KO) mice. In vitro study, the cultured tubular epithelial cell line NRK-52E (TECs) were employed and the expression of caspase-1 and caspase-7 was modulated by transfection of Lentiviral expression vector.

Results: In current study, we found both Caspase-1 and Caspase-7 protein levels were elevated in UUO WT mice. While in UUO mice with Caspase-1 KO background the increased Caspase-7 was suppressed significantly along with the minimized extracellular matrix accumulation which was demonstrated by western blot, immunohistochemistry and Masson trichrome staining. In vitro TGF-β1 stimulation promoted the expression of Caspase-1 and Caspase-7 simultaneously in TECs. Notably, genetic deletion of either Caspase-1 or Caspase-7 could abrogate TGF-β1 driven TECs' transdifferentiation and apoptosis. In addition, knocking down Caspase-1 impaired Caspase-7 upregulation in TGF-β1 treated TECs which was consistent with in vivo study. However genetic deletion of Caspase-7 did not influence Caspase-1's abundance.

Conclusions: Our observation firstly links inflammatory and apoptotic Caspases together in TIF and further elucidates Caspase-1 activation is an upstream event of apoptotic Caspase-7 induction during TIF and TECs' transdifferentiation and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO295

MAD2B-Sno-Smad3 Signaling Pathway Is Implicated in Fibroblast Activation and Tubulointerstitial Fibrosis

Chun Zhang, Hui Tang, Hua Su. Nephrology, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.

Background: Mitotic arrest deficient protein MAD2B, an anaphase-promoting complex (APC)/cyclosome inhibitor, is indispensable for mitotic checkpoint control. Previously we found MAD2B was expressed in glomerular and tubulointerstitial compartment. In addition our data indicated MAD2B was involved in podocyte injury triggered by high glucose. But its role in renal fibrosis remains elusive.

Methods: The object of this study included patients with renal tubulointerstitial fibrosis (TIF) (secondary glomerulonephritis and interstitial nephritis were excluded), Unilateral Ureteral Obstruction(UUO) mice and in vitro cultured tubular epithelial cell line (NRK-52E) and renal fibroblast cell line (NRK-49F). In vivo gene silencing of MAD2B was carried out using Lentiviral gene delivery.

Results: 1. The results of our study indicated patients with renal tubulointerstitial fibrosis (TIF) (secondary glomerulonephritis and interstitial nephritis were excluded), Unilateral Ureteral Obstruction(UUO) mice and in vitro cultured tubular epithelial cell line (NRK-52E) and renal fibroblast cell line (NRK-49F). In vivo gene silencing of MAD2B was carried out using Lentiviral gene delivery.

Conclusions: Our observation firstly links inflammatory and apoptotic Caspases together in TIF and further elucidates Caspase-1 activation is an upstream event of apoptotic Caspase-7 induction during TIF and TECs' transdifferentiation and apoptosis.

Funding: Government Support - Non-U.S.
Results: By immunohistochemistry and western blot, it showed the expression of Markers of cell differentiation in TIF patients, which allowed us to identify the types of cells contributing to the elevated MAD2B abundance. It is well known that TECs and fibroblast are the main culprits in TIF. Our data suggested that TGF-β1 exposure to the level of MAD2B in NRK-52E was not altered, whereas in NRK-49F MAD2B was upregulated in a time- and dose-dependent manner. Furthermore TGF-β1 induced fibroblast activation can be abrogated by MAD2B genetic deletion. Intriguingly, Snod, a repressor of Smad3, was decreased in NRK-49F cells treated with TGF-β1 which could be alleviated by MAD2B knocking down. Consistently, in UUO mice the expression of Snod was significantly increased in the renal cortex accompanying with enhanced activation of Smad3 and locally genetic deletion of MAD2B by Lenti viral transfection preserved Snod’s abundance and consequently suppressed Smad3 signaling which finally dampened the fibroblast activation and ECM accumulation in UUO mice.

Conclusions: Our observation proposes that MAD2B participates in fibroblast activation and tubulointerstitial fibrosis by repressing Snod and subsequently activating Smad3 signaling pathway. Regulation of MAD2B-Snod pathway may be a promising strategy for tubulointerstitial fibrosis. However, the regulatory mechanisms between MAD2B and Snod and still need further investigation.

Funding: Government Support - Non-U.S.

FR-P0298

FHL2 Promotes Tubular Epithelial-to-Mesenchymal Transition by Regulating β-Catenin Activity Ting Cai, Danqin Sun, Chunshan Dai, Junwei Yang, Weichun He. Center for Kidney Disease, 2nd Affiliated Hospital of Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Fibrotic kidneys exhibit aberrant activation of β-catenin signaling, one of the main pathways that play a critical role in mediating tubular epithelial-to-mesenchymal transition (EMT). FHL2 (four-and-a-half-LIM-IM only protein 2), an adapter protein, is an endogenous regulator of β-catenin activity.

Methods: To determine whether FHL2 is also involved in the EMT process, we investigated its regulation and function during TGF-β1-stimulated EMT.

Results: TGF-β1-induced FHL2 mRNA and protein expression in rat proximal tubular epithelial cells (NRK-52E) in a time- and dose-dependent manner was significantly dependent on intracellular Smad signaling. Overexpression of FHL2 suppressed E-cadherin, increased α-smooth muscle actin (α-SMA), vimentin and fibronectin expression, whereas knockdown of FHL2 via small interfering RNA partially reduced TGF-β1-mediated α-SMA, vimentin and fibronectin expression, and restored E-cadherin. TGF-β1-induced FHL2 physically interacts with β-catenin in the nuclei in NRK-52E cells. Ectopic expression of FHL2 promoted β-catenin nuclear translocation, induced β-catenin-mediated gene transcription, and upregulated the expression of β-catenin target genes such as plasminogen activator inhibitor-1 (PAI-1) and Twist. Conversely, downregulation of FHL2 expression reduced β-catenin nuclear translocation, abolished β-catenin-mediated gene transcription, and inhibited PAI-1 and Twist expression in the basal and TGF-β1-stimulated conditions. In a mouse model of obstructive nephropathy, FHL2 expression increased in a time-dependent manner, suggesting that it may play a role in tubular EMT and renal fibrosis in vivo.

Conclusions: We speculate that, through manipulating β-catenin activity, FHL2 may be a potential future therapeutic target to prevent progression of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-P0299

Cell Extract Ameliorates Fibrosis Kei Matsumoto,1 Sandhya Xavier,1 Jun Chen,1 Yujiro Kida,1 Brian B. Ratliff,1 Stefan Rose1,2 Michael S. Goligorsky. 1 New York Medical College; 2Showa Univ, Tokyo, Japan.

Background: Accumulation of myofibroblasts is a hallmark of renal fibrosis. These studies suggest that PBI-4050 significantly inhibits the development of renal fibrosis in homozygous HB-EGF mice through multiple mechanisms, including through anti-inflammatory influences.

Funding: NIDDK Support, Pharmaceutical Company Support - ProMetic Biosciences

FR-P0300

FR-P0927

PBI-4050 Inhibits the Development of Renal Fibrosis in a Model of Tubulointerstitial Fibrosis Ming-Zhi Zhang,1 Lyne Gagnon,2 Raymond C. Harris.1 1Medicine, Vanderbilt Univ, Nashville, TN; 2ProMetic Biosciences, Laval, QC, Canada.

Background: Kidney fibrosis occurs in chronic kidney diseases and leads to gradual loss of kidney function. Although the etiology of kidney fibrosis is multifactorial, there is increasing evidence linking chronic inflammation to kidney fibrosis. PBI-4050, a novel first-in-class orally active low molecular weight compound currently in phase II clinical trials, has anti-fibrotic and anti-inflammatory properties in different models.

Results: In vivo, we used α-SMA-GFP mice to visualize fibroblast-to-myofibroblast transition (EMT). PBI-4050 (200 mg/kg/day) by daily gastric gavage from 4 to 14 weeks of age. Immunohistochemical analysis showed that in untreated homozygous HB-EGF mice, α-SMA expression levels of the pro-fibrotic and fibrotic components including CTGF and TGF-β, α-SMA (a marker of myofibroblasts), fibronectin, collagen I and IV were increased in Sirt1 mutant kidneys compared to control kidneys, suggesting that pericyte detachment and subsequent pericyte-myofibroblast transition are augmented in Sirt1 mutant kidneys, resulting in excessive fibrosis.

Conclusions: Functional depletion of Sirt1 in endothelial cells aggravates capillary rarefaction and tissue fibrosis following kidney injury. Consistent with this finding, detachment of PDGFβR+ pericytes was increased in Sirt1 mutant kidneys compared to control kidneys, suggesting that pericyte detachment and subsequent pericyte-myofibroblast transition is augmented in Sirt1 mutant kidneys, resulting in excessive fibrosis.

Funding: NIDDK Support

FR-P0296

Losartan Reduces Renal Fibrogenesis by Up-Regulating Klotho in Uremic Rats Edgar Maciquzquez,1 Josse Carla Paterno,2 Gabriel H. Polokony,1 Mariana S. Perez,3 Nestor Schor, Mirian A. Boim.

1Nephrology, UNIFESP; 2Sao Paulo, Brazil.

Background: Klotho is a transmembrane protein expressed mainly in the kidney. Soluble Klotho (sKlotho) is an anti-aging hormone factor with diverse functions through mechanisms involving Wnt and TGFβ1 signaling. Renal fibrosis is the end stage of the progressive chronic kidney disease (CKD) and renal klotho is markedly decreased in CKD patients. Renin angiotensin system (RAS) blockade is a relevant therapy to reduce CKD progression and the beneficial effects go further to the anti-inflammatory effect. The aim of this study was to investigate a possible link between RAS and Klotho by evaluating the effects of losartan on Klotho/Wnt signaling in 5/6 nephrectomy model of CKD in rats.

Methods: Adult male Wistar rats were underwent 5/6 nephrectomy (Nx). The Nx animals were separated into three groups: control, with no treatment (Nx), treated with losartan (LOS; 25 mg/kg/day, p.o.) or propranolol (PROP; 25mg/kg/day, p.o.). Results were compared with SHAM group. Blood pressure was measured by tail-cuff plethysmography. After 8 weeks, animals were sacrificed and the remnant kidney was removed to determine the renal expression of collagen, fibronectin, epithelial-to-mesenchymal transition (EMT) markers (FPSP1 and a-SMA) and Klotho signaling (Klotho, Wnt5 and GSK3β) by real time PCR.

Results: Nx rats presented hypertension that was blunted by both losartan and propranolol. The expression levels of collagen and fibronectin were increased in Nx group, which was reverted only in LOS group. The presence of the EMT markers, FPSP1 and a-SMA , was observed in Nx group which was decreased with losartan treatment. Klotho was reduced in Nx animals and LOS but not propranolol significantly increased klotho expression. Nx animals showed upregulation of GSK3β, Wnt 7a and Wnt 3. LOS treatment prevented the decrease in Wnt 7a and GSK3β but not Wnt 3.

Conclusions: These data suggest that the beneficial effect of losartan on renal fibrosis is independent of blood pressure reduction and may be, at least in part, due to upregulation of klotho. In conclusion, losartan induced no change in klotho expression. The interaction between the RAS and Klotho could inactivate the Wnt pathway.

Funding: Government Support - Non-U.S.
In vitro treatment of TGF-β1-activated fibroblasts with EPC extract prevented reversion of fibroblastic phenotype but did not reverse expression of endothelial markers. In two distinct models of renal fibrosis, unilateral ureteral obstruction (UUO) and chronic phase of folic acid-induced nephropathy (FAN), subcapsular injection of EPC extract to the kidney prevented and reversed accumulation of α-SMA-positive myofibroblasts and reduced collagen deposition. The expression of ECM marker for cytokine-induced myofibroblasts was reduced in EPC treated rats. Interestingly, TGF-β1 was mediated via a 130-kDa MT1-MMP pathway resulting in induction of pluripotency transcription factors KLF4, C-Myc, OCT4, and Nanog in association with the open chromatin confirmation.

Conclusions: EPC extract does not reverse endothelial-mesenchymal transition, but it prevents and reverses fibroblast-to-myofibroblast transition and renal fibrosis. The component of EPC extract, LIF, is capable of preventing development of the contractile phenotype of activated fibroblasts, but does not eliminate TGF-β1-induced collagen synthesis in cultured fibroblasts and models of renal fibrosis. LIF component of EPC extract is a participant of its antifibrotic effect, but not the sole one, as other yet undiscovered factors contribute to the antifibrotic effect of the extract.

Funding: NIDDK Support

FR-P0301
Mitochondrial Metabolic Switch to Glycolysis in Proximal Tubular Epithelial Cell in Fibrotic Kidneys
Lei Jiang, Jianwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ; Nanjing, Jiangsu, China.

Background: Renal proximal tubule is susceptible to hypoxic injury since its reliance on aerobic oxidative metabolism. Mitochondrial dysfunction contributes to progression of chronic renal disease. However, the profile of the energy metabolism of renal tubule in progression of fibrosis is uncertain, and the relationship between the change of energy metabolism and tubular epithelial cell damage is unclear.

Methods: Gene expression profiles related to energy metabolism of the proximal tubule in fibrotic kidneys were analyzed. 2-Dexoyglucos (2-DG) was given to CD-1 mice under UUO intraperitoneally. Primary tubular epithelial cells (PTC) cultured from normal CD-1 mice renal cortex was used. 2-DG (inhibitor of glycolysis), bromopyruvic acid (inhibitor of hexokinase), dichloroacetate (inhibitor of glycolysis), oligomycin (inhibitor of oxidative phosphorylation), etomoxir (inhibitor of fatty acid oxidation), DOH (inhibitor of gluconeogenesis, w), PAK RNAi or HIF-1α siRNA was used in PTC with or without TGF-β1 stimulation. The oxygen consumption rate (OCR) and extracellular acidification rate (ECR) were detected by Seahorse Metabolic Analyzer.

Results: I. Glycolysis was upregulated in the proximal tubule in fibrotic kidney. 2. Genes related to glycolysis were upregulated, however, genes related to oxidative phosphorylation, fatty acid metabolism and glutamine metabolism were downregulated. The key limiting-rate enzymes for glycolysis were upregulated in the fibrotic kidney. 3. 2-DG could block the renal fibrosis under UUO. 4. OCR was decreased under TGF-β1 stimulation in PTC, however, ECAR was increased after TGF-β1 stimulation. 5. Inhibiting oxidative phosphorylation, fatty acid oxidation or glutamine metabolism could increase the lactate production in PTC. Lactate could directly induce PTC damage. 6. Inhibiting glycolysis could ameliorate the damage of PTC under TGF-β1 incubation.

Conclusions: The mitochondrial metabolism including oxidative phosphorylation, fatty acid oxidation and glutamine metabolism is defective in proximal tubular epithelial cell in fibrotic kidney. The metabolism is switch to glycolysis, and the glycolytic pathway further aggravates the injury.

Funding: Government Support - Non-U.S.

FR-P0302
The Effects of CCN3/NOV on the Formation of Extracellular Matrix in Human Mesangial Cells
Haifei Liu, Long Chen, Hong Liu, Bi-Cheng Liu. Dept of Nephrology, Zhong Da Hospital, Southeast Univ; Nanjing, Jiangsu, China.

Background: Glomerulosclerosis is characterized by mesangial cells proliferation and accumulation of extracellular matrix (ECM) in glomeruli. ECM accumulation is a variety of damage factors, leading to ECM deposition. ECM accumulation is the net result of the balance between synthesis and degradation. CCN3, a matricellular protein of the CYR61-Ctgf-NOV (CCN) family, associates specifically with ECM. A recent study found that treatment with the matricellular protein CCN3 can block and/or reverse fibrosis development in obesity with diabetic nephropathy. However, whether CCN3 can alleviate the formation of glomerulosclerosis by inhibiting the production of ECM and/or promoting the degradation of ECM is still unknown. This study aims to explore the potential role of CCN3 in ECM accumulation of mesangial cells induced by TGF-β1.

Methods: Human mesangial cells lines were stimulated with TGF-β1 (2ng/ml) and CCN3 for different concentration (5 to 500 ng/ml) after 24 hours of serum starvation. The expressions of fibronectin (FN), type I collagen (COLI), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) were identified by Western blot analysis. In vivo study: Urinary unilateral obstruction model was induced in adult male B6 mice (6 months, 20–25 g). Mice with UUO were given with intra-peritoneal Syk inhibitor (20 and 40 mg/kg, bid) or saline daily, one day prior the uro surgery. Both obstructed and contralateral kidneys were harvested 7 days after surgery. Kidney tissues were prepared for further pathological and molecular biological analysis.

Results: Our results demonstrated that the inhibition of Syk in NRK49F cells inhibited the stimulation effect of TGF-β1 leading to fibroblast to fibroblast transition, but it prevents and reverses fibroblast-to-myofibroblast activation and also reduces the tubulointerstitial fibrosis in UUO mice. The mechanism may be related to anti-inflammatory effects and down-regulate MAPK-p38 pathway.

Conclusions: In conclusion, we demonstrated that Syk inhibitor ameliorates TGF-β1 induced kidney myofibroblast activation and also reduces the tubulointerstitial fibrosis in UUO mice. Both obstructed and contralateral kidneys were harvested 7 days after surgery. Kidney tissues were prepared for further pathological and molecular biological analysis.

Funding: Government Support - Non-U.S.

FR-P0304
Optimization of Identification of the Glomerular Extracellular Matrix Proteome
Liliang Hobeika, Michelle T. Barati, Jon B. Klein, Kenneth R. McLiech, Michael Merchant. Medicine, Univ of Louisville; Dept of Veterans Affairs, Louisville, KY.

Background: Increased glomerular extracellular matrix (ECM) is present in many glomerular disorders, eg, diabetic nephropathy and FSGS. Defining the ECM proteome by mass spectrometry (MS) offers the opportunity to determine the mechanism for increased ECM and identify disease specific markers. The optimal conditions for ECM isolation and MS analysis have not been determined. This study compared three extraction techniques in glomeruli isolated by laser capture microdissection (LCMD) from two types of tissue preparation.

Methods: Frozen (FR) and formalin-fixed paraffin embedded (FFPE) tissue from the same human kidney were cut into 10mm sections, stained with hematoxylin, glomeruli in glomeruli isolated by laser capture microdissection (LCMD) from two types of tissue preparation.

Results: The total protein yield and number of proteins identified were determined in various conditions of ECM (ECM) isolation of glomeruli. The ECM isolated by LCMD was enriched in LIF and VEGF. Only LIF was capable of reducing fibroblast-to-myofibroblast transition and renal fibrosis. Screening the composition of EPC extract for cytokines revealed that it is associated with down-regulation of MAPK-p38 pathways.

Conclusions: In conclusion, we demonstrated that Syk inhibitor ameliorates TGF-β1 induced kidney myofibroblast activation and also reduces the tubulointerstitial fibrosis in UUO mice. The mechanisms may be related to anti-inflammatory effects and down-regulate MAPK-p38 pathway.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO305

BMP-7 Inhibits Renal Akt Signaling
Debra F. Higgins, Catherine Godson. School of Medicine, Conway Inst, Univ College Dublin, Dublin, Ireland.

Background: Bone morphogenetic protein-7 (BMP-7), a member of the TGFβ superfamily, counteracts pro-fibrotic TGFβ, and protects from fibrosis in acute and chronic renal injury models.

Methods: Using the chronic fibrosis model, unilateral ureteral obstruction (UUO), we investigated exogenous-rhBMP-7 on signaling pathways involved in hypoxia and TGFβ-induced fibrosis. Mice undergoing UUO were treated with either vehicle or rhBMP-7 (300ng/kg.i.p.), kidneys were harvested on day 8 post-obstruction and analysed for markers of renal fibrosis and activation of SMAD, MAPK, and PI3K signaling. Results: rhBMP-7 response to UUO, SMAD1/5/8 activity was lost in vehicle-treated kidneys yet maintained in BMP-7-treated kidneys. Collagen accumulation was significantly increased in obstructed kidneys of vehicle-treated animals compared with contralateral and this response was not observed in BMP-7-treated obstructed kidneys. Immunohistochemical analysis of type I, III, and IV collagen revealed that accumulation of type I collagen was significantly impaired in BMP-7-treated obstructed kidneys. Activation of SMAD2, SMAD3, ERK, p38 and Akt signaling pathways occurred during fibrogenesis and BMP-7 significantly attenuated SMAD3 and Akt signaling in vivo. In the kidney, inner medullary collecting duct and tubular epithelial cells are responsive to BMP-7. Analysis in mouse inner medullary collecting duct (mIMCD) and human tubular epithelial (HK-2) cells stimulated with either TGFβ, hypoxia (1% oxygen) to induce Akt activation provided further evidence that BMP-7 could specifically inhibit PI3K / Akt signaling.

Conclusions: These data demonstrate an important mechanism by which BMP-7 orchestrates renal protection through Akt inhibition and strengthens the argument for use of Akt inhibitors as anti-fibrotic therapeutics.

Funding: Pharmaceutical Company Support - Hoffmann La Roche, Government Support - Non-U.S.

FR-PO306

Prevention of Renal Interstitial Fibrosis by Simultaneous Deletion of Bax and Bak
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Background: Proximal tubular injury and apoptosis are key mediators of development of kidney fibrosis, a hallmark of chronic kidney disease. However, the molecular mechanism by which tubular apoptotic cell death leads to kidney fibrosis is poorly understood.

Methods: Here we tested the roles of Bax and Bak, two crucial proteins involved in intrinsic apoptotic cell death, in progression of kidney fibrosis. Mice with proximal tubular deletion of Bax or Bak and double deletion of Bax and Bak were subjected to unilateral ureteral obstruction (UUO).

Results: Dual deficiency of Bax and Bak inhibited tubular apoptosis and atrophy. Consistent with decreased tubular injury, dual ablation of Bax and Bak suppressed UUO-induced inflammation and kidney fibrosis with decreased tubular cell cycle arrest, expression of fibrogenic and inflammatory cytokines, and oxidative stress in the kidney. Bax or Bak deficiency was insufficient to prevent apoptosis and all other aforementioned malevolent effects, suggesting compensatory mediation by each in the respective signaling pathways.

Conclusions: These data suggest that dual ablation of Bax and Bak in the kidney is required to prevent UUO-induced tubular apoptosis and the consequent kidney inflammation and fibrosis.

Funding: NIDDK Support

FR-PO307

Investigating the Role of Cilia in Regulating Fibrosis in the Kidney and Liver Using PKD Mouse Models

Background: Cystic kidney disorders are frequently caused by mutations in cilia associated proteins (intratubular lagular transport, IFT) or ciliary signaling proteins (polycystin-1 or polycystin-2). Comorbidities commonly associated with renal cysts include biliary abnormalities with associated fibrosis in both tissues. In the kidney of cilia mutants, ischemia-reperfusion (IR) injury greatly exacerbates the rate of cyst development; however, it is not known whether IR injury will similarly affect the liver and how loss of cilia affects injury induced fibrosis.

Methods: To address these questions, we are utilizing Oak Ridge Polycystic Kidney (ORPK) mice that have a congenital hypomorphic IFT88 mutation and conditional mutant mice where cilia are disrupted in the kidney (CaggCreER). The conditional mutant mice used in IR injury studies were injected with rhadenosine-rhBMP-7 on proliferation and inflammation responses and production of extracellular matrix (ECM) and pro-fibrotic factors.

Results: Our preliminary studies in the kidney indicate that IFT88 mutant mice receiving IR injury have increased ECM transcription (Col Iα2, Col IIIα1, and fibronectin) compared to the sham operated kidney. Despite the increased ECM production, the pro-fibrotic growth factor TGF-β, which is frequently associated with fibrosis, was not significantly elevated in mutant mice. However, another TGF-β family member, inhibin βA, was increased in the injured kidney of mutant mice suggesting a possible mechanism for ECM production. ORPK mice have a noticeable liver phenotype characterized by biliary hyperplasia and, similar to the kidney, an increase in Col Iα4 and Col IIIα2 transcripts. ORPK mutant mice also have increased transcript levels of the microcotranscript protein, MCP1, and the pro-inflammatory cytokine, IL-1β.

Conclusions: Together, our preliminary data suggest that defects in cilia formation promote fibrotic disease progression possibly through altered cytokine production and enhanced recruitment of infiltrating monocytes.

Funding: NIDDK Support, Other NIH Support - MERIT fellow grant number: 2K12GM08810-06 to Kurt Zimmerman

FR-PO308

Klotho Suppresses Epithelial-Mesenchymal Transition (or Transformation in Adriamycin Nephropathy
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Background: Klotho interacts with various proteins to alter their function. Klotho may bind to the receptor for WNT and TGFbeta, inhibiting their signals.

Methods: Experiments were performed to assess how klotho protects kidney from its injury. Adriamycin (5 mg/kg) was injected into rats to induce nephropathy. Human reconstituent klotho (K, 50 micro-g/kg/day), 4-benzyl-2-methyl-1,2,4-thiadiazole-3,5-dione (GSK3beta blocker, 0.2mg/kg/day) and vehicle (V) was administered. Rats which were untreated with Adriamycin were used as control (U). Animals were killed 8 weeks later. Renal expressions of Wnt1, GSK3beta, Tbeta1, and collagen I were assessed by RT-PCR against GAPDH. Western blot was used for p-GSK3beta and beta-actin.

Results: Adriamycin increased albuminuria, renal expression of Wnt1, p-GSK3beta, TGF and collagen I in comparison to the control. Klotho and T beta suppressed increased albuminuria and the phosphorylated GSK3beta in the kidneys, with decreased elevations of Wnt1, supporting that klotho inhibits Wnt signaling without changes in Wnt level. While klotho and T reduced TGFbeta, klotho preferentially ameliorated collagen I in comparison to T.

Funding: Government Support - Non-U.S.

FR-PO309

The Molecular Mechanism of miR-382 in the Pathogenesis of Renal Tubulointerstitial Fibrosis
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Background: To investigate the roles of microRNA-382 (miR-382) in the pathogenesis of renal tubulointerstitial fibrosis.

Methods: Human kidney epithelial (HK2) cells that transfected with a miR-382 inhibitor (antagomir-382) was used to examine the effect of miR-382 abundance on cell polarity, as well as to test the complementary relationship between miR-382 and its predicted target gene, heat shock 60kDa protein 1(HSPD1), which was further verified by site-directed mutagenesis. We also examined the in vivo role of miR-382 in the development of renal interstitial fibrosis, in a mouse unilateral ureteral obstruction (UUO) model. Locked nucleic acids (LNA) and anti-miR-382 was intravenously delivered via tail vein less than 30minutes prior to UUO, and repeated the dosage 24 hours after the surgery. For clinical verification, renal biopsy specimens from 12 IgA nephropathy (IgAN) patients were collected, 6 with moderate to severe tubulointerstitial fibrosis (TIF) and 6 with no TIF. The relative abundance of miR-382 and HSPD1 protein was analyzed using in situ hybridization and immunohistochemistry.

Results: HSPOD1 was confirmed to be a new, direct target gene of miR-382 by in vitro transfect technique and mutation experiments. The development of epithelial transformation or renal interstitial fibrosis was accompanied with up-regulated abundance of miR-382. Down-regulation of miR-382 was associated with significant reductions of interstitial fibrosis, but increase protein expression of HSPD1 and thioeodizin, both in the obstructed mouse kidneys and renal biopsy specimen from IgAN patients.

Conclusions: MiR-382, a profibrotic microRNA, is up-regulated with the development of renal interstitial fibrosis. The down-regulation of miR-382 and HSPD1 protein was used analyzing in situ hybridization and immunohistochemistry.

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Conclusions: MiR-382, a profibrotic microRNA, is up-regulated with the development of renal interstitial fibrosis. The down-regulation of miR-382 and HSPD1 protein was used analyzing in situ hybridization and immunohistochemistry.

Funding: Government Support - Non-U.S.

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Underline represents presenting author.

425A
FR-P0310
Assessing the Role of Gremlin-1 on Renal Fibrosis In Vitro Marcela Herrera, Liuhan Liang, Asha Seth, Carol Patricia Moreno Quinn. Cardiovascular & Metabolic Diseases, Medimmune, Cambridge, United Kingdom.

Background: Bone Morphogenic Proteins (BMPs) signal through SMAD-1/5/7 to upregulate genes that antagonize fibrosis. The endogenous antagonist gremlin-1 binds to BMPs and antagonizes extracellular BMPs, inhibiting their anti-fibrotic effects. Gremlin-1 is upregulated in the proximal tubular (PT) of DN patients. We hypothesized that Gremlin-1 participates in the development of renal fibrosis by inducing a pro-fibrotic phenotype in proximal tubules and renal interstitial fibroblasts.

Methods: To test this hypothesis we used HK-2 (human PT cell line) and NRK49F (rat renal fibroblasts) cells where the pro-fibrotic phenotype was induced by Transforming Growth Factor b1 (TGFb1: 2.5 ng/mL, 72 hrs). Gremlin-1 secretion and protein expression was measured by Western blotting and gene expression by qPCR.

Results: In PT cells, TGFb stimulated gremlin-1 protein secretion by 2.3 fold (from 57 ± 3 to 134 ± 8 ng/mL) and mRNA expression of (Gremlin-1: p = 0.05), increased expression of fibronectin (FN, an extracellular matrix component) by 50% (p < 0.05) and reduced expression of c-aldh (c-CAD, an epithelial marker) by 95% (p = 0.05). All changes also occurred at the mRNA level. Gremlin-1 sRNA significantly reduced gremlin-1 mRNA expression and efficiently blocked the TGFb-induced Gremlin-1 release by 100%. However, Gremlin-1 knockdown did not prevent the pro-fibrotic changes of TGFb. In contrast to PT cells, TGFb did not induce gremlin-1 secretion in renal fibroblasts. TGFb increased FN and a-smooth muscle actin (aSMA, marker of fibroblast activation) in a dose-dependent manner. Addition of gremlin-1 (mimicking the in vivo setting) did not exacerbate fibrosis at any dose of TGFb. Addition of recombinant BMP2 was not sufficient to prevent TGFb-induced fibrosis in either cell type. Recombinant BMP2 alone (1 nM) increased SMAD5 phosphorylation and the expression of ID1 (a marker of BMP signalling) at 1 and 24 hrs post treatment. The stimulatory effect of BMP2 was blocked by pre-treatment with recombinant Gremlin-1 (2 mM). These data confirm intact BMP2/gremlin-1 signalling in both cell types.

Conclusions: Our data does not support the participation of gremlin-1 in TGFb-dependent renal fibrosis in vitro.

Funding: Pharmaceutical Company Support - Medimmune

FR-P0311
Vitamin (Vit) D Repletion Ameliorates Muscle Wasting and Muscle Fibrosis in Mice with Chronic Kidney Disease Wei Ding, Wei W. Cheung, Mary Christine Esparza, Ping Zhou, Richard L. Lieber, Robert H. Mak. Pediatric Nephrology, Univ of California, San Diego, La Jolla, CA

Background: Cachexia presenting as muscle wasting and weakness is prevalent in CKD patients and may impact their quality of life. We investigated the effects of vitamin D repletion in a mouse model of CKD-associated cachexia and vitamin D deficiency.

Methods: CKD in c57BL/6 mice were induced by 5/6 nephrectomy. CKD and sham mice were treated with 25VitD (25 mg/kg/day), 1.25VitD (40 ng/kg/day) or vehicle (V) for 6 weeks via a subcutaneous osmotic pump. CKD-V mice were fed ad libitum while other groups of mice were pair-fed to CKD+V mice. Parameters of energy homostasis, skeletal muscle histomorphometry and in vivo muscle function were measured. The expression of key molecules implicated in myogenesis and fibrosis pathway was assessed using a focused PCR array.

Results: Serum 25VitD and 1.25VitD levels were significantly lower in CKD than sham mice (p < 0.01) and was increased, within the physiological range, by 25VitD and 1.25VitD repletion in CKD mice. CKD mice exhibited reduced weight gain, increased body mass index (BMI) and increased expression of the BMI-related gene, leptin. Increased energy expenditure in CKD mice was associated with upregulation of uncoupling proteins (UCPs) in skeletal muscle and adipose tissues. Soleus muscle fiber area, soleus collagen content as well as aberrant gene expression involved in muscle function was significantly reduced in CKD mice than sham mice (p < 0.01). Skeletal muscle fibrosis, a major pathological hallmark of myopathies, is evident in CKD mice. Soleus collagen content was significantly increased in CKD than sham mice (p < 0.01). Gene expression of myogenesis and fibrotic pathways were increased in CKD than sham mice (p < 0.01). Perturbations in weight gain, energy expenditure, UCPs, lean mass decrement and muscle function tests, soleus muscle fiber area, soleus collagen content as well as aberrant gene expression involved in myogenesis and muscle fibrotic pathway in CKD mice were normalized by 25VitD but only partially attenuated by 1.25VitD repletion.

Conclusions: 25VitD and 1.25VitD repletion have differential effects on muscle wasting and muscle fibrosis in CKD mice.

Funding: Other NIH Support - R24-HD05837

FR-P0312
The Effect of Cell Culture Surface Coating on Glomerular Endothelial Cell Phenotype Kamilla Campanholle,4 Signe Holm,4 Kamilla Tove Skrede,4 Signe Camilla Holm,4 Kamilla Aasa Campanholle,4 Kamilla Ritsuko Campanholle,4 Holm,4 Southern Denmark Univ, Odense, Denmark.

Background: Renal interstitial fibrosis is characterized by dysregulated extracellular matrix turnover and protease activity. ECM protein fragments generated by protease cleavage can be measured by specific ELISAs, providing a protein fingerprint of the disease. The aim of this study was to set up an ex vivo model for renal interstitial fibrosis in order to investigate the ECM turnover profile in the fibrotic kidney.

Methods: 14 male 12 weeks old Sprague-Dawley rats underwent Unilateral Ureteral Obstruction (UUO) surgery by ligation of the right ureter. The left kidney (contralateral) was used as internal control. 6 rats were sham-operated and used as control group. Rats were terminated 2 weeks after the surgery, when advanced fibrosis is known to be present. The kidneys were excised and processed to tissue slices (PCTS) were cultured for 5 days in serum free medium. Markers of collagen type I formation (P1NP), collagen type III degradation (C3M) and α-smooth muscle actin (α-SMA) were measured in the PCTS supernatants. The extent of tubulointerstitial fibrosis was evaluated by histology.

Results: P1NP, C3M and α-SMA were significantly increased in supernatants of tissue slices from the UUO ligated kidneys compared to the contralateral kidneys (p < 0.001) and to sham operated animals (p > 0.0001). However the markers had a high inter-individual variability in the UUO group. When comparing the levels of the markers from the UUO kidney to those from the corresponding contralateral kidney, animals with pronounced differences were those presenting advanced fibrosis in histology.

Conclusions: The UUO PCTS ex vivo model provides a valuable translational tool for investigating the ECM remodeling associated with renal interstitial fibrosis. Since the ECM content is not measured, the markers measured in the supernatants also in circulation and in urine, these markers have the potential to accurately and non-invasively describe the tissue remodeling during fibrosis.

FR-P0313
Development of an Ex Vivo Model to Elucidate the Matrix Turnover Profile in Renal Interstitial Fibrosis Signe Holm Nielsen,1, 2 Zsolt Soma Karpati,1 Daniel Guldgard Kring Rasmussen,2 Morten Asser Karsdal,1 Federica Genovesi,1 1Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; 2System Biology, Denmark Technology Univ, Kgs. Lyngby, Denmark; 3Southern Denmark Univ, Odense, Denmark.

Background: Extracellular Matrix Biology, Fibrosis, Cell Adhesion - I


FR-P0314
Collagen Degradation Profile in a Nephrotic Nephritis Model Signe Holm Nielsen,1, 2 Daniel Guldgard Kring Rasmussen,1, 2 Gabriela Campanholle,1 Robert V. Martinez,2 Morten Asser Karsdal,1 Federica Genovesi,1 1Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; 2System Biology, Denmark Technology Univ, Kgs. Lyngby, Denmark.

Background: The nephrotic nephritis (NTN) mouse model is characterized by a rapid onset of nephritis, followed by tissue destruction and progression to renal scarring. We aimed at identifying markers for early disease onset that were directly linked to the events of scar formation in the kidney.

Methods: Neo-epitope degradation fragments of collagen type I, III and IV generated by MMP cleavage were measured by specific ELISAs (namely C1M, C3M and C4M) in urine of NTN and healthy mice terminated at 7 and 21 days after injury (NTN: n=21, Controls: n=6). Urinary albumin/creatinine (A/CR), urinary proteinuria, plasma creatinine and blood urea nitrogen (BUN) were measured as markers of renal function. Intestinal fragments of glomerulosclerosis were evaluated by histology and quantification of α-SMA and collagen type I in immunohistochemistry.

Results: While C1M levels in urine were not different between NTN mice and controls, C3M levels were elevated in NTN rats at 7 days (p < 0.05) and decreased to levels close to the controls at 21 days. This elevation was also reflected in proteinuria, peaking at 7 days, but not in BUN and plasma creatinine. C4M levels were elevated at 21 days and not at 7 days (p > 0.01), and correlated with the extent of interstitial fibrosis.
Funding: Private Foundation Support

FR-PO316

Multi-Clonal Population of Cells of Renin Lineage (CoRL) Transdifferentiate into Podocytes and PECs in Experimental FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is secondary to podocyte injury and loss. Because adult podocytes cannot proliferate, their replacement by progenitors is critical for their repair and regeneration in disease. Here we explored whether single or multiple clones of cells of renin lineage (CoRL) serve as a local progenitor source to replace damaged podocytes in experimental FSGS.

Methods: Experimental FSGS was induced following abrupt podocyte depletion by administration of a cytotoxic anti-podocyte antibody in two confetti mouse reporters. First, to confirm adult podocyte regeneration following abrupt depletion, podocytes were genetically fate-mapped in adult NPHP2+/CreConfetti1/1VGF reporter mice with experimental FSGS. Second, to prove that adult podocyte regeneration by CoRL was multi-clonal, CoRL were fate mapped in RenCre / Confetti1/1VGF reporter mice with experimental FSGS. Results: FSGS in NPHP2+/Confetti1/1VGF mice was characterized by marked podocyte depletion (45% decrease) on d7. A multi-clonal repopulation of podocytes resulted in an increase in their overall number to 77% of normal by d28. No podocyte proliferation was detected by BrdU staining. In RenCre / Confetti1/1VGF mice, a multi-clonal expansion of 4-color-labeled CoRL (GFP, RFP, CFP, YFP) was detected in glomeruli at FSGS d28. A subset of all clonal reporters co-expressed 5 podocyte markers (podocin, synaptopodin, p57, WT-1, nephrin). CoRL were also observed usingBowman’s capsule and capsule-adjacent PEC markers (PA2X, claudin-1). BrdU staining did not co-localize with CoRL reporters. Conclusions: Following an abrupt depletion of adult podocytes in experimental FSGS, their number was increased in the absence of podocyte proliferation. Regeneration of adult podocytes was likely in part due to multiple clones of CoRL serving as local progenitors.

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FR-PO317

Macula Densa-Derived Factors Control Glomerular Cell Remodeling

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Background: Macula densa (MD) cells are strategically positioned at the vascular entrance of the glomerulus and control renal hemodynamics and renin. In this study, we addressed a novel, non-traditional role of MD cells regulating glomerular cell plasticity/remodeling by mesenchymal progenitor cells.

Methods: For genetic cell fate tracking, tamoxifen-induced NG2CreERT2-Tomato mice were fed either a control or salt-deficient + ACE inhibition (SD+ACEi) diet, for 2 weeks to achieve strong MD stimulation. We observed a 5-fold increase in renal interstitial density of NG2-derived (+) cells (5.9±1.1 cells per field in control, 30.2±4.5 in SD+ACEi), and the homing of NG2+ cells to the mesangium under the MD and into the glomerulus. This effect was blunted by the selective COX-2 inhibitor SC38236 (COX-2i) or the nNOS inhibitor 7-NI (13.2±2.2 cells per field with COX-2i+7-NI and 11.6±1.7 with 7-NI). Immunofluorescence (IF) of Claudin-1 showed a 4-fold increase in the number of NG2+ cells in the glomerular parietal layer (0.5±0.2 cells per glomerulus in control, 2.0±0.4 in SD+ACEi). Podocin IF identified a few NG2+ podocytes. NG2+ cell homing was blunted by COX-2i and 7-NI (SD+ACEi, 0.1±0.2 cells per glomerulus with COX-2i+7-NI). Co-localization of endogenous NG2-Tomato fluorescence with IF of renin revealed an increase in the proportion of NG2+ renin-expressing cells from 22.0±6.6% to 70.6±7.4% after SD+ACEi, inhibited by COX-2i. Similarly, the density of proliferating cells expressing Ki67 increased after treatment (11.7±1.0 cells per field with control, 23.3±2.8 with COX-2i+7-NI). In the vicinity of the juxtaglomerular area, inhibited by COX-2i (5.6±1.0) and 7-NI (2.7±0.3).

Conclusions: Our results suggest that NG2+ pericytes may be an important progenitor cell population in the kidney. In response to MD-derived (from COX-2 and nNOS) paracrine factors, MD cells rapidly recruit cells from the renal interstitium proliferate and migrate towards the MD along the arteriolar territory and via the vascular pole into the glomerular epithelium and mesangium. In conclusion, MD cells play new important roles in the maintenance and remodeling of the glomerulus.

Funding: NIDDK Support

FR-PO318

A Novel Method for Assessing Podocyte Depletion in Whole Glomeruli

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Background: Podocyte depletion plays a major role in the development and progression of glomerulosclerosis. Given that glomerulosclerosis is often focal, affecting some but not all glomeruli, our aim was to develop a rapid, accurate and precise method for quantifying podocyte depletion in whole glomeruli.

Methods: Pod+ iDTR mice, in which expression of the human diphtheria toxin (DT) receptor is driven by the podocin promoter, and iDTR mice (controls) (mice controls) were injected with 3.6x107 (TUNel)/kg). Tissue was collected at day 35 for podocyte analysis (n=3 mice per group). A 100μm thick kidney slice from the pronephros and synaptopodin. Slices were cleared with benzyl alcohol, benzyl benzote (BABBB). An SP8 confocal microscope (Leica, Germany) fitted with a BABB objective (NA: 0.95; working distance: 2mm) was used. Total podocyte number was obtained by manual counting and used to calculate percent podocyte depletion in each glomerulus.

Results: In iDTR mice (controls), total podocyte number per glomerulus was almost identical between manual counts (66.6±1.92) and Imaris (65.47±9.26; P=0.65). In Pod+ iDTR mice, total podocyte number was also similar between manual counts (52.96±1.17) and Imaris (53.5±11.35; P=0.81). With both methods, podocyte counts were obtained in less than 2 minutes per glomerulus, a significant time reduction compared to existing methods. Imaris also facilitates the estimation of podocyte and glomerular volumes for a more accurate assessment of podocyte morphology in the glomerulus and synaptopodin. Slices were cleared with benzyl alcohol, benzyl benzoate (BABBB). An SP8 confocal microscope (Leica, Germany) fitted with a BABB objective (NA: 0.95; working distance: 2mm) was used. Total podocyte number was obtained by manual counting and used to calculate percent podocyte depletion in each glomerulus.

Conclusions: This is the first method to combine immunofluorescence, BABB-clearing and confocal microscopy to count podocytes in whole glomeruli. The method is accurate, precise and rapid, and provides a novel approach for podocyte morphometrics in settings where sufficient tissue is available for analysis.

Funding: NIDDK Support

FR-PO319

Characterization of Heterogenous Podocyte Biomiechanics Using Atomic Force Microscopy

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Background: Biomiechanical signals play a key role in glomerular physiology, where pathological changes in blood pressure can significantly affect podocyte morphology and function. While there has been a great focus on mechanobiochemical signaling in podocytes, their spatial biomechanical properties have been largely overlooked due to a lack of
FR-PO320

Identification and Validation of Fluid Flow Shear Stress (FFSS)-Induced Changes in Podocyte Signaling Pathways Using Bioinformatic Tools

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Background: In Fabry disease the deficiency of the enzyme α-galactosidase A leads to an accumulation of globotriaosylceramide (Gb3). An enzyme replacement therapy with agalsidase alfa (Replagali®) or beta (Fabrazyme®) is licensed since 2001. The establishment of an α-galactosidase A-deficient human podocyte cell line has already been published by our group. These podocytes accumulate Gb3, exhibit dysregulated AKT and mTOR signaling and dysregulated autophagy. We analyzed changes in cellular signal transduction by our group. These podocytes accumulate Gb3, exhibit dysregulated AKT and mTOR signaling and dysregulated autophagy. We analyzed changes in cellular signal transduction

Methods: We performed microarray analysis (Affymetrix GeneChip Mouse Exon 1.0 ST Array) on immortalized podocytes without FFSS (Control), immediately after FFSS (End-FFSS), 2 hours (post-2hr FFSS), and at 24 hours (post-24hr FFSS) after cessation of FFSS at 2 dynes/cm² for 2 hr. Mouse exon 1.0 ST Array has ~4 probes/exon and ~40 probes/gene. Data from the microarray were log transformed, normalized and filtered to generate a set of 17,494 genes. Genes that were significant at p<0.01 were analyzed using Ingenuity Pathway Analysis (IPA) and Enrichr Program to identify key pathways.

Results: IPA showed Akt, COX-2, and AMPK (at End-FFSS); TGF-β (at post-2hr FFSS) and p38MAPK, ERK1/2 (at post-24hr FFSS) in the main network. Enrich Kinase Enrichment Analysis showed GSK3β, ERK1/2 in all three treatment groups compared with the control group. ChiP-X Enrichment Analysis identified transcription factor β-catenin. Western blotting, fluorescence microscopy and immunocytochemistry were used to validate changes in these signaling molecules.

Conclusions: Increased FFSS affects pathways that mediate podocyte survival and inflammation, and provide targets to address the mechanism of hyperfiltration-mediated glomerular injury.

FR-PO321

A Podocyte-Based Screening Assay Identifies Paulowne-Derivatives as Novel Podocyte Protective Agents

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Background: Podocyte injury and loss is an early hallmark in the pathogenesis of a variety of glomerular diseases. Therefore, podocytes are an excellent cellular target for the development of kidney directed therapeutics. We recently described a novel cell-based high content screening (HCS) assay for quantifying podocyte damage in vitro. Here, we describe utilization of this HCS assay to identify a family of small molecules that significantly protect podocytes from injury.

Methods: We utilized cultured murine podocytes in an HCS assay using 96-well imaging plates to screen drugs for quantifying podocyte damage in vitro. Here, we describe utilization of this HCS assay to identify a family of small molecules that significantly protect podocytes from injury. We modified our drug screening platform for high throughput imaging (HT-Imaging pipeline) and automated drug screening for thousands of podocytes per condition. Identified hits were confirmed and a number of biochemical and cell biological assays were used to validate the findings.

Results: We identified a family of small molecules, Paulowne, as highly potent agents that protected podocytes. Among these, three other podulates (paullone, 1-azakenpaullone, and alsterpaullone) showed dose-dependent protection of podocytes from PAN-damage induced loss in F-actin fibers. Among the four paulonines identified, 1-azakenpaullone and alsterpaullone showed the highest level of protection. At cellular level, alsterpaullone reduced the elevation in the expression of Desmin, a podocyte damage marker, and inhibited PAN-induced podocyte migration. While PAN treatment reduced AKT phosphorylation in podocytes, alsterpaullone maintained the levels of phosphorylated AKT in podocytes.

Conclusions: Employment of our newly described podocyte-based screening assay results in the discovery of podocyte-directed therapeutics for treating a number of glomerular diseases. Paulonines represent a family of small molecules that show podocyte protection from damage. We also describe a proposed molecular mechanism for the efficacy of these novel agents. We hope that these methodologies will lead to the development of novel types of specific kidney protective drugs.

FR-PO322

NovoNordisk Podocyte Quantification Assay to Ascertain Patient Serum Toxicity

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Background: Septicemia/renal failure is a common indication for dialysis or renal transplantation. In > 50% of patients, the disease is idiopathic and may recur post-transplant suggesting the presence of a pathogenic toxic factor(s) circulating in the blood. The identity of this factor and the pathogenic mechanisms remain enigmatic. Recent in vitro studies from our lab showed that plasma from recurrent FSGS patients disturbs the human podocyte cytoskeleton and focal adhesion complexes (FACS). We developed a novel unbiased assay to quantify the toxic effects of patient plasma and nephrotoxic drugs on cultured human podocytes and to identify strategies that block serum toxicity.

Methods: Cultured human differentiated podocytes are exposed to adriamycin, recombinant TNFa or human sera from patients with various forms of FSGS. FACS are visualized with anti-vinculin antibody, and cell images are analyzed to define the number of FACS/1000μm² cell area. We analyzed sera from 12 patients: 2 with idiopathic, 4 recurrent FSGS, 4 non-recurrent FSGS and 2 de novo FSGS.

Results: Both adriamycin and recombinant TNFa disrupt podocyte actin cytoskeleton and FACS in a dose-dependent manner. Comparing to healthy control, sera from patients with de novo FSGS (no known mutations identified), FSGS and de novo FSGS post-transplant drastically reduces FACS number, yet sera from mFSGS post-transplant does not statistically affect FACS. In ~60% of the patients with serum toxicity, these effects on podocytes can be averted by TNFa pathway blockade.

Conclusions: Our in vitro podocyte assay provides, for the first time, means to reliably identify those patients with idiopathic FSGS who are at high risk of recurrence post-transplant. It may also identify FSGS patients who may be candidates for anti-TNFa therapy that could prevent progressive glomerular injury.

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FR-PO324

Loss of Robo2 in Podocytes Protects Adult Mice from Acute Glomerular Injury

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Background: SLIT2 and its receptor ROBO2 play an important role during kidney development. We have recently found that ROBO2 is expressed in developing glomerular podocytes. However, the role of ROBO2 in the adult mouse kidney, particularly under acute glomerular injury conditions, is not clear.

Methods: To test the hypothesis that loss of Robo2 in glomerular podocytes affects the outcome of acute glomerular injury, we applied two in vivo acute glomerular injury models induced by nephrotoxic serum (NTS) injection and proteinuric saline (PS) perfusion, in Robo2 podocyte specific knockout mice (Robo2 KO) and wild type controls. Kidney glomerular ultrastructure was analyzed by scanning and transmission electron microscopy before and after injury. Podocyte foot process width and slit diaphragm density were measured to quantify the severity of the glomerular injury. Urine albumin to creatinine ratio was measured in the NTS model. Podocyte specific gene expression was analyzed using TaqMan real time PCR for mRNA and Western blot for protein levels.

Results: Robo2 podocyte specific knockout mice developed less proteinuria after the NTS injury with lower urine albumin/creatinine ratio as compared to the wild type controls. Electron microscopy showed that Robo2 KO mice have milder foot process effacement and less defects in the slit diaphragm induced by either NTS or PS injury. TaqMan and Western blot analyses revealed that nephrin, a crucial transmembrane component of the podocyte slit diaphragm, was significantly up-regulated at both mRNA and protein levels in the Robo2 KO mice before NTS injury and at the late stage of heterologous phase after the NTS injury. In addition, the mRNA levels of Robo2 and Slit2 in the wild type kidneys were also upregulated after the NTS injury.

Conclusions: SLIT2-ROBO2 signaling pathway plays an important role in the adult mouse kidney and loss of Robo2 in podocytes from acute glomerular injury. Our findings suggest that SLIT2-ROBO2 signaling might also have a negative impact on nephrin expression during podocyte injury and be a potential therapeutic target.

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FR-PO325

Inducible Knockdown of Shroom3 Induces Proteinuria with Podocyte Dedifferentiation

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Background: Intrinsic loci in Shroom3 have been associated with CKD and CAN. A role for Shroom3 in the podocyte cytoskeleton has been shown. However Shroom3 knockout mice die neonatally with neural tube defects and detailed renal phenotypes are unknown. Here we report our findings from Doxycycline (DOX) inducible, shRNA-mediated shroom3 knockdown mice.

Methods: In these mice Shroom3-specific shRNA expression was induced upon DOX feeding, with RTTA expression in all cells driven by CAGS-promoter. Six-wk old mice were fed DOX-feed/water. Non-DOX fed littermates were controls (n=6 each). At 4- and 8-weeks, renal tissue was obtained for histology. Twenty-five glomeruli were analyzed per mouse and quantification was used imaging.

Results: DOX-mice developed significantly increased Albumin-to-creatinine ratios starting at 2 weeks compared to controls.

Proteinuria persisted at 8 weeks of DOX feeding. No light microscopic changes were detectable on PAS-stained sections in Shroom2 knockout mice or control mice. Kidney mesangial matrix expansion or intratubular protein casts was observed up to 8-weeks of DOX feeding. Assessment of WT-1 stained nuclei/glomeruli by immunofluorescence (IF) showed no reduction in podocyte number at 4- or 8-weeks in DOX-mice compared to controls (p>0.05). By 8-weeks, however, IF staining revealed that area and intensity of glomerular synaptopodin staining was observed by 4 weeks in DOX-mice compared to controls (p<0.001; n=3 each at 4-wks, Fig 2). Electron microscopic studies are ongoing.

Conclusions: Our preliminary findings suggest that inducible and global knockdown of Shroom3 induces podocyte dedifferentiation features of podocyte dedifferentiation without evidence of podocyte loss. Further studies are needed to elucidate the precise role of Shroom3 in proteinuria and its function in the glomerular filtration barrier.

FR-PO326

Protective Role of Cyclodextrin in Focal Segmental Glomerulosclerosis (FSGS)

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Background: We recently demonstrated that cholesterol accumulation contributes to podocyte injury in diabetic kidney disease (DKD), where 2-hydroxypropyl-β-cyclodextrin (CD) protects podocytes from cholesterol-dependent damage in vitro and in vivo. We hypothesize that lipid related genes are affected in glomeruli of patients with primary FSGS and that these genes are associated with experimental podocytes high in CD.

Methods: Microarray analysis on glomerular transcripts of lipid-related genes from patients with FSGS (n=54) and from normal living donors (n=6) were obtained from patients enrolled in NEPTUNE, a longitudinal observational cohort looking at individuals with proteinuria. 5-week-old BALB/c female mice were injected with a single intravenous dose of adriamycin (ADR, 11 mg/kg) to develop FSGS-like lesions. 24-hours after ADR injection, osmotic pumps with CD in 0.9% saline solution (40 mg/kg/day) were implanted under the skin for 10 weeks. Measurements of body weight and urine collections for ACR (Albumin/creatinine ratios) were performed weekly. At time of sacrifice, serum creatinine and Blood Urea Nitrogen (BUN) were determined and kidneys collected for histological analysis.

Results: Microarray analysis of the glomerular transcripts in the NEPTUNE cohort demonstrated that cholesterol efflux related genes, such as PLIN3, S1PR2, S1PR1, S1PR1, and lipid dysmetabolism related genes, such as SCD, LDLR, ABCG1, were increased in FSGS. CD administration reduced mesangial expansion as well as ACR and BUN observed at 10 weeks in the ADR+CD group compared to the ADR group (p<0.05). No changes in body weight were found.

Conclusions: We demonstrated that glomerular lipids are altered in FSGS and that 2-hydroxypropyl-β-cyclodextrin protected podocytes in an experimental model of FSGS. Our data suggest that CD could be used as a safe and effective drug therapy in FSGS patients.

Funding: NIDDK Support

FR-PO327

Podocyte-Derived Cxcl12 Has a Dual Role in Glomerular Injury and Regeneration

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Background: Stromal-derived factor (SDF)-1/CXCL12 is a homeostatic chemokine facilitating homing and activation of stem cells. Podocytes constitutively produce CXCL12, hence, we speculated on a role of CXCL12 in glomerular regeneration upon injury.

Methods: Glomerular injury was induced by a single i.v. injection of 13mg/kg adriamycin (ADR) in male Balb/c mice, which received either the CXCL12 inhibitor NOX-A12 or the inactive control s.c. at 13.4mg/kg thrice a week. Renal progenitor cell properties (RPC) were used for in vitro studies.

Results: ADR-induced podinuria peaked at day 7 (injury phase), which subsequently declined without returning back to baseline and being associated within FSGS lesions after 14 days (repair phase). CXCL12 blockade aggravated ADR-induced A/C and podocyte loss at day 7, which implies an autocrine role of CXCL12 for podocyte survival. In contrast, CXCL12 blockade reduced A/C levels and the glomerular sclerosis scores as well as increased podocyte numbers at 14 days indicating a beneficial effect of CXCL12 blockade during the repair phase. The pro-survival effect of CXCL12 on podocytes was further confirmed in a model of dipheria toxin-induced podocyte depletion using CXCL12 blockade. To investigate the dual effect of CXCL12, we focused on the Notch signaling pathway. ADR injection reduced native Notch expression, which was reversed following CXCL12 blockade. In vivo studies with RPC revealed that CXCL12 suppressed RPC proliferation, which was reversed with CXCL12 inhibitor. Similar results were obtained when RPC were exposed to supernatants from necrotic podocytes. CXCL12 blockade also increased the capacity of RPC to differentiate into podocytes.

Conclusions: Podocyte-derived CXCL12 has a dual role in glomerular injury. CXCL12 protects podocytes during the injury phase in an autocrine manner by suppressing Notch signaling, which otherwise triggers mitotic catastrophe and podocyte loss. Podocyte-derived CXCL12 assures Notch-mediated quiescence of RPC. Our data also demonstrate that therapeutic CXCL12 inhibition in glomerular injury can improve long term outcomes possibly by enforcing the intrinsic regenerative capacity of RPC.

FR-PO328

Shank2 Modulates Glutamatergic Signaling in Podocytes

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Background: Shank2 is a large scaffolding protein that is a master regulator of glutamate receptors at the neuronal postsynaptic density. Knockout (KO) of Shank2 in mice leads to autistic behaviours and abnormal glomerular filtration. Shank2 is also known to be expressed in podocytes. Shank2 has been shown to express functional N-methyl D aspartate (NMDA) and metabotropic glutamate receptor 1 (mGluR1) receptors which are both members of the glutamate receptor family.

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Results: We have found that podocytes express Shank2 in vivo and in vitro. Since Shank2 plays an important role in regulating glutamate receptor function, we examined the effect of Shank2 knockout on NMDA and mGlur1 expression and function in podocytes. Shank2 KO resulted in decreased expression of NMDA and mGlur1 receptors in glomeruli. We isolated podocytes from wild type and Shank2 knockout mice and created conditionally immortalized Shank2 KO podocytes. Conditionally immortalized Shank2 KO podocytes also demonstrated decreased expression and altered localization of glutamate receptors. In neurons, activation of glutamate receptors modulates intracellular calcium levels by allowing calcium influx into the cell (NMDA receptors) or release of calcium from intracellular stores (mGlur1). Fluo-4, a calcium sensing dye, we examined intracellular calcium levels in wild type and Shank2 KO podocytes. At baseline, Shank2 knockout podocytes had significantly fewer calcium spikes than wild type podocytes. Treatment with NMDA and gluta-mate increased the number of calcium spikes in both wild type and Shank2 KO podocytes but the number of spikes in the KO podocytes was significantly reduced compared to wild type. Podocytes have been shown to communicate with each other via calcium waves. To examine podocyte to podocyte communication after injury, we “burned” a podocyte using high intensity laser power and then examined calcium wave propagation from the site of injury. After burning, wild type podocytes exhibited calcium waves emanating from the injured podocyte whereas no waves were seen in the knockouts.

Conclusions: Taken together these data indicate that Shank2 regulates glutamate receptor function in podocytes.

Funding: NIDDK Support

FR-PO329
Podocytes Transcytose Albumin and IgG Using the Neonatal Fc Receptor (FcRn) In Vitro and In Vivo
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Background: Proteinuria is strongly associated with kidney disease progression. Podocytes are key constituents of the glomerular filtration barrier (GFB), which determines the selectivity of protein filtration. By even the most conservative estimates between 2 and 9 g of serum proteins a day normally pass through the GFB. The molecular mechanisms whereby podocytes handle albumin and IgG remain to be fully determined.

Results: We have found that transcytosis is the major pathway whereby cultured podocytes handle albumin and IgG. In other epithelial cell types, the neonatal Fc receptor (FcRn) is required to transcytose endocytosed albumin and IgG, thereby salvaging these proteins from degradative pathways. To examine the role of FcRn in albumin and IgG transcytosis in podocytes, we knocked down FcRn in cultured podocytes using lentiviral short hairpin (shRNA). FcRn knockdown (KD) resulted in a 71 ± 9% decrease in FcRn expression compared to control. In an in vitro transcytosis assay, FcRn KD increased intracellular accumulation and decreased appearance of albumin and IgG in the supernatant, suggesting impaired transcytosis, but the differences were not statistically significant, possibly due to residual FcRn. We therefore isolated podocytes from wild type (WT) and FcRn knockout (KO) mice and created conditionally immortalized WT and KO podocyte lines. Knockout of FcRn resulted in significantly increased intracellular accumulation, assessed by immunostaining and Western blot (demnetometric analysis of intracellular protein 1 hr after loading showed 0.37 ± 0.1 (WT) vs 0.97 ± 0.2 (KO), p<0.05 for albumin and 0.52 ± 0.04 (WT) versus 1.03 ± 0.19 (KO), p<0.05 for IgG), and decreased appearance of supernatant albumin or IgG, indicating defective transcytosis. We extended our studies to an in vivo model by creating a podocyte-specific FcRn KO mouse. Podocyte-specific FcRn KO mice demonstrated impaired transport of endocytosed albumin or IgG by 8 weeks of age, assessed by immunostaining. Studies of albuminuria are in progress.

Conclusions: Taken together, these studies indicate that podocytes in vitro and in vivo transcytose albumin and IgG using FcRn.

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FR-PO330
Transcriptional Reprogramming by Wilms' Tumor 1 and FoxC2 in Glomerular Disease
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Background: Wilms’ Tumor-1 (WT1) and FoxC2 have been associated with glomerular disease. WT1, which is important for barrier function. We detected a filamentous pattern of the hantaviral cytoskeleton, because the filamentous pattern protein has been associated with glomerular disease.

Methods: We now use ChIP-Seq to study the DNA binding of WT1 to target genes in the context of Adryanicism-induced podocyte injury that is considered a model for human FSGS. WT1 ChIP-Seq was performed using isolated glomeruli from 6 days post-injection or control Balb/C mice. FoxC2 binding was determined by direct ChIP-qPCR.

Results: Expression of WT1 and FoxC2 decreased in podocytes, as did binding of WT1 and FoxC2 to their common targets. WT1/FoxC2 target gene expression was also reduced. In contrast to these WT1/FoxC2 target genes that represent a set of genes normal for podocyte function, we identified a second set of WT1-bound genes, not bound by FoxC2, including Hduc5 and 7, whose expression increased after podocyte injury and whose binding decreased, suggesting that WT1 acts as a repressor for a distinct set of target genes.

Conclusions: These results suggest a model whereby WT1 and FoxC2 activate gene expression in normal podocytes, while WT1 represses other genes in normal podocytes independently of FoxC2.

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FR-PO331
A Basophilic Kinase Site at the N-Terminus of TRPC6 Controls Channel Activity
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Background: The non-selective cation channel TRPC6 plays a pivotal role in the development of proteinuric kidney disease. Hyperactivity of TRPC6 either through gain of function mutations, increased total protein levels or membrane abundance of the channel protein has been associated with glomerular disease.

Methods: To investigate regulation of the TRPC6 channel activity we conducted mass spectrometry experiments to screen for phosphorylation sites in the TRPC6 protein. We identified several new actions as previously known phospho-peptides. The serine residues in position 13 and 14 of the human TRPC6 protein are phosphorylated and embedded in a basophilic kinase motif. Substitution of the serine residue in position 14 with alanine (S14A) leads to a reduction of TRPC6 conductance in voltage clamp experiments in Xenopus oocytes.

Results: The atypical cyclin-dependent kinase (Cdks), a serine- threonine kinase expressed in the podocyte, is directed to basophilic motives. In the podocyte, Cdks is activated by the specific activators p35, p25, and Cyclin L1 in cell culture experiments a direct phosphorylation of TRPC6 by Cdks/p35 at position S14 could be confirmed with mass spectrometry and radioactive in vitro kinase assays. Co-expression of Cdks/p35 and TRPC6 enhanced channel conductivity of TRPC6 in voltage clamp experiments. This effect was abrogated by the amino acid substitution S14A.

Conclusions: A basophilic kinase site at the N-terminus of TRPC6 was identified which controls channel activity. As exemplarily shown for Cdks/p35, basophilic kinases phosphorylate TRPC6 at serine 14 and affect channel function. This site may serve as a molecular switch for TRPC6 activity and as a potential future drug target.

Funding: Private Foundation Support

FR-PO332
Hantaviruses Associate with Actin Fibers and Cause Podocyte Damage
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Background: Characteristic for the clinical picture of Old World hantaviruses is an acute renal failure with often massive non-selective proteinuria. Previously, we showed that cell-to-cell contact proteins were disrupted and levels were decreased in infected human renal cells, correlating with the clinical picture. However, the exact mechanisms driving hantaviral pathogenesis are not well characterized.

Methods: Renal biopsies of patients with acute hantavirus infection were analyzed by electron microscopy. A human podocyte cell line was used for infection with Hantaan virus (HTNV). Cell-to-cell contact proteins were analyzed by immunoblotting, qRT-PCR and immunofluorescence. The cytoskeleton was examined by confocal microscopy and by depolymerising drugs. Cell motility was measured by migration assays.

Results: Analysis of renal biopsies revealed podocyte foot process effacement with loss of cell-to-cell contacts. To examine the underlying mechanism of hantavirus-induced alterations, we performed in vitro infection studies. We showed that HTNV had no influence on transcription levels of cell-to-cell contact proteins, indicating another mechanism of cell-to-cell contact disruption. Next, we focused on an impact on the cytoskeleton which is important for barrier function. We detected a filamentous pattern of the hantaviral nucleocapsid (N) protein which was associated with actin fibers. This N protein localization depends on the integrity of the actin cytoskeleton, since the filamentous pattern disappeared after actin depolymerization. Correspondingly, we measured decreased viral release waves after loss of N protein filaments. During infection, we revealed impaired podocyte motility as a functional consequence due to hantavirus-induced effects on actin dynamics and focal adhesions.

Conclusions: These results demonstrate that hantavirus infection leads to podocyte injury by morphological changes. Disruption of cell-to-cell contacts may be caused by the association of N protein and actin leading to changes in podocyte motility. These findings provide useful insights into the mechanism inducing renal failure.

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Results: The mice showed variable levels of proteinuria and GS. p110γ-positive cells per glomerulus were correlated significantly with glomerular COL1A2 mRNA content. In culture, p110γ KD podocytes, but not WT cells, demonstrated increased membrane ruffling along with distinct Rac1 staining at the membrane, and KD podocytes were resistant to in vitro ADR treatment. WT cells expressing constitutively active p110γ showed decreased cytoskeletal stress and DEATH early after injury was detected, suggesting that p110γ activity directly mediates podocyte dysfunction.

Conclusions: p110γ expression in podocytes correlates with degree of GS, and therefore, a potential maker for GS. p110γ activity mediates podocyte damage by affecting signals that is critical for cytoskeletal structure.

Funding: NIDDK Support

FR-P0336

Effects of FSGS-Associated Mutations on the Stability and Function of Myosin II

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Background: Myosin is expressed in podocytes and plays a key role in regulating the integrity of their cell-cell junctions, however, the effects of FSGS mutations on MyoII motor activity and stability have not been directly tested. In this study, we used a simple model organism, fission yeast Schizosaccharomyces pombe, to test the effects of FSGS-associated mutations on myosin activity. Fission yeast has only one class I myosin, MyoII, which is involved in actin patch assembly at the sites of endocytosis.

Methods: The amino acid residues mutated in the FSGS patients are conserved between human MyoII and yeast MyoII, which allowed us to introduce equivalent mutations into yeast myosin and use the resulting mutant strains for functional analysis. MyoII-GFP localization and stability was analyzed using fluorescence imaging and Western blotting, while MyoII functional activity was tested using growth and endocytosis assays.

Results: Yeast strains expressing mutant MyoII exhibited defects in growth and endocytosis similar to those observed in the myoII deletion strain. These mutations also disrupted MyoII localization to endocytic actin patches and resulted in mis-localization of MyoII to endosomes, linear membrane microdomains found in yeast cells. While both mutants examined in this study showed loss of function, one of these mutants was also characterized by the decreased protein stability.

Conclusions: Using the yeast model system we were able to determine that the kidney disease-associated mutations impair myosin functional activity and have differential effects on protein stability. This study provides the first example of using fission yeast as a model system to test the effects of FSGS mutations on MyoII function. This novel system allowed us to definitively establish for the first time the connection between the myosin motor activity and its ability to support normal glomerular filtration.

Funding: NIDDK Support

FR-P0337

Vinculin Bind Zonula Occludens-1 (ZO-1) and Is Required for Podocyte Stabilization of the Slit Diaphragm following Injury

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Background: Cell-matrix interactions and intercellular junctions in podocytes are important factors to prevent protein leakage through the glomerular filtration barrier. Vinculin, a cytoplasmic protein, links the actin filaments to integrin-based cell-matrix proteins and cadherin-based intercellular junctions. We have observed that vinculin is highly expressed in podocytes, and appears to be critical in maintaining slit diaphragm integrity following injury through its interaction with ZO-1.

Methods: Wild type and Vcin−/− mice were analyzed to determine the role of vinculin in vivo, and primary podocytes were isolated for in vitro studies.

Results: Podocyte specific ablation of Vcin resulted in no significant difference in body weight, albuminuria, and kidney histology up to 18 months when compared to littermate controls. However, Pod−/−KO mice had significantly increased albumin/creatinine ratios following lippopolysaccharide (LPS) or rabbit anti-mouse glomerular basal membrane (NTS) induced podocyte damage respectively (284±40 vs 411±31 mg/mg, and 205±28 vs 314±38 mg/mg, P<0.05). In addition, loss of Vcin in podocytes resulted in worsened foot process effacement. Co-immunostaining of ZO-1 with Vcin in primary podocytes and isolated glomeruli with ZO-1 in the primary podocytes and isolated glomeruli respectively. Cell fractionation of control and Pod−/−KO podocytes treated with either LPS or proteinase sulfate (PS) revealed a mislocalization of ZO-1 and nephrin to the cytoplasm in the mutant podocytes when compared to the control. These findings were further validated by immunofluorescence imaging of the primary podocytes following LPS or PS-stimulation and from isolated glomeruli following LPS or NTS-stimulation. No changes in cell adhesion or focal adhesion number were observed between the control and Pod−/−KO podocytes following LPS or PS stimulation on various substrates.

Conclusions: Our results reveal an association between vinculin and ZO-1 in podocytes. Loss of Vcin in podocytes results in the mislocalization of slit diaphragm proteins ZO-1 and nephrin following injury, thus exacerbating proteinuria.

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mRNA and protein expressions of Cytochrome P450 Family 24 (CYP24A1), VDR and vitamin D receptors. Proteins of co-repressors, proteins-activators of co-repressors, proteins-activators of co-activators and protein interactions in these complexes were evaluated by immunoprecipitation (IP) studies followed by Western blot analysis. Role of proteosomal degradation of VDR in AMs was determined.

Results: Both AT1R-BLK and VDA stimulated VDR complexes formation that differed in their composition and in their functionality. AT1R-BLK-induced VDR complexes contained unliganded VDR, SMRT, and phospho-histone deacetylase (HDAC3), whereas, VDA-VDR complexes were constituted by liganded VDR and CBP/p300. AT1R-BLK-induced complexes attenuated podocyte acetylin- histone (Ac-H3) levels and CYP24A1 expression, whereas VDA induced increasing and repressive expressions. On the other hand, VD-VDR complexes not only increased podocyte Ac-H3 levels but also enhanced CYP24A1 expression, thus suggesting their acetylating and gene activation properties. AT1R-BLK-induced podocyte SMRT inhibited expression of the pro-apoptotic gene BAX through down regulation of WIP1, and phosphorylation of Chk2 in high glucose milieu. Since SMRT-depleted podocytes lacked AT1R-BLK-mediated protection against DNA damage, it appears that SMRT is necessary for DNA repairs during AT1R-BLK.

Conclusions: AT1R-BLK provides podocyte protection in AMs predominantly through VDR expression and partly through unliganded VDR expression in 1, 25(OH)2D deficient states, on the other hand, AT1R-BLK contributes to liganded VDR expression in 25(OH)2D sufficient states.

Funding: NIDDK Support

FR-P0341


Background: Missense mutations in the NPHS2 gene, encoding podocin, are a major cause of familial and sporadic forms of steroid-resistant nephrotic syndrome (SRNS). Among them, those encoding endoplasmic reticulum (ER)-resident mutant proteins, e.g. R138Q, correlate with the most severe cases of SRNS.

Methods: We generated two human podocyte cell lines stably expressing 2HA-podocin or 2HA-podocinR138Q to perform comparative studies on podocin post-translational modifications and podocin degradation.

Results: We detected increased podocin S-nitrosylation and N-glycosylation in 2HA-podocinR138Q vs. 2HA-podocinwt podocytes, which may modify podocin topology, degradation and trafficking. We also suggest that a further interaction of podocinR138Q with the NADPH oxidase complex may contribute to its ER-retention.

Conclusions: These findings show podocin S-nitrosylation for the first time and suggest that increased S-nitrosylation and N-glycosylation may contribute to the defective trafficking and degradation of podocinR138Q, the product of the most frequent human podocin missense mutation and possibly of other pathogenic podocin missense mutants.

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FR-P0343

RAS Inhibition Enhances Proliferation and Migration of Cells of Renin Lineage (CoRL) as Progenitors in Experimental FSGS Julia Lichtnerk, Diana G. Eng, Jeffrey W. Pinnick, Kenneth W. Gross, Stuart J. Shankland.

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Background: RAS inhibitors are used therapeutically in proteinuric glomerular diseases. In focal segmental glomerulosclerosis (FSGS) where podocyte number is depleted, recent data showed that ACE-Inhibitors could improve podocyte number. Because adult podocytes cannot proliferate, their replacement by renal progenitors is critical for their regeneration in disease. The impact of RAS blockade on adult podocyte progenitors is not well understood.

Methods: Experimental FSGS characterized by podocyte depletion was induced by an antipodocyte antibody in two strains of Cells of Renin Lineage (CoRL) reporter mice (RenCre and RenCreER) where CoRL are fate mapped. Diseased mice were randomized at day 3, when podocyte number was depleted by 40%, to receive Enalapril or Losartan, or an anti-podocyte antibody in two strains of Cells of Renin Lineage (CoRL) reporter mice

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: Following the abrupt depletion of adult podocytes in experimental FSGS, RAS inhibition induced slight regeneration of their progenitors. This regeneration of adult podocytes is likely in part due to proliferation and migration of CoRl progenitor cells into the glomerular compartment. We show the first time that RAS inhibition has the potential to stimulate progenitor cells necessary for kidney repair and regeneration following podocyte depletion.

FR-PO343
SheCa Influences Nephrin Endocytosis and Protects from Glomerular Injury Claire E. Martin,1,2 Kelly A. Petersen,2 Lamine Aoudjijt,3 Tomoko Takano,2 Nina Jones.1 1Molecular and Cellular Biology, Univ of Guelph, Guelph, ON, Canada; 2Dept of Medicine, McGill Univ, Montreal, QC, Canada.

Background: The transmembrane protein nephrin is a key component of the slit diaphragm (SD). It has recently been postulated that nephrin turnover plays a key role in maintaining a healthy SD, and multiple theories regarding the role of nephrin phosphorylation in endocytosis are emerging. Tyrosine phosphorylation of the cytoplasmic tail of nephrin facilitates recruitment of several signaling proteins that regulate podocyte shape and thereby permselectivity of the SD. Previous work from our lab has identified and mapped the interaction between nephrin and the SheCa adaptor protein and demonstrated an early requirement for SheCa in maintenance of the filtration barrier in mice. Given SheCa's established role in endocytosis, we now hypothesize that SheCa may regulate nephrin endocytosis to ultimately maintain filtration barrier integrity.

Methods: Multiple approaches were used to measure the influence of SheCa and SheCa domain mutants on the levels of surface nephrin and signaling downstream of nephrin. Paroxynin aminocellulose (PAN) nephrin was induced in Sprague-Dawley rats for 0, 4, 7, or 14 days and nephrin endocytosis was monitored via biochemical analysis and immunofluorescence experiments.

Results: We demonstrate that SheCa expression is increased in podocytes in response to PAN injury, which is accompanied by activation of the stress-activated p38 and JNK MAP kinases. Interestingly, we found that transactivation of AP-1, which occurs downstream of nephrin activation as well as p38 and JNK, is attenuated by SheCa, and this effect is reversed by mutation of the SheCa SH2 domain, which mediates nephrin binding. Further investigation revealed that SheCa promotes nephrin endocytosis in a phospho-dependent manner by enhancing Src-mediated nephrin phosphorylation, its own binding to nephrin and endocytosis into EEA1-positive endosomes both in vitro and in PAN-treated rats.

Conclusions: Together these findings suggest a protective effect of SheCa in podocytes by influencing phospho-dependent nephrin endocytosis and possibly attenuating nephrin-mediated p38/JNK signaling in response to injury.

Funding: Government Support - Non-U.S.

FR-PO344
Podocyte Specific Response to Complement Challenge AnneKatrin Dettmar,1,2 Magdalena Riedl,2 Fred G. Pluthero,2 Moin Saleem,2 Jun Oh,2 Christoph Licht.1 1Dept of Pediatrics, Univ Medical Center Hamburg-Eppendorf; 2Dept of Pediatric Nephrology, Hospital for Sick Children; 3Academic Renal Unit, Univ of Bristol.

Background: There is a multilayered system of fluid phase and surface bound complement regulatory proteins, which ensure that complement activation occurs only on specific sites and spares the body’s own organs. Unrestricted complement activation is a main cause for damage in complement-mediated glomerulopathies such as CSG or membranous nephropathy (MN). In MN, podocytes, key components of the glomerular filtration barrier, are target of overshooting complement activation. The aim of this study was to characterize the complement defense mechanisms in podocytes and their response to complement challenge (CC).

Methods: We analyzed complement regulators by immunofluorescence, flow cytometry and qRT-PCR in immortalized human podocytes and compared them to blood grown endothelial cells (BOECs). Functionality of secreted complement factor H (CFH) was tested via a cofactor assay. In a model for CC (sensitization with antibodies against grown endothelial cells (BOECs). Functionality of secreted complement factor H (CFH)

Results: Inhibition has the potential to stimulate progenitor cells necessary for kidney repair and regeneration following podocyte depletion.

Funding: Private Foundation Support

FR-PO345
Ephrin-B1 Is Essential for the Formation and the Maintenance of the Integrity of the Silt Diaphragm Component: Inducible Podocyte-Specific Ephrin-B1 Deletion Causes Irregular Localization of Nephrin, NEPH1, CD2AP and ZO-1 Yoshiyasu Fukushima, Hiroshi Kawachi. Dept of Cell Biology, Inst of Nephrology, Nippon Univ Graduate School of Medical and Dental Sciences, Nigata, Japan.

Background: Ephrin and eph function as receptor-ligand pairs, and are reported to play multiple functions in several tissues. We have reported ephrin-B1 was expressed at the podocyte slit diaphragm (SD) and had an interaction with nephrin, a critical component of the SD (Kidney Int 72: 934, 2007). However, the function of ephrin-B at the SD is not well defined. In this study, the role of ephrin-B at the SD and the functional association of ephrin-B expression on podocytes were elucidated.

Methods: (i) The expression of the SD components (nephrin, NEPH1, podocin, CD2AP and ZO-1) were analyzed in tamoxifen-inducible podocyte-specific Ephrin-B1 knockout (KO) mice (Podocin-CreERT2; Ephrin-B1 fox/fox). (ii) The effect of the nephrin secretion on the molecular conformation of ephrin-B was analyzed.

Results: (i) Tamoxifen-induced inactivation of the ephrin-B1 gene at E18.5 resulted in the dislocalization of nephrin, NEPH1, CD2AP and ZO-1, although podocin dislocalization was not detected. These alterations of the molecular arrangement of the SD components were also detected in the mice of which ephrin-B1 was deleted at 3 month-old with tamoxifen (KO vs. cont, n=5: nephrin, score 3.11 vs 3.40, p<0.01; NEPH1: 2.97 vs 3.36, p<0.05; CD2AP, 3.01 vs 3.24, p<0.05; ZO-1: 3.28 vs 3.66, p<0.05). (ii) Not only nephrin but also ephrin-B was phosphorylated in the rat nephritic model caused by the injection with the antibody against nephrin, although phosphorylation of these molecules was not detected in SD of normal kidneys. The phosphorylation of these molecules were detected already at 1 h after the antibody injection. The ephrin-B phosphorylation was also induced by the treatment with the anti-nephrin antibody in HEK293 cells co-transfected with ephrin-B and nephrin. Conclusions: Ephrin-B1 is essential for the formation and the maintenance of the proper arrangement of the SD molecules. The stimulation to nephrin by the antibody phosphorylated not only nephrin but also ephrin-B, indicating ephrin-B is functionally associated with nephrin.

Funding: Government Support - Non-U.S.

FR-PO346
Ubiquitin C-Terminal Hydrolyse-L1 Deficiency in Podocytes Protects from Immune Complex Nephritis in Mice Julia M. Fechter,1 Marlies Sachs,2 Thorsten Wiech,2 RoFA. Stahl,2 Catherine Meyer-Schwesinger,1 Nephrology, University Clinic Hamburg, Hamburg, Germany; 2Pathology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Ubiquitin C-terminal Hydrolyse-L1 (UCH-L1) is a central deubiquitinating enzyme of the neuronal ubiquitin proteasomal system. UCH-L1 is thought to regulate the intracellular pool of monoubiquitin in neurons. Recently we identified a de novo expression of UCH-L1 in podocytes of patients with membranous nephropathy. Upregulation of UCH-L1 correlated with disease progression, accumulation of ubiquitinated proteins and increased expression of podocyte-specific proteins in human and rodent podocytes. Inhibition of UCH-L1 enzymatic function in a rat model of membranous nephropathy decreased the abnormal protein accumulation and ameliorated the clinical course of disease. We generated mice with podocyte-specific UCH-L1-deficiency to investigate the role of UCH-L1 on novel expression in podocytes.

Methods: Mice with podocyte-specific UCH-L1-deficiency were generated by Cre-Lox technology and back-crossed into the C57/Bl6 background. Podocyte phenotype were evaluated by morphological (immunohistochemistry, electron microscopy) and biochemical techniques (Western blotting, proteasomal activity assays, real-time PCR) in unchanged and anti-podocyte antibody challenged wildtype and knockout mice.

Results: Unchanged podocyte-specific UCH-L1-deficient mice exhibited normal podocyte morphology throughout life and delayed age-related proteinuria accompanied by a decreased accumulation of poly-ubiquitinated proteins. Following induction of anti-podocyte nephritis, podocyte-specific UCH-L1-deficient mice showed decreased signs of podocyte injury and decreased proteinuria despite a comparable immunologic reaction to the injected anti-podocyte antibodies. Podocyte-specific proteins such as nephrin and podocin were increased and protein accumulation was decreased. UCH-L1-deficiency resulted in increased proteasomal capacity and activity in injured podocytes.

Conclusions: Podocyte-specific UCH-L1-deficiency protects podocytes from age-related degenerative changes and from immune complex nephritis through increased proteasomal capacity.

Funding: Government Support - Non-U.S.

FR-PO347
Adhesion and Repulsion of Podocytes: Role of EphB-Receptors Eva Koenjehausen, Julius Hoffacker, Lukas Ludwig Peter Heimann, Nils Tim Haep, Magdalena Woznowski, Ivo Quack, Lars C. Rump, Lorenz Sellin. Univ Hospital Duesseldorf.

Background: Eph-receptor kinases mediate cell adhesion and repulsion at specialized cell contacts. Eph-receptor kinases bind to their cell-membrane bound ligands, the ephrines. EphB1 and EphB4 have been localized at the slit diaphragm. The molecular function of the EphB1,2,3 receptors in podocytes is unknown so far. Permeability is a hallmark for
glomerular disease and results from disruption of the glomerular filter. The slit diaphragm is a specialized intercellular domain of EphB2 as EphB2.DC-YFP cells adhere to ephrinb1-CFP and vice versa) occurs in both cell types during repulsion. The repulsion is dependent on the intracellular domain of the EphB2 receptor and ephrinb1 ligand, truncated mutants of EphB2 (ephrinb1.CDC-CP) were analyzed.

**Results:** Human podocytes as well as murine glomeruli express EphB1, 2 and 3 receptors. Co-cultures of differentiating EphB2-YFP and ephrinb1-CFP podocytes show repulsion between the two cell types. Transendoxytosis (YFP particles in CFP cells and vice versa) occurs if both cell types during repulsion. The repulsion is dependent on the intracellular domain of EphB2 as EphB2.DC-YFP cells adhere to ephrinb1-CFP and ephrinb1.DC-CFP cells. However, repulsion is maintained in co-cultures of EphB2-YFP with ephrinb1.DC-CFP cells. Co-culture experiments of differentiated, confluent podocytes confirm the results presented above.

**Conclusions:** EphB2 receptors mediate podocyte repulsion upon binding to their ligand ephrinb1. The EphB2 receptor cytoplasmic domain seems to be crucial for repulsion. Maintaining the correct podocyte distance within the highly organised glomerular architecture is not well understood. These cell culture data provide a promising concept of potential regulation of podocyte distance in vivo.

**FR-PO348**

Overexpression of the Splice Isoform VEGF165b Is Sufficient for Kidney Function in Mice When VEGF Receptors Are Depleted

**Background:** Podocyte over-expression of VEGF isoforms is low during normal physiological conditions. However, it is increased in renal pathologies like diabetic nephropathy and glomerular microaneurysms. VEGF isoforms increase podocyte permeability. Electron microscopy was used to examine the ultrastructure of the glomeruli, and immunofluorescence microscopy to determine the expression levels of podocyte and endothelial-specific proteins. Glomerular endothelial cells (GEnCs) in culture were used to determine the mechanism of action of VEGF isoform through VEGFR-2.

**Methods:** Podocyte-specific VEGF-A KO was induced via doxycycline for 10-14 weeks in WT, VEGF-A-KO and VEGF-A KO n/n-VEGF-A-b mice. In situ hybridisation confirmed a knock-down of VEGF-A. The kidney functional phenotype was determined through the urinary albumin creatinine ratio (uACR) and measurement of glomerular water permeability. Electron microscopy was used to examine the ultrastructure of the glomeruli, and immunofluorescence microscopy to determine the expression levels of podocyte and endothelial-specific proteins. Glomerular endothelial cells (GEnCs) in culture were used to determine the mechanism of action of VEGF isoform through VEGFR-2.

**Results:** The VEGF-A isoform alone is sufficient to increase the expression of anti-angiogenic VEGF-b, those studies suggest that VEGF-b is protective in renal function in diabetic rodent models. This study aimed to investigate whether constitutive podocyte over-expression of VEGF-b is able to rescue the injury phenotype seen in the inducible podocyte-specific VEGF-A KO mouse. The mechanism of action of VEGF-b within the glomeruli was also investigated.

**Conclusions:** Our study indicates that VEGF-A splice isoform manipulation could be a novel therapeutic avenue in chronic glomerular disease.

**Funding:** Other NIH Support - Medical Research Council & The Richard Bright VEGF Trust

**FR-PO349**

Rituximab Prevents TNFa Induced Podocyte anb3 Integrin Activation

**Background:** Podocyte over-expression of VEGF isoforms is low during normal physiological conditions. However, it is increased in renal pathologies like diabetic nephropathy and glomerular microaneurysms. VEGF isoforms increase podocyte permeability. Electron microscopy was used to examine the ultrastructure of the glomeruli, and immunofluorescence microscopy to determine the expression levels of podocyte and endothelial-specific proteins. Glomerular endothelial cells (GEnCs) in culture were used to determine the mechanism of action of VEGF isoform through VEGFR-2.

**Methods:** Podocyte-specific VEGF-A KO was induced via doxycycline for 10-14 weeks in WT, VEGF-A-KO and VEGF-A KO n/n-VEGF-A-b mice. In situ hybridisation confirmed a knock-down of VEGF-A. The kidney functional phenotype was determined through the urinary albumin creatinine ratio (uACR) and measurement of glomerular water permeability. Electron microscopy was used to examine the ultrastructure of the glomeruli, and immunofluorescence microscopy to determine the expression levels of podocyte and endothelial-specific proteins. Glomerular endothelial cells (GEnCs) in culture were used to determine the mechanism of action of VEGF isoform through VEGFR-2.

**Results:** The VEGF-A isoform alone is sufficient to increase the expression of anti-angiogenic VEGF-b, those studies suggest that VEGF-b is protective in renal function in diabetic rodent models. This study aimed to investigate whether constitutive podocyte over-expression of VEGF-b is able to rescue the injury phenotype seen in the inducible podocyte-specific VEGF-A KO mouse. The mechanism of action of VEGF-b within the glomeruli was also investigated.

**Conclusions:** Our study indicates that VEGF-A splice isoform manipulation could be a novel therapeutic avenue in chronic glomerular disease.

**Funding:** Other NIH Support - Medical Research Council & The Richard Bright VEGF Trust

**FR-PO350**

Deletion of the Major Soluble Flt1 Isoform from Mice Reveals New Vegf Decay Variants

**Background:** VEGF is an angiogenic cytokine that can induce vasculogenesis and angiogenesis in many different cell types. However, VEGF is also known to have anti-angiogenic effects, especially in the kidney. The mechanism of action of VEGF-A is complex and involves multiple isoforms. Ultra structural studies show glomerular basement membrane thickening and thickening of the basement membrane. Measurement of glomerular water permeability confirmed a knock-down of VEGF-A. The kidney functional phenotype was determined through the urinary albumin creatinine ratio (uACR) and measurement of glomerular water permeability.

**Methods:** To determine function of the soluble variant of Flt1 in the glomerulus, we generated a conditional KO model for the single sFlt1 (sFlt1 cKO) isoform reported in mice (removal of intron 13). Renal phenotype was examined by evaluating kidney function and histology. qPCR and Northern blot were used to identify splice variants of Flt1; 3’RACE was used to clone the spliced genes. Proteins of splice variants were generated by BacMam system.

**Results:** We generated sFlt1 cKO mice, and confirmed the deletion of Flt1 intron 13 using Southern blot. Surprisingly, it did not result in any overt kidney phenotype by 6 months of age. Northern blot and Western blot analyses revealed the existence of a major compensatory isoform, previously reported as human-specific. We also confirmed the existence of 17 new sFlt1 isoforms in RNA isolated from mice and 12 from human primary podocytes as well as mouse and human placenta samples. We present that the existence of these isoforms compensates for the loss of sFlt1 in our transgenic model. The functions of these isoforms warrant further investigation and may provide insight into regulation of Vegf levels, podocyte function and preeclampsia.

**Funding:** Government Support - Non-U.S.

**FR-PO351**

Polarity Signaling at the Kidney Filtration Barrier: Questioning the Function of Par3A

**Background:** The slit diaphragm (SD) represents the only cell-cell contact in between neighbouring podocytes. Classical adherence as well as tight junction proteins are part of this protein-protein supercomplex including ZO-1, occludin, catenins and cadherins. Polarity signaling is critical to maintain the SD complex as the Par3/Par6/aPKC complex clusters at the SD via direct interaction of Par3 with nephrin via its PDZ-domains.

**Methods:** To understand the role of the Par3 proteins at the slit diaphragm, we generated a novel podocyte specific Par3A knockout mouse model where exon 6 is flanked by loxP sites. Following podocin:cre mediated recombination expression of all known Par3A clusters at the SD via direct interaction of Par3 with nephrin via its PDZ-domains.

**Results:** Mice were born in predicted Mendelian frequency. Par3A-/-mice were born as heterozygous Par3A+/− mice at birth and did not show any signs of disease in their later life. Even challenging Par3A-/- mice with the albumin overload model did not result in an overt glomerular phenotype. Therefore, we performed additional immunoprecipitation experiments for aPKCota out of immortalized mouse podocytes and carried out in LCM/MS analysis to identify the aPKCota podocyte interactome. Interestingly, the most abundant aPKCota interacting proteins were Par6 and Lgl1/2.

**Conclusions:** Our results challenge the current view of the aPKCota/PAR6 complex and its role at the slit diaphragm. In contrast to tight junctions where aPKC-signaling diagnosis clustering by Par3A, its role at the SD is independent of Par3A. Here Lgl1/2 seem to be the predominant interactors clustering aPKCota at the SD.

**Funding:** Government Support - Non-U.S.
FR-PO352
Focal Segmental Glomerulosclerosis (FSGS) Permeability Factor (FSPF) Interacts with Glomerular Filtration Barrier Through Glycoconjugates Ram Sharma,1 Ellen T. McCarthy,2 Tarak Srivastava,2 Virginia J. Savin,3 Mukut Sharma.1 1Renal Research, KC VA Medical Center - MBRF, Kansas City, MO; 2Kidney Inst, KU Medical Center, Kansas City, KS; 3Renal Div, UMKC Children’s Mercy Hospital, Kansas City, MO.

Background: Galactose (Gal) blocks the FSGS serum-unduced increase in in vitro glomerular albumin permeability (P_{a}) (Trans Res 2008, 151:288-292) and decreases proteinuria in some patients with recurrent FSGS (NDT 2009, 24:2938-2940). Thus, the interaction of FSPF with glomerular cell surface glycoconjugates may play an essential role in its effect on the filtration barrier.

Methods: We selected sugars and lectins to model the interaction between glomerular glycoconjugates and FSPF. We used, (a) affinity techniques to evaluate the binding of FSPF with immobilized sugars (b) immunodeaminase to assess its significance in FSPF-induced increase in P_{a} and (c) Gal/N-acetyl Gal (GalNac)-specific lectin to determine the site of action of FSPF as FSPF mimetics.

Results: Plasma FSPF activity was retained by immobilized Gal, GalNac or galactosamine. Gal dose-dependently blocked FSPF-induced increase in P_{a} and partially reversed the effect of FSPF on P_{a} (p<0.01). In contrast, glucose, glucosamine or mannose did not interact with FSPF. Removal of sialic acid by neuraminidase diminished the FSPF-induced increase in P_{a}. We screened twenty Gal/GalNac-specific lectins as potential mimetics of FSPF. Only Dolichos biflorus agglutinin (DBA, 10 mg/mL) and Helix pomatia lectin (10 mg/mL) increased P_{a} to 0.65 and 0.55, respectively (p<0.001). The increases in P_{a} were like that induced by FSPF were blocked by Gal (100 µM) (p<0.001).

Discussion: The interaction of FSPF with glomerular cell surface glycoconjugates may play an essential role in its effect on the filtration barrier. Our novel findings regarding the affinity of FSPF for select sugars, the loss of activity after removal of sialic acid and the direct effect of certain lectins on barrier function provide new information regarding the molecular composition of FSPF and its interaction with glomerular proteins/glycolipids.

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FR-PO353
EPB41L5 Is a Critical Regulator of the Kidney Filtration Barrier Christoph Schell,1 Martina Suhm,1 Manuel Rogg,1 Martin Helmstaedter,1 Mariko Hirano-Kobayashi,2 Tobias B. Huber.1 1Dept of Nephrology, Univ Medical Center Freiburg, Freiburg, Baden-Württemberg, Germany; 2Laboratory for Vertebrate Body Plan, Center for Developmental Biology - RIKEN, Kobe, Kobe, Japan.

Background: Podocyte loss represents the final common pathway of various glomerular pathologies. Hence, tightly regulated adhesion towards the glomerular basement membrane is a fundamental biological process of podglomerulopathy.

Methods: Based on podocyte single cell isolation and a mass-spec candidate approach the composition of podocyte focal adhesions was resolved. A combinatorial nephropathy model with a newly generated conditional mouse model and various high resolution microscopy techniques (TEM, STORM) the candidate protein EPB41L5 was analyzed.

Results: Knockdown of the EPB41L5 homolog Yurt in drosophila nephropathy resulted in abnormal glomeruli and decreased podocyte capacity. Evaluation of a condition laminin knockout model revealed a rapid loss of podocytes implicating its role in podocyte adhesion. Employing immunoglobulin electron microscopy and STORM super resolution microscopy EPB41L5 was clearly localized towards the basal compartment of podocytes, in close proximity to INTEGRIN-beta1. Further functional experiments revealed that loss of EPB41L5 resulted in decreased activation of INTEGRIN-beta1, reflected by altered migratory behavior of primary podocytes.

Conclusions: Our findings indicate that EPB41L5 is a highly conserved, specific regulator of podocyte adhesion by modulating focal adhesion composition and function. Future studies will need to clarify its potential implications in genetic and acquired glomerular pathologies.

FR-PO354
The Effect of Anti-PLA2R Autoantibodies on Human Podocytes In Vitro Marvline Fresaquet,1 Rachel Lennnon,2 Paul E. Brenchley.1 1Wellcome Trust Centre for Matrix Research, Univ of Manchester, Manchester, United Kingdom; 2Inst of Cardiovascular Sciences, Manchester Royal Infirmary, Manchester, United Kingdom.

Background: PLA2R was identified as a major target antigen in idiopathic membranous nephropathy. 70% of patients have circulating autoantibodies which bind this receptor on the podocyte leading to immune complex deposition in the glomerular basement membrane. We recently characterized the interaction on PLA2R antibodies. Herein, we present the first 3D model of PLA2R, domains and demonstrated that autoantibodies are of high affinity. We seek to understand if affinity-pure anti-PLA2R alone in the absence of complement can modulate podocyte function.

Methods: We prepared affinity-purified human anti-PLA2R (91% IgG4, 9% IgG2) and assessed podocyte morphology following autoantibody treatment using immunofluorescence staining of actin and measurement of cell surface area and circularity. Integrity of the filtration barrier was assessed by Electric Cell-substrate Impedance Sensing and the response of a confluent monolayer of differentiated podocytes to 10mg/ml purified human anti-PLA2R and apoptosis was measured by cleaved caspase-3 staining in podocytes and oxidative stress was measured with CellROX reagent in differentiated podocytes challenged with the autoantibody.

Results: We have developed an in vitro podocyte model to define mechanisms of anti-PLA2R effects on cell morphology and function. Purified anti-PLA2R altered podocyte shape, with rounding and loss of actin stress fibres within 24 hours. Integrity of a confluent podocyte monolayer was significantly reduced at 72 hours by anti-PLA2R but not by the IgG control. Within 30 minutes of anti-PLA2R treatment, there was evidence of caspase-3 cleavage in podocytes peaking at 6 hours promoting apoptosis. In the same time frame anti-PLA2R induced free radical generation (P<0.0001, treated v. untreated), triggering oxidative stress which could be neutralised using a scavenger.

Conclusions: Anti-PLA2R in the absence of complement activation modulates podocyte cell function by inducing changes in cell shape and monolayer permeability, activation of free radical production and apoptosis.

Funding: Private Foundation Support

FR-PO355
Deletion of the Ste20-Like Kinase, SLK, in Podocytes Induces Injury Andrey V. Cybulsky,1 Elena Torban,2 Joan Papillon,1 Julie Guillermette,2 Natalya Belkina.1 1Medicine, McGill Univ, Montreal, QC, Canada; 2NIH, Bethesda, MD.

Background: SLK is essential for embryonic development, and may play a key role in wound healing, tumor growth and metastasis. Expression and activation of SLK is increased during recovery from ischemic acute kidney injury. Overexpression of SLK in glomerular epithelial cells/podocytes in vivo induces injury and proteinuria. Conversely, reduced expression of SLK protects against acute kidney injury and modulates cytokine expression and, motility. Tight regulation of SLK expression thus appears to be critical for normal renal structure and function. We address the role of SLK in podocyte function.

Methods: Podocyte-specific SLK knockout (KO) mice were produced by breeding mice with an FSPF transgenic mouse bearing exon 8-7 with podocin (NPHS2)-Cre mice. Loss of expression results in deletion of the kinase domain. Deletion of SLK exon 4-7 in glomeruli was confirmed with PCR.

Results: Podocyte-specific deletion of SLK resulted in albuminuria at 4-5 months of age in male mice, and 8-9 months in female mice, which persisted for up to 13 months (albumin/creatinine in KO was 2-3-fold above control). At 11-12 months, KO mice did not show renal histologic abnormalities by light microscopy, and glomerular area of KO was comparable to control. However, by electron microscopy, KO mice showed focal foot process effacement and microvillous transformation of podocyte plasma membranes. Mean foot process width was ~2-fold greater in KO, compared to control. By immunofluorescence microscopy, WT1-positive cells were reduced by 35% in KO mice compared to control, and staining for nephrin and podocytin was reduced in KO mice by 20-30%. SLK is reported to phosphorylate ezrin. Staining for phosphorylated ezrin/radixin/moesin (ERM) was reduced by 20% in KO glomeruli, in keeping with reduced SLK catalytic activity in glomeruli; however, tubular phospho-ERM staining was comparable in KO and control.

Conclusions: Podocyte-specific deletion of SLK leads to albuminuria, loss of podocytes and morphologic evidence of podocyte injury. Thus, SLK is essential to the maintenance of podocyte integrity as mice age. The mechanism may, at least in part, relate to ezrin phosphorylation and cytoskeletal integrity.

Funding: Government Support - Non-U.S.

FR-PO356
A Podocyte-Specific Knockout of the DNA Repair Gene Ercle Leads to Proteinuria and Focal Segmental Glomerulosclerosis Fabian Braun,1 Roman Aaron Akbar,1 Björn Schumacher,2 Wilhelm Bloch,1 Berhard Scherner,1,2 Thomas Benzing,1,2 Christine E. Kurschat,1,2 1Nephrology, Univ Hospital Cologne, Cologne, Germany; 2CECAD, Univ Hospital Cologne, Cologne, Germany; 3German Sport Univ Cologne, Cologne, Germany.

Background: The prevention and therapy of aging-related diseases will become a major public health problem. Among elderly patients mild to severe impairment of kidney function is common. Models to study renal aging have not been established yet. In a previous study, we identified a progeria mouse model of Ercc1-deficiency to exhibit expression profiles similar to those of glomerular aging in wt mice. Erc1 is involved in nucleotide excision repair, facilitating 5’ incision around bulky DNA lesions. In humans, the lack of Erc1 leads to a progeria phenotype. Thus, a podocyte-specific knockout of Erc1 may help us gain new insights into glomerular and podocyte aging processes.

Methods: Erc1fl/fl mice were bred in a mixed CD1/FVB background with CD1 mice to produce the Cre recombinase under the podocin promoter. We analyzed weight, urine and serum of animals at 7, 9, 11 and 13 weeks of age. Kidneys were fresh-frozen in OCT, fixed in paraformaldehyde and embedded in paraffin or prepared for electron microscopy.

Results: Erc1fl/fl mice are born in normal median rations and show no developmental abnormalities. We detected an onset of proteinuria at week 8 in aged animals. The normal weight curve compared to controls until week 11 to 18. 7 week old kidneys showed no morphological changes in light or electron microscopy. Male and female mice develop foot process effacement and focal segmental glomerular sclerosis at 9 weeks of age. This phenotype is aggravated by the knockout of Erc1 and kidney function showed sclerosis, interstitial fibrosis with tubular atrophy and tubular protein casts. We observed an increase in DNA damage shown by positive pH2A.X staining in glomerular nuclei at week 11.

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Underline represents presenting author.
Conclusions: Our study reveals a critical role for nucleotide excision repair in murine podocytes. This finding underscores the importance of podocyte DNA maintenance in these postmitotic cells. In ongoing studies we will characterize the role of Ercc1 in a podocyte cell culture model.

Funding: Government Support - Non-U.S.

FR-PO357

Mice Heterozygous for Rac1 in the Podocyte Are Protected against Nephrototoxic Serum Nephritis-induced Albuminuria, but Knockout Mice Are Not

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Background: Podocyte injury, either by genetic or acquired abnormalities, can lead to progressive proteinuria and glomerulosclerosis. Current treatments are not designed to specifically target the podocyte but are used for broader immunotherapeutic or anti-inflammatory purposes, thus podocyte-targeted therapies are needed. Rac1, a member of the Rho GTase family, has been suggested as a therapeutic target for podocyte injury. However we previously demonstrated that podocyte-specific Rac1 knockout mice have exacerbated albuminuria with a hypertensive injury model. We hypothesize that partial reduction of podocyte Rac1 is protective.

Methods: We employed the nephrotic serum (NTS) nephritis model, which causes predominant podocyte injury and high-grade proteinuria without appreciable inflammation, in wild-type (WT), podoRac1-KO (podoRac1-KO), and podocyte-specific Rac1 heterozygote mice (podoRac1-HET). A separate group of NTS-treated WT mice were given EHT1864 (40mg/kg), a Rac inhibitor. Mice were injected with NTS (1.5 mg/kg body weight) (n=8-10 mice per group) and placed in metabolic cages for 1 or 2 days for daily urine collection. Urine albumin was measured by SDS-PAGE gel with standard curve, normalized by urine creatinine.

Results: NTS treatment resulted in robust albuminuria in wild-type mice on days 1 and 2 with albumin-to-creatinine ratios (ACR) of 400-500 µg/mg. However, podoRac1-KO mice showed an equally robust albuminuric response on day 1, but less on day 2 compared to wild-type, suggesting accelerated recovery. In contrast, NTS treated podoRac1-HET mice demonstrated nearly 70% reduction in ACR compared to wild-type (130 versus 390 µg/mg, P<0.01). The Rac inhibitor EHT1864 was equally effective.

Conclusions: These results demonstrate that a partial reduction in Rac1 activity, through genetic or pharmacologic inhibition, provides a protective effect against NTS-mediated podocyte injury, whereas Rac1 deletion is not beneficial. Our findings should help guide the development and assessment of Rac1 inhibitors to target podocyte injury.

Funding: NIDDK Support, Private Foundation Support

FR-PO358

The Ectodomain of Syndecan-4 Increases Surface Expression of Podocyte TRPC6 Channels: An Essential Role for Integrin Signaling

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Background: Excessive activation of podocyte TRPC6 channels has been implicated in glomerular diseases. Syndecan-4 (Sdc-4) is a type-1 single-pass proteoglycan that can be cleaved to produce a soluble product capable of paracrine and autocrine signaling. A previous study (1) showed that the Sdc-4 core protein increases the surface expression of TRPC6 in podocytes. Here we show that the Sdc-4 ectodomain can also modulate TRPC6 channels and describe some of the pathways that surround this effect.

Methods: Cell surface expression of TRPC6 was monitored using surface biotinylation assays and whole-cell patch clamp recordings from cultured mouse podocytes. Signaling pathways were examined using assays for activated components and selective inhibitors. Protein interactions were examined by co-immunoprecipitation and confocal microscopy.

Results: We have confirmed previous studies showing effects of over-expression and knockdown of Sdc-4 core protein on podocyte TRPC6 (1). In addition, exposing podocytes to Sdc-4 ectodomain caused an increase in the surface abundance of TRPC6, accompanied by an increase in cationic currents evoked by diacylglycerol (DAG). Sdc-4 ectodomain increased the generation of reactive oxygen species (ROS) and effects of Sdc-4 on TRPC6 were blocked by the ROS quencher TEMPOL. Exposure to Sdc-4 ectodomain caused activation of NFAc1 and Rac1, inhibition of RhOa, and increased the total abundance of b3-integrin in its severally phosphorylated forms. Hyperosmotic effects on TRPC6 persisted after inhibition of calcineurin or NFAT. The Sdc-4 core protein immunoprecipitated and co-localized with b3-integrin in podocytes. Moreover, effects of Sdc-4 ectodomain were inhibited by cileintide, an inhibitor of outside-in signaling through av-containing integrins. Exposure to TNF caused a marked increase in shedding of Sdc-4 ectodomain from podocytes into the surrounding medium. This also occurred after over-expression of Sdc-4 core protein.

Conclusions: Locally produced Sdc-4 ectodomain may play a role in regulating podocyte TRPC6 channels and may contribute to glomerular pathology. (1) Liu et al. (2012). Atheroscler Thromb Vasc Biol 32: 378-385.

Funding: Private Foundation Support

FR-PO359

Regulation of Fascin-1 by Mechanical Stress in Podocytes

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Background: Glomerular hypertension causes glomerulosclerosis via the loss of podocytes, which are challenged by an increased mechanical load. We and others have demonstrated that podocytes are mechanosensitive cells. However, the response of podocytes to stretch remains incompletely understood.

Methods: Using 2D fluorescence gel electrophoresis (2D DIGE), we analyzed the proteome of cells of our mouse podocyte cell line that were cultured on flexible membranes with or without cyclic biaxial mechanical stress (0.5 Hz, 5% linear strain, 3 d).

Results: Mechanical stress profoundly altered the podocyte proteome. Several spots containing the actin-bundling protein fascin-1 were differentially regulated by mechanical stress. By immunofluorescence, fascin-1 was found to colocalize with nephrin in mouse kidney sections. The presence of fascin-1 in foot processes was confirmed by immunoelectron microscopy. Knockdown of fascin-1 in cultured podocytes increased the cell loss in response to mechanical stress. The mRNA levels of fascin-1 were not affected by mechanical stress. However, mechanical stress resulted in an almost complete dephosphorylation of fascin-1. It is known that phosphorylation at Ser-39 regulates the bundling activity of fascin-1, e.g. required for filipodia formation. Podocytes expressing wild type GFP-fascin-1 and non-phosphorylatable GFP-fascin-1-S39A showed marked filipodia formation, being absent in podocytes expressing phosphorymorphic GFP-fascin-1-S39D. Finally, the immunofluorescence signal of phosphorylated fascin-1 was strongly reduced in glomeruli of patients with diabetic nephropathy as compared to glomeruli of healthy controls.

Conclusions: In summary, mechanical stress dephosphorylates fascin-1 in podocytes thereby increasing the actin-bundling activity of fascin-1. Fascin-1 may play an important role in the adaptation of podocytes to mechanical stress.

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FR-PO360

Deletion of the Vps34 Downstream Effector PIKfyve Establishes Milder Endocytic Dysfunction in Healthy Glomerular Podocytes Compared to Proximal Tubular Cells

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Background: The mechanisms by which the glomerular filtration barrier prevents the loss of large macromolecules and at the same time maintain the filter remain poorly understood. Recent studies have proposed that podocytes play an active role in both endocytosis of filtered macromolecules and maintaining the filtration barrier.

Methods: We generated podocyte and proximal tubular specific deletion of PIKfyve using the cre-loxP system. Indirect IF and immune EM was used to assess the endocytic pathways.

Results: Deletion of a key endosomal trafficking regulator, the class III phosphoinositoid 3-kinase or Vps34 in podocytes results in aberrant endosomal membrane morphology and podocyte dysfunction. We recently demonstrated that the vacuolation phenotype in cultured Vps34-deleted podocytes is due to the absence of a substrate for the Vps34 downstream effector PIKfyve. PIKfyve is a Fyve finger domain containing phosphoinositide 5-kinase that phosphorylates Vps34-generated phosphatidylinositol (PtdIns)3P to produce PtdIns(3,5)P2. PIKfyve perturbation and PtdIns(3,5)P2 reduction have been shown to result in massive membrane vacuolation along the endosomal system. We show here that deletion of PIKfyve in endocytically active proximal tubular cells resulted in the development of large cytoplasmic vacuoles that appear as a result of arrested endocytic traffic progression at a late-endosome stage. In contrast, deletion of PIKfyve in podocytes did not alter significantly the endosomal morphology even in aged, 18-month-old mice. However upon culturing, the PIKfyve-deleted podocytes obtained from the knockout mouse developed massive cytoplasmic vacuoles. Measurement of phosphoinositides using HPLC shows reduction of both PtdIns(3,5)P2 and PtdIns(3)P in PIKfyve deleted podocytes in vitro confirming reduced PIKfyve enzymatic activity following deletion. Using double fluorescent mtnmG mouse we were able to confirm Cre-mediated gene deletion in both podocytes and proximal tubular cells in vivo.

Conclusions: In summary, these data suggest that healthy podocytes have a low level of endocytic flux in vivo.

Funding: NIDDK Support

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Underline represents presenting author.

436A
FR-PO361

Albumin-Induced Podocyte Injury Can Be Endocytosis-Independent
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Background: Endocytosis plays a crucial role in podocytes in nephrotic syndrome, wherein podocytes are exposed to serum levels of albumin. We have previously reported an association between podocyte exposure to albumin (and its associated factors) and podocyturia, cell injury and induction of pro-inflammatory genes. We thus hypothesized that albumin-induced podocyte injury can also be partially endocytosis independent.

Methods: Endocytosis was analyzed by fluorescent microscopy and fluorometry in cultured differentiated podocytes at varying temperatures and times and in the absence or presence of inhibitors of clathrin- and caveole-mediated endocytosis. Cells were analyzed for viability, activation of major kinases (p38, ERK1/2, JNK, MK2), and expression of pro-inflammatory, heat shock, and glucocorticoid-regulated genes.

Results: Endocytosis occurred at 37°C, but not at 4°C, and was attenuated by inhibitors for both clathrin- and caveole-mediated endocytosis. Inhibition of endocytosis, however, did not correlate with reductions in kinase activation or pro-inflammatory gene induction. While albumin exposure resulted in lower endocytosis in murine vs. human podocytes, murine cells activated kinases, induced pro-inflammatory genes and exhibited cell death more than human podocytes.

Conclusions: Inhibition of both clathrin- and caveole-mediated albumin endocytosis did not correlate with activation of kinases and induction of pro-inflammatory genes in podocytes. Moreover, disparate responses were identified in human vs. mouse podocytes with regard to albumin endocytosis, cell injury, kinase activation, and pro-inflammatory gene induction. Taken together, our data suggest that podocytes endocytose albumin in both clathrin- and caveole-mediated manners, albumin-induced podocyte injury can occur in an endocytosis-independent manner.

Funding: NIDDK Support

FR-PO362

Genome-Modeled Pluripotent Stem Cells Reveal a Critical Role for Podocalyxin in Human Podocyte Morphogenesis
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Background: Human pluripotent stem cells (hPSCs) can self-renew extensively and differentiate into diverse tissues. We investigated the potential of hPSCs to differentiate into kidney podocytes, and used CRISPR/Cas9 gene editing to explore the function of podocalyxin, an apical sialomucin altered in glomerular disease states.

Methods: Cas9 nucleases and guide RNAs targeting PODXL were transfected into hPSCs. PODXL+ clones were identified by chromosome and immunoblot analysis. hPSCs were differentiated stepwise with growth factors into kidney progenitor cells (Six2+PAX2+) and subsequently kidney tubular organoids. Podocyte marker expression was investigated by confocal microscopy in unmodified or PODXL- organoids of otherwise identical genetic background.

Results: In kidney organoids, podocyte markers including podocalyxin, WT1, and synaptopodin were strongly expressed in tight clusters of spherical cells, which resembled capillary or early-stage podocytes by electron microscopy. These cells did not react with LTL, but arose in capsule-like termini in LTL LRP+ proximal tubules. Podocalyxin coated the plasma membrane, whereas ZO-1, synaptopodin, and β-catenin co-localized in linear tracks between adjacent cells. PODXL- hPSCs differentiated into similar clusters, which did not express podocalyxin. In PODXL+ clusters, ZO-1, synaptopodin, and β-catenin failed to organize into linear tracks, instead migrating laterally in a diffuse expression pattern. This correlated with a ~ 40 % decrease in intercellular distance between nuclei, compared to unmodified isogenic controls.

Conclusions: hPSCs can differentiate into cells resembling immature podocytes. Podocalyxin is dispensable for podocyte specification, but is required for proper organization of junctional complexes and podocyte spacing. Our findings suggest a functional role for podocalyxin in the establishment of human podocyte architecture. Genome-modified hPSC-podocytes present a new tool for investigating human podocytes, with potential for ‘disease in a dish’ models and therapeutic screens.

Funding: NIDDK Support, Private Foundation Support

FR-PO363

Molecular Targeting of Nephi 1 Signaling: A Therapeutic Approach to Protect Podocyte Injury
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Background: Glomerular injuries that induce podocyte dysfunction are the leading causes of renal malfunction. Podocyte proteins Nephrin and Nephrin are essential components of the glomerular filtration barrier and signaling from these proteins is involved in maintaining podocytes structure and function. Thus understanding the mechanisms that regulate signaling and organization of these proteins are therapeutically valuable.

Methods: This study presents a novel hypothesis that attenuating Nephrin in Nephrin and Nephrin signaling is therapeutically significant in protecting podocytes from injury. Consistent with this hypothesis, using a unique protein transduction approach, we recently demonstrated that inhibiting Nephrin signaling protected podocytes from injury. Since we first reported the structural properties of Nephrin1-PODXL-67, we used recombinant novel molecules or compounds that can specifically bind Nephrin and target its interactions.

Results: Using a novel approach of targeting protein-protein interaction, we identified many potential molecules and to test the proof of principle and the validity of this approach, we evaluated compounds ID (sodiumcitrate) was commercially procured and investigated. Biochemical experiments suggested that addition of ID under in vitro and in vivo conditions significantly increased and stabilized the interaction between Nephrin and ZO-1. As a consequence, induction of glomerular injury by PAN (purnomycinaminonucleoside) did not significantly increase expression of Nephrin or podocyte cell death. Addition of ID to these cells resisted injury induced changes in their actin cytoskeleton. Furthermore, using an in vivo zebrashif model system, we demonstrated that pre-treatment with ID rescued zebrasfish from adriamycin induced toxicity and preserved their renal filtration system.

Conclusions: Collectively, this is the first study that provides compelling evidence that molecular approaches can be used to directly target slit diaphragm proteins to prevent podocyte damage.

Funding: NIDDK Support

FR-PO364

Extracorporeal Mesenchymal Stromal Cell Therapy for Critical Care
Biju Parekkadan, Surgery (Bioengineering), Harvard Medical School, Massachusetts General Hospital, Boston, MA.

Background: Human mesenchymal stromal cells (MSCs) metabolette and secrete anti-inflammatory and regenerative factors that can be of systemic benefit to acute, critical injury. When transplanted MSCs are limited in dose and rapidly cleared by the host when they are prohibited or reduced, we investigated if this therapy for the development of a bioreactor technology to maintain MSC viability at high fidelity and continuously deliver secreted factors into the blood stream in a clinical setting.

Methods: MSCs were integrated into hollow-fiber bioreactor devices whereby the cells, separated by a permeable membrane, can directly and dynamically provide systemic therapy without entering the body. We present a human scale prototype of the technology that has shown sustained cell viability and function throughout cGMP manufacturing in preparation for a Phase I human trial set to begin in 2015.

Results: The presentation will also report encouraging in vivo therapeutic trials in a large animal (canine) model of ischemic acute kidney injury (AKI) where 91% of animals survived compared to 50-60% in control arms. Pharmacological analysis of this bioreactor technology in vivo allowed for an unprecedented look at MSC function during product use and verified potency that is unattainable by conventional intravascular delivery of MSC.

Conclusions: A combined approach to optimize MSC therapy that employs pharmacology principles and cell delivery strategies will be essential to translating this cell therapy product to humans for AKI and other critical organ dysfunction syndromes.

Funding: NIDDK Support, Pharmaceutical Company Support - Senetim Biotechnologies, Inc.

FR-PO365

Extracorporeal Diffusive Clearance of Silicon Nanopore Membranes in a Pulmonary Porous Blood Circuit
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Background: Silicon nanopore membranes designed for hemofiltration (HF-SNMP) have demonstrated increased permeability compared to polymer membranes. Previously, we reported in-vitro data showing a 3-fold improvement in diffusive clearance using SNMP optimized for diffusion (HD-SNMP). Here we test the diffusive clearance of HD-SNMP vs HF-SNMP in an extracorporeal pore model without a blood pump.

Methods: A microelectromechanical systems fabrication technique was used to decrease the SNMP thickness (HD-SNMP 100 µm vs HF-SNMP 400 µm). Polyethylene glycol coated HD-SNMP (n=3) and HF-SNMP (n=3) with sub-10nm pore sizes were tested in a single channel flow circuit (h=1mm). Vascular access was obtained by placing tunneled catheters within the carotid artery and jugular vein of healthy ~50kg pigs. Blood flow was achieved via the arterial-venous pressure differential (35-120ml/min). Dialysate was recirculated in a counter-current fashion (30ml) and flow rates were adjusted to ensure 0 transmembrane pressure. Dialysate creatinine concentration was measured hourly and serum creatinine was measured at time 0 and hours thereafter. The pore size of each SNM was measured before and after blood exposure using hydraulic permeability.

Results: Blood flow was maintained via the arterial-venous pressures differential with <5mmHg pressure drop. The average plasma creatinine concentration was 1.38±0.1mg/dL. The creatinine clearance was 37.2±3.9ml/min/m² (HF-SNMP) vs 126.0±27.1ml/min/m² (HD-SNMP) at 92.5±36.6ml/min. There was no detectable albumin transport into the dialysate and HD-SNMP maintained the mechanical integrity at over 250mmHg in vitro. These pore size changes following blood exposure was 1.4±2.3nm to 1.9±1.2nm for HF-SNMP and HD-SNMP, respectively.

Conclusions: This study demonstrates the successful transport of creatinine in an extracorporeal circuit without a blood pump. We also showed a ~3-fold improvement in diffusive clearance of creatinine using HD-SNMP in a blood circuit.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

437A
FR-PO366
Hemofilter Design Based on Computational Simulations of Pulsatile Flow
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Background: In the US, the ratio of patients with end stage renal disease (ESRD) on dialysis to annual kidney transplants for ESRD is 20:1 (USRDS 2014 Annual Data Report), underscoring the grave need for an artificial kidney alternative. Hypothesis: For the development of a hemofiltration device, computational fluid dynamics (CFD) simulations can predict potentially thrombogenic zones [e.g. low and high wall shear stress (WSS) areas, associated with stasis and shear induced cell damage, respectively] and can be used to refine device design to minimize such areas.

Methods: CFD simulations of pulsatile blood flow through a prototype hemofilter were validated in vitro using MR velocimetry. Hemofilters were implanted in large animals (n=4) for 30 days or until thrombosis and then explanted. Based on the CFD results, a subsequent flow path was devised to minimize predicted thrombogenic regions, and simulations were conducted on the second design.

Results: The in vitro and in silico models showed strong agreement. Pulsatile CFD simulations of the prototype device demonstrated zones of low WSS, and clot formation occurred in two of the four implants at the CFD-predicted sites. Flow simulations of the second-generation design showed reduced areas of low WSS.

Conclusions: Thrombogenic low WSS regions predicted in silico correspond with clot formation in vivo. In addition to predicting areas of thrombogenicity, CFD can be used to guide hemofilter device design to minimize these sites.

FR-PO367
Characterization of Dialyzer Membranes by MALDI-Mass-Spectrometric Imaging Techniques
Joachim Jankowski, Vera Jankowski. Inst of Molecular Cardiovascular Research, Univ Hospital RWTH, Aachen, Germany.

Background: Dialyzer polymer membranes are grossly classified as cellulose-based and synthetically produced membranes. Although cellulose membrane's clearance and mechanical properties qualify it for use in dialyzer membranes, hydroxyl groups of these membranes lead to strong activation of the complement system. Therefore, recent membranes are manufactured from synthetic polymers.

Methods: For physical and chemical characterization of these materials of dialyzer membranes a wide range of analytical methods is available. Over the last few years, MALDI mass-spectrometric analysis with imaging as additional spatial information has developed as a powerful tool for space-resolved analysis, not least because of its mass accuracy and high sensitivity. MALDI imaging techniques combine the potential of mass-spectrometric analysis with imaging as additional spatial information with relevance for biocompatibility of the dialyzer membranes. MALDI imaging enables the visualization of localization and distribution of biomolecules, chemical compounds and other molecules on different surfaces.

Results: In this study, surfaces of polymeric dialyzer membranes, consisting of polysulfone (PS) and polyvinylpyrrolidone (PVP) were investigated, regarding to chemical structure and compound's distribution. According to the manufacturing process laminar and abulmen membrane surfaces are characterized by differences in chemical composition and physical characteristics. MALDI imaging demonstrated that the abluminal membrane surface is more consisting of polysulfone than polyvinylpyrrolidone, the luminal membrane surface displayed more PVP than PS. The addition of PVP as hydrophilic modifier to polysulfone-based membranes increases the biocompatibility of the dialysis membranes. The analysis of polymer distribution is a relevant feature for characterization of dialysis membranes.

Conclusions: In conclusion, MALDI imaging is a powerful technique for polymer membrane analysis, regarding not only detection and identification of polymers but also localization and distribution in membrane surfaces, which has strong impact on the biocompatibility of the dialyzer membranes.

FR-PO368
Effect of Peristasis with Pediatric Catheters
Anna Lorenzin, Francesco Garzotto, Claudio Ronco. Nephrology and International Renal Research Inst Vicenza, St. Bortolo Hospital, Vicenza, Italy.

Background: Thanks to the technological advances of the last years, Continuous Renal Replacement Therapy CRRT machines have been upgraded and equipped with circuits specific for pediatric patients. To date, to treat these patients the most used catheter is the small T-French, however with a neonate this is inadequate for the dimensions. It is not clear if it is possible to use a smaller catheter with adult CRRT machine or a specific pediatric machine is needed. We set up a dedicated circuit to assess the usability of a peristaltic blood pump designed for adults and compare it with a pediatric pump in terms of access pressure. Frequency of pump was performed in vivo test with the pediatric pump and in vitro test with the adult pump.

Methods: A bilumen catheter was implanted in four adult patients with a venous pressure sensor. The device was validated in vitro using MR velocimetry. Hemofilters were implanted in large animals (n=4) for 30 days or until thrombosis and then explanted. Based on the CFD results, a subsequent flow path was devised to minimize predicted thrombogenic regions, and simulations were conducted on the second design.

Results: The in vitro and in silico models showed strong agreement. Pulsatile CFD simulations of the prototype device demonstrated zones of low WSS, and clot formation occurred in two of the four implants at the CFD-predicted sites. Flow simulations of the second-generation design showed reduced areas of low WSS.

Conclusions: Thrombogenic low WSS regions predicted in silico correspond with clot formation in vivo. In addition to predicting areas of thrombogenicity, CFD can be used to guide hemofilter device design to minimize these sites.

FR-PO369
Hemodialysis with CARPEDIEM Machine: An In Vitro Test
Anna Lorenzin, Dario Galaceo, Stefania Areu, Francesco Garzotto, Claudio Ronco. Nephrology and International Renal Research Inst Vicenza, St. Bortolo Hospital, Vicenza, Italy.

Background: Despite the development of continuous renal replacement therapies machines, their employment still remain unsuitable in new born and infants. This gap has been filled thanks to the coming of a specific pediatric dialysis machine CARPEDIEM. To date it is set up only for continuous hemofiltration CVVH: to provide a wider range of applications, specific filters have been conceived to implement a continuous hemodialysis CVVHD. We tested a prototype kit to evaluate its performance in terms of clearance K.

Methods: We performed in vitro test with plasma for the 3 filters HD010 HD020 HD050 (surface 0.1, 0.2, 0.35m²). Fibers were put manually into the housing of CVVH filters. CVVHD in cocurrent configuration: otherwise a longer circuit is required. We set up a dedicate circuit to assess the usability of a peristaltic blood pump designed for adults and compare it with the adult pump in terms of access pressure.

Results: We are presenting the data of the two pumps with 5Fr catheter and 15ml/min flow rate. Analyzing the arterial pressure values, we found that the spikes are more frequent with the CARPEDIEM pump than with the adult one. The min and max value are respectively (-50, -28mmHg) and a mean Dp = 18mmHg with CARPEDIEM pump; (-61, -20mmHg) and a mean Dp = 40mmHg with adult pump (Fig.1).

Conclusions: We can notice that there is an high discrepancy in terms of Dp between the two pumps: high values of Dp lead to an high shear stress. As the shear stress is one of the main causes of hemolysis, it seems that a specific pediatric machine is advisable for neonates that need small catheter. Further investigation have to be perform with blood to confirm our results.
FR-PO370

Removal of Protein-Bound Uremic Toxins: Simulating the Effect of Toxin Displacement versus Increase in Dialyzer Clearance

Vaibhav Maheshwari, Stephan Thijsen, Doris H. Fuertinger, Franz Kappel, Peter Kotanko. Renal Research Inst, NY; Univ of Graz, Austria.

Background: Protein-bound uremic toxins (PBUT) exert numerous deleterious effects. Their removal with standard hemodialysis (HD) is poor. Meyer et al. have modeled the impact of increasing dialysate flow rate and dialyzer mass transfer area coefficient on PBUT removal [JASN, 2004]. Here, we compare those results to a novel approach based on PUBT displacement by infusion of binding competitors [Tao, Blood Purif, 2015].

Methods: We developed a multi-compartment patient model and a dialyzer model depicting spatiotemporal dynamics based on law-of-mass-action kinetics. We chose indoxyl sulfate (IS) as a prototypical PUBT and ibuprofen as the binding competitor. We modeled IS removal during a 4-hr HD (Q_{d}=250 mL/min, Q_{f}=750 mL/h, initial total IS 100 µmol/L, initial free fraction of IS 8%), with IS dialyzer clearances from 150 to 200 mL/min. This was compared to IS removal achieved by ibuprofen infusion (800 µg/200 mL) into the arterial line at 50 mL/hr (IS clearance 150 mL/min).

Results: IS removal during HD with a clearance of 150 mL/min was 438 µmoles (plasma reduction ratio 34%), which conforms to literature data [Niwa, Blood Purif, 2012]. With IS clearance of 200 mL/min, removal improved by 8.7% to 476 µmoles. With ibuprofen infusion (IS clearance back at 150 mL/min), removal improved by 11.2% to 487 µmoles.

Conclusions: Our model yields predictions of IS kinetics that agree with empirical and modeled data [Niwa et al.; Meyer et al.]. Of note, a mere 8.7% improvement in IS removal would require an increase in dialysate flow rate from 800 to 1350 mL/min plus a 70% increase in membrane surface area. The modeled ibuprofen infusion alone yields an 11.7% improvement even absent an increase in dialyzer clearance. The use of binding competitors holds great promise. These results require validation in vivo.

FR-PO372

Membrane versus Peristaltic Blood Pumps for Extracorporeal Therapies: Comparison on Index of Hemolysis

Francesco Garzotto, Sean M. Bagshaw, Claudia Ronco. Nephrology and IRRIV, St. Bortolo H., Italy; Critical Care Medicine, Univ of Alberta Hospital.

Background: Hemolysis during extracorporeal treatments mainly occurs as a consequence of mechanical stress on the blood. Red blood cell deterioration is undetected because it is far from any acute hemolytic threshold but represents a potential harm for patients. A new membrane-piston driven pump has been recently proposed on the S.A.M.(©Spectral Medical Inc, Toronto) device designed for continuous renal replacement therapies (CRRT). Aim of this investigation is to compare the membrane with peristaltic pumps by measuring the Normalized Index of Hemolysis NIH during in vitro testing.

Methods: Three sessions of hemoperfusion with a line inserted in place of a hemofilter were performed both with SAM and Prismaflex (©Baxter International). A single pool of fresh heparinized bovine blood (Heparin 500 UI/L, Hb 122 g/dL, Base Excess 0±5 mmol/L) were split into three aliquots containing 900 mL (Control, SAM, Prismaflex) and circulated for 6 hours/session. Blood:total samples were drawn at baseline, 30 min and every 1 hour. NIH were calculated as median hourly variation of free hemoglobin and used for comparison. Data was compared with two tailed Student’s t-test based on F-Test results.

Results: NIH values of 0.12±0.03 and 0.13±0.09 mg/100L for SAM and Prismaflex respectively are lower than those reported in literature due to the simplified circuit used (no vascular access and filter). Creation of hemoglobin between sam and control, and prisma and control are non-significant fig 1a. Slope of the curves that describe the creation of hemolysis are nearly identical with a slow rate of production of free hemoglobin.

FR-PO371

Membrane Driving Blood Flow for Extracorporeal Therapies

Francesco Garzotto, Sean M. Bagshaw, Anna Lorenzin, Mauro Neri, Claudia Ronco. Nephrology, St. Bortolo H.

Background: From the first application of Continuous Venovenous Hemofiltration CVVH, the blood flow has been driven by a peristaltic pump. Several attractive alternatives, with both advantages and disadvantages, have been proposed for many years. SAM (Spectral Medical Inc.; Toronto, Canada) is a novel instrument, in which the pumping of whole blood and fluids is performed through the use of pistons, chambers and valves. A plastic cartridge blood circuit system fig 1b incorporates all of the pumps, air trap system, pressure monitors and clamps. This circuit is covered on one side by a plastic membrane adhered to the pumping pistons via a drawn vacuum. Aim of the present is to evaluate the new pumping system.

Methods: We set up the machine for CVVH. An 11.5 Fr 20 cm catheter was connected to the lines. We ran the machine for 6 hours in order to characterize the performance of the system. During the first cycle, suction generated by the drawing back of the piston, moves the blood into the arterial-chamber AC. Positive pressure generated by the piston then drives the blood through the circuit. The camshaft design can allow different profiles for Withdrawal and infusion flows. The largest Priming volume measured (both the ACs full), is 98 ml with a stroke volume for each AC of 14ml.

Conclusions: CVVHD with CARPEDIEM seems to be effective for diffusion transport of small molecular weight solutes, according to specific clinical needs. In the light of these findings CARPEDIEM can be a promising alternative to peritoneal dialysis, i.e. in treating electrolyte imbalance with accurate fluid removal. Limitation: handmade filters could induce variability in the results due to disposition and variable number of fibers.

FR-PO375

Comparison of Blood Flow Profile Between a Two-Chamber Piston Pump and a Peristaltic Pump

Stephan Thijssen, Doris H. Fuertinger, Franz Kappel, Peter Kotanko. Renal Research Inst, NY; Univ of Graz, Austria.

Background: Protein-bound uremic toxins (PBUT) exert numerous deleterious effects. Their removal with standard hemodialysis (HD) is poor. Meyer et al. have modeled the impact of increasing dialysate flow rate and dialyzer mass transfer area coefficient on PBUT removal [JASN, 2004]. Here, we compare those results to a novel approach based on PUBT displacement by infusion of binding competitors [Tao, Blood Purif, 2015].

Methods: We developed a multi-compartment patient model and a dialyzer model depicting spatiotemporal dynamics based on law-of-mass-action kinetics. We chose indoxyl sulfate (IS) as a prototypical PUBT and ibuprofen as the binding competitor. We modeled IS removal during a 4-hr HD (Q_{d}=250 mL/min, Q_{f}=750 mL/h, initial total IS 100 µmol/L, initial free fraction of IS 8%), with IS dialyzer clearances from 150 to 200 mL/min. This was compared to IS removal achieved by ibuprofen infusion (800 µg/200 mL) into the arterial line at 50 mL/hr (IS clearance 150 mL/min).

Results: IS removal during HD with a clearance of 150 mL/min was 438 µmoles (plasma reduction ratio 34%), which conforms to literature data [Niwa, Blood Purif, 2012]. With IS clearance of 200 mL/min, removal improved by 8.7% to 476 µmoles. With ibuprofen infusion (IS clearance back at 150 mL/min), removal improved by 11.2% to 487 µmoles.

Conclusions: Our model yields predictions of IS kinetics that agree with empirical and modeled data [Niwa et al.; Meyer et al.]. Of note, a mere 8.7% improvement in IS removal would require an increase in dialysate flow rate from 800 to 1350 mL/min plus a 70% increase in membrane surface area. The modeled ibuprofen infusion alone yields an 11.7% improvement even absent an increase in dialyzer clearance. The use of binding competitors holds great promise. These results require validation in vivo.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America
FR-PO373
Enhanced Molecule Molecule Clearance by a Biomimetic Dialyzer Membrane
Joseph J. Groszek,1 Jin Cheng,1 Charles Blaha,2 Rishi Kant,2 Jaehyun Park,2 Benjamin Chui,3 Ken Goldman,4 Shuvo Roy,2 William Henry Fissell,1
1Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; 2Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA; 3Ben Chai Consulting, Sunnyvale, CA; 4H-Cubed, Inc, Olmstead Falls, OH.

Background: Although polymer dialyzers attain very high small solute clearance rates, polydispers pore sizes limit middle molecule clearance by conventional polymer dialyzers. We hypothesized that a biomimetic membrane with uniform slit pores would enhance middle molecule clearance.

Methods: Thin film silicon membrane samples (surface area 1.4 x 10^4 m^2) with monodisp pore size of 5-8 nanometer pores (“SNM-HD”) were manufactured as previously described, surface-modified with polyethylene glycol and mounted in a custom designed cartridge. Membrane pore size was estimated from hydraulic permeability measurements. Human blood was spiked with PABA and fluorescent-labelled Ficol, a polyanl sucrose globular polysaccharide. Blood flow was set at 100 ml/min and dialysate flow varied between 70 and 140 ml/min. Blood and dialysate concentrations of PABA and Ficol were measured by size-exclusion chromatography. Clearance as a function of dialysate flow rate was extrapolated to estimate Kea as a function of molecular weight.

Results: B2M clearance in high-flux dialyzers is typically 5-8% of the value of urea clearance. PABA clearance was 139 ml/min/m^2. 15.7Angstrom Ficol (same radius as B2M) clearance in the SNM dialyzers was 16.9 ml/min/m^2, 3.5 fold higher than reported B2M clearance in polymer dialyzers.

Conclusions: A biomimetic membrane of uniform slit pores potentially offers much higher middle molecule clearance than conventional polymer dialyzers.

Funding: Other U.S. Government Support

FR-PO374
Anti-Fouling of Silicon Nanopore Membranes Using SLIPS Bas Meusen,1,2 Steven Kim,3 Zohora Iqbal,1 Charles Blaha,2 William Henry Fissell,1 Shuvo Roy.1 1UCSF, 2Univ of Eindhoven; 3Silicon Kidney; 4Vanderbilt Univ.

Background: Silicon Nanopore Membranes (SNM) have been developed for application in an implantable bioartificial kidney. However, SNM are subject to fouling and thrombosis with continuous blood exposure. Thin polymer coatings have been applied to SNM as a strategy to limit cell adhesion and protein adsorption. Slippery Liquid Infused Porous Surface (SLIPS) is a biotriposed “omniphobic” surface coating that has been reported to prevent thrombosis and fouling on arteriovenous shunts. Here we present the application of SLIPS coating to SNM and evaluate protein adsorption in vitro.

Methods: SNM with –10 nm pores were coated with SLIPS and incubated with BSA-FITC (2 mg/ml in PBS) for 24 hours at 37°C. Uncoated (bare) silicon substrates served as controls. Fluorescence microscopy and ellipsometry were used to evaluate the surfaces and water transport through the SNM was tested using established hydraulic permeability assays.

Results: SLIPS strongly reduced BSA-FITC adsorption on SNM compared to bare silicon. Ellipsometry confirmed the presence of SLIPS coating with a thickness of 0.5±0.2mm, which is theoretically thin enough to keep open the pores open in the membrane. However, hydraulic permeability testing revealed no ultrafiltration through the SNM for at least 24 hours and transmembrane pressures of up to 5 psi.

Conclusions: SLIPS is a promising and easy-to-apply protein repellent coating, but its highly omniphobic characteristic prevents ultrafiltration even through pores that are over 5x the coating thickness. For use in the bioartificial kidney, SLIPS has relevant implications as an anti-fouling coating where an ultra-thin blood compatible, but non-filtering surface is desired.

Funding: Other NIH Support - NIBIB

FR-PO375
Measuring Spatial Trends of Single Nephron Filtration with Molecular MRI
Edwin Baldegger1, Jennifer R. Charlton,2 Kevin M. Bennett,1 1U. of Hawaii, Honolulu, HI; 2U. of Virginia, Charlottesville, VA; 3U. of Hawaii at Manoa, Honolulu, HI.

Background: To better develop drugs to treat kidney disease their physiologic mechanisms during development, noninvasive techniques to measure whole kidney function at the level of the single nephron are needed. We investigated the combined use of two MRI contrast agents, cationic ferritin (CF) and Gd-DTPA, to measure local (voxel) macromolecular uptake and glomerular filtration rates of single nephrons over the whole rat kidney with 3D MRI using the isolated, perfused rat kidneys under physiological conditions.

Methods: Krebs-Ringer (KR) bicarbonate solution with 7.5 mg/100mL of Fraction-V BSA and a bubbling infusion of carbonate was perfused into isolated rat kidney. Temp was maintained at 37°C. CF in KR solution (0.071 mg/mL of CF), was infused into the system first. Next, a bolus of 0.25 mmol Gd-DTPA in 10mL of KR solution was infused into the perfusion system. (All rates = 5ml/min) Kidneys were imaged during the perfusion with MRI. Voxel time courses were then fitted to a bi-exponential model.

Results: Glomeruli were distinguished by uptake of CF and a distribution of CF accumulation rates and gd-DTPA elimination rates was visible. (Fig 1a-b) We used the location of the glomeruli in 3D and the time course of CF labeling (Fig 1c-d) to discern spatial trends in uptake rate of CF. Time course structures also mapped well with the different morphological structures in the kidney (Fig 1e).

Conclusions: Our results demonstrate that automated quantification is capable of not only distinguishing between anatomical features of kidneys, but also characterizing the degree of abnormality in diseased tissue.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

440A
Results: the developed contrast agent (µ-Angiofil) turned out appropriate for µCT ex vivo with superior perfusion and contrast-to-noise features. The obtained µCT datasets were of superior quality and allowed clear visualization of the microvasculature and glomeruli.

In kidney, modern high-resolution microCT (SkyScan-1172) provided the whole mouse kidney vasculature in 3D with the spatial resolution of approx. 2 µm. The sample is fixed prior the micro-CT-scan and therefore can be processed for the histological evaluation after the scan. This circumstance brings multiple advantages, including much easier localization of the µCT-findings in the post-scan histological sections.

Conclusions: using µ-Angiofil we obtained 3D-µCT datasets of superior quality, which are sufficient for estimation of relevant kidney morphometry parameters. The developed angiographic approach will substitute the existing golden-standard. Besides classical kidney morphometry, it provides the data on the vasculature through the whole kidney in 3D what makes the technique even more beneficial.

Funding: Government Support - Non-U.S.

FR-PO378
Rising Accuracy of Transcutaneous GFR Measurement Jochen Friedemann,1 Ralf Heinrich,1 Yury Shullevich,1,2 Johannes Pill,1 Daniel Schock-Kusch,1,2 1Mannheim Univ of Applied Sciences, Inst for Process Control and Innovative Energy Conversion, Germany; 2Mannheim Pharma & Diagnostics GmbH, Germany; 2Freudenberg New Technologies SE & Co. KG, Weinheim, Germany.

Background: Transcutaneous measurement of GFR (GFR) is now getting used frequently in animal studies. tGFR allows consecutive GFR measurements in the same clearance, automatically correcting influences like bleaching of skin fluorescence.

Methods: Bolus clearance (GFR was measured in awake Spraque Dawley (SD) rats using the commercially available NIC-Kidney system, immediately followed by a blood sampling based constant infusion clearance (cGFR). GFR was calculated by a one compartment model (GFRexo), GFRnew and cGFR. Also 46 GFR measurements in SD rats were reevaluated by GFRexo.

Results: Results are given in table 1. Mean values of the three methods are comparable with no significant difference. The accuracy (larger STD) of GFRexo is lower compared to GFRnew and cGFR. This finding was verified by the 46 measurements in SD rats (GFRexo: 0.97 ± 0.18 ml/min/100g b.w.; GFRnew: 0.95 ± 0.14 ml/min/100g b.w.).

<table>
<thead>
<tr>
<th>n=11 SD rats</th>
<th>cGFR</th>
<th>GFRexo</th>
<th>GFRnew</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean ± STD</td>
<td>0.94 ± 0.13</td>
<td>1.00 ± 0.18</td>
<td>0.88 ± 0.12</td>
</tr>
<tr>
<td>effect size</td>
<td>0.73</td>
<td>0.55</td>
<td>0.73</td>
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</tbody>
</table>

Conclusions: The results indicate that GFRexo yields data in comparable accuracy as cGFR. For an apriori estimation of the sample size to detect a change in GFR of 10% in the SD rats investigated, the effect size rises from 0.55 (GFRexo) to 0.73 (GFRnew). The required sample sizes in fig. 1. illustrate the strong contribution of GFRexo to the concepts of refining and reduction of animal studies.

Figure 1: Impact of the increased effect size yield with GFRexo compared to GFRcGFR.

FR-PO379
Quantification of the Progressive Fibrosis Development in Mouse Kidney Unilateral Ureteral Obstruction Model Using Fluorescence Lifetime and Second Harmonic Generation Imaging Microscopy

Funding: Government Support - Non-U.S.

Background: Renal fibrosis is considered to be the final common pathway for most forms of chronic kidney disease (CKD) and involves glomerular sclerosis and/or tubulointerstitial fibrosis. There is great interest in identifying renal fibrosis in the early stages of CKD to predict progression. Unilateral ureteral fibrosis (UUO) is a well-characterized model of CKD and renal fibrosis. Kidney injury and fibrosis usually are assessed by Picrosirius Red staining or immunohistochemistry for collagen isoforms.

Methods: The goal of this study is to compare histologic measures of renal fibrosis to Fluorescence Lifetime Imaging (FLIM) and Second Harmonic Generation (SHG) techniques in our deep imaging microscope DIVER.FLIM and SHG allow quantification of collagen in unstained tissue and can be adapted for live animal imaging. Male C57BL/6 mice were subjected to UUO of right kidney. At 7, 14 and 21 days, both kidneys were harvested. The uninjured left kidney was used as a control. Serial sections of both kidneys were analyzed by Picrosirius Red staining or FLIM with SHG.

Results: We performed quantification of Picrosirius Red stained-kidneys using polarized light. This showed progressive increase for the number of positive pixels for fibrosis in the left kidney 9631.9 ± 1626.2, 16167.8 ± 6647.7 and 20511.5 ± 5727.6 compared to 5625.3 ± 770.6, 3909.3 ± 2395.9 and 4493.8 ± 2011.8 in the control kidney respectively. Using the Phasor approach to FLIM, comparisons between the two kidneys show that the auto fluorescence lifetime signature give rise to two well separate phaser clusters. Quantification of ten different fields of view for each kidney at the above time-points for SHG signal confirms Picro-Sirius Red scoring.

Conclusions: Finally, the combined FLIM and SHG images let us establish a criterion for quantitative determination of fibrosis directly from the microscopic images.

Funding: NIDDK Support

FR-PO380
Chemical Imaging: A Novel Approach to Obtaining Label-Free Biochemical Information in Renal Transplant Patients with Recurrent Diabetic Nephropathy

Background: The main treatment for end-stage renal disease is kidney transplantation, which over time undergo chronic rejection including changes in the glomerular, tubulointerstitial and vascular compartments. Also, recurrence of disease in diabetics can mimic transplant glomerulopathy. We have identified biochemical markers using Chemical imaging that were associated with recurrent diabetic nephropathy. Chemical Imaging is an emerging approach to obtain images of the biochemical composition of tissue biopsies in a label-free fashion.

Methods: An initial study focused on identifying patients with no evidence of diabetic nephropathy and patients with advanced diabetic nephropathy in native kidneys. Serial sections were acquired and stained with PAS or imaged using chemical imaging. IR spectra were extracted to identify biomarkers associated with diabetic nephropathy progression. A second study identified transplanted patients who underwent very rapid recurrent diabetic nephropathy and patients with no evidence of diabetic nephropathy.

Results: Biomarkers were identified that were changed in renal structures associated with the progression of diabetic nephropathy, including increased levels of glycation. These biomarkers were found to be increased in the cohort of transplant patients that underwent rapid diabetic nephropathy recurrence. In addition, the early biopsies from the patients that underwent later diabetic nephropathy progression were biochemically different from the non-progressive patients, suggesting that chemical imaging may identify pre-histological biomarkers that will predict outcome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: We have identified a number of biomarkers that are associated with the advancement of diabetic nephropathy and that we can track the early recurrence of diabetic nephropathy in surveillance biopsies. In addition, we have highlighted a 'biochemical signature' that may be predictive of the later progression of diabetic nephropathy recurrence.

Funding: NIDDK Support

FR-PO381

Contrast-Enhanced Ultrasound Characterizes Kidney Lesions with Accuracy Comparable to Contrast-Enhanced CT or MR

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Background: Incidental kidney lesions are often detected on imaging performed for other reasons. Indeterminate lesions are further characterized with a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). These tests have many limitations and are contraindicated in patients with allergies to contrast, metallic hardware and chronic kidney disease (CKD). An accurate alternative study is needed. Contrast-enhanced ultrasound (CEUS) is one potential alternative. CEUS uses microbubbles, non-contrast, gas filled bubbles with lipid or albumin shells, as the contrast agent. We investigated the accuracy of CEUS for malignancy in patients with incidental kidney lesions.

Methods: CEUS was performed on 33 patients. Results were independently interpreted by 2 blinded readers and risk-stratified by the Bonniah classification system. Sensitivity, specificity and predictive values were calculated for lesions with histologic diagnosis as the gold standard. As histology was available for 58 lesions only, we performed secondary analyses using an expanded gold standard definition that included clinical recommendation.

Results: Of the 33 patients, 12 had CKD and 14 had histologic diagnoses. There was 100% inter-reader agreement in the primary analysis (Figure 1A) and 97% agreement in the secondary analysis (Figure 1B). Sensitivities (94-100%), positive (70-93%) and negative predictive (90-100%) values for CEUS were comparable to CT (83-100, 50-67 and 77-100%, respectively) and MRI (81-100, 60-78 and 80-96%, respectively). CEUS specificity (0-56%) was lower than MRI (71-100%).

Figure 1. Diagnostic accuracies based on gold standard of histologic diagnosis (A) and histologic diagnosis or clinical recommendation (B).

Conclusions: CEUS has excellent potential as an alternative diagnostic tool for kidney lesions among patients with CT/MRI contraindications. Further evaluation is needed.

Funding: Other NIH Support - CTSA (Clinical and Translational Science Awards) funding, University of North Carolina at Chapel Hill (UL1TR001111)

FR-PO382

Lead-Free Drape Aided to Xray Detector Significantly Decreased Radiation Scatter During Access Intervention

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Background: Exposure from scattered radiation can be very high during access interventional procedures because of the relatively closer operative position. The purpose of this study is to evaluate whether applying a lead-free, sterile, disposable drape can decrease scatter radiation exposure during access intervention.

Methods: An upper extremity phantom was placed on the angiography table to mimic real-time patient’s upper extremity access. Using this model, measurement of scatter radiation was made every one foot away from the phantom before and after applying the drape using a collimated and low-output condition. The scattered radiation dose was measured three times in each spot. And the measurement was taken at 0.9m (waist level) and 1.5m (neck level) as well as neck level (1.5m). Statistical significance was compared using t-test.

Results: Scatter radiation was attenuated throughout the measurement field when the drape was applied. The degree of scatter radiation reduction was distance and height dependent. Scatter radiation decreased 61.6% at the waist level and 81% at the neck level (P<0.05).

Conclusions: The application of this sterile, lead-free drape can significantly reduce scatter radiation in the procedure room. This novel technique can be used to reduce exposure radiation dose to the operators.

FR-PO383

Pathogenesis of Brain Damages in Chronic Kidney Disease and Clues for Early Diagnosis

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Background: There is globally increased prevalence of chronic kidney disease (CKD). Vigorous efforts have been devoted to ameliorate renal deterioration and prevent cardiovascular morbidity/mortality. However, patients also have enough incubation time to develop deranged cognition that severely disturbs quality of life. Neurological pathology/damages may occur in CKD patients long before any overt clinical symptoms can be noticed. Given the similar embryological development as brain, the eyes can be the windows to pinpoint the initial brain pathology. Herein we employed proteomics, animal model and behavior analysis to investigate the possible overlapping biological signatures in the eyes and brain of CKD.

Methods: Subtotal nephrectomized rats were established as CKD model. Open field and object recognition tests were adopted as neurological screen. Brain and eyes were harvested for proteomic analysis. Western blotting and immunohistochemistry were used to confirm and localize the identified proteins. To elucidate the global protein changes in the brain and eye of SNX rats, the data was analyzed by Ingenuity Pathways Analysis (Ingenuity Systems, http://www.ingenuity.com/).

Results: The eye pathology appeared in parallel with the brain damages. The significantly dysregulated proteins in the SNX rat eyes were spectrin beta 3, 26S proteasome non-ATPase regulatory subunit 2, 6-phosphofructokinase, dihydroyirimidinase-related protein, and the heat shock 70, 90a, and chaperonin containing Tep1, subunit 6a (Zeta 1).

All these proteins have been linked to the neuro-degeneration in humans.

Conclusions: There were overlapping eye and brain biological networks. Our results might pave the way for early diagnosis of CKD-neurological pathology via eye examinations, and targeted interventions towards the neurological diseases.

Funding: Government Support - Non-U.S.

FR-PO384

Metabolomic Profiling of Chronic Kidney Disease Using a Local Exhaustive Exploration Approach

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Background: 1H Nuclear Magnetic Resonance (NMR)-based metabolomic profiling is useful for the diagnosis of CKD stages. Due to the high dimension of NMR spectra datasets and the complex mixture of metabolites in biological samples, the identification of discriminant biomarkers of a disease is challenging. None of the widely used chemometric methods in NMR metabolomics performs local exhaustive exploration of the data.

Methods: We developed a descriptive and easily understandable approach searching for discriminant local phenomena. We selected the most discriminant features from the dataset based on both the normalized mutual information and the chi-2 test. We studied the local distribution of the patient subgroups with identical degree of CKD severity on each feature, using the proprietary algorithm HyperCube, which searches for local overdensities of an explanatory variable modality, and identifies a combination of variables as well as their value ranges that give the optimal prediction of the outcome of interest. Further, logistic regression on these discriminant features was used to build a predictive model of the CKD severity stage.

Results: We explored a complex dataset that includes 1H-NMR urinary metabolomics, clinical, demographic, clinical chemistry and histo-pathological variables, in a cohort of 110 individuals with a CKD. The HyperCube algorithm combined with logistic regression supports the discriminant metabolites obtained with standard Orthogonal Projection to Latent Structure Discriminant Analysis (O-PLS-DA) model. Unlike the O-PLS-DA model, HyperCube algorithm provided clues into the distribution of the CKD severity subgroups.
with respect to spectral data. The built predictive model identifies metabolomics profiles containing metabolic pathways such as citrate/citrate, dimethylsulfoxide, trigonelline and glycine. The majority of the predictive variables were urinary metabolites identified by 1H-NMR, indicating that CKD significantly impacts the urinary metabolism.

**Conclusions:** Our findings indicate that HyperCube is a valuable analytical method for the description of CKD severity phenotypes.

**FR-PO385**  
**RNA-seq Profiling in Unip nephrectomized Rats**  
Jaee Woook Lee, Mark A. Knepper. NHILB, NIH, Bethesda, MD.

**Background:** Renal hypertrophy occurs as a compensatory response to reduction in nephron mass. To identify early gene expression changes in renal hypertrophy, we profiled whole-kidney transcriptome in the contralateral kidney of unip nephrectomized rats using RNA-seq.

**Methods:** 5-week-old male Sprague-Dawley rats received right uninephrectomy (UNx; n=4 at each time point) or sham surgery (S, n=4 at each time point). Rats were sacrificed at 24, 48, and 72 hours after surgery. 1.5 µg of total RNA from the left kidney was used to make cDNA libraries for Illumina sequencing. Reads were mapped to Ensembl genes and 103 downregulated transcripts were identified in UNx. Among upregulated transcripts were cell cycle genes including centromere proteins (Cenpa, Cenpf, and Cenpc); MMC helicase subunits (Mmc3, Mmc5, and Mmc8); cyclins (CcnA, CcnA, Ccna, and Ccna); cyclin-dependent kinase (Cdk1); and polo-like kinase (Plk1). Among downregulated transcripts at 48 h were transcription factors (Jun, Hmz2, Klf15, Foxa5, Zfp36, Zfp354a, Zbtb16, and Zic3). At 72 h, 769 transcripts were upregulated and 704 downregulated in UNx. Upregulated transcripts included Cgfl, Rgs1, and Tsc22d2, which may trigger this response. The urine and plasma samples were collected at the time of renal biopsy from 50 patients at Imperial College Renal & Transplant Centre, London, UK and compared with healthy volunteers. All samples were measured by FTIR spectrometer and analysed by the established method. The biochemistry results such as urine protein/creatinine ratio (uPCR), Scr and renal histopathology were collected.

**Results:** Total RNA yields did not differ significantly between UNx and sham kidneys. Each library had 35-42 million reads and more than 80% of reads were uniquely aligned. At 24 h, 45 transcripts were upregulated and 72 downregulated in UNx. Upregulated transcripts included connective tissue growth factor (Ctgf), regulator of cell cycle (Rgcg), serum/glucocorticoid-regulated kinase (Skg1), glucocorticoid-induced leucine zipper protein (Tic22d3), a zinc finger transcription factor (Zbtb16), and genes related to steroid biosynthesis (e.g. Insg1). At 48 h, 183 transcripts were upregulated and 103 downregulated in UNx. At 72 h, 769 transcripts were upregulated and 704 downregulated in UNx. Upregulated transcripts included Cgfl, Skg1, Zbtb16, and cyclins (CcnB1, CcnA2, and CcnB1). Interestingly, Cgfl, Skg1, Zbtb16, and Tic22d3 showed a triplication response, upregulated at 24 h and 72 h and downregulated at 48 h, consistent with an undamaged control sample. The urine and plasma samples were collected at the time of renal biopsy from 50 patients at Imperial College Renal & Transplant Centre, London, UK and compared with healthy volunteers. All samples were measured by FTIR spectrometer and analysed by the established method. The biochemistry results such as urine protein/creatinine ratio (uPCR), Scr and renal histopathology were collected.

**Results:** In comparison with healthy volunteers, patients with GN, diabetic nephropathy (DN), membranous nephropathy and FSGS exhibited significantly higher levels of the urine 1545 cm⁻¹ marker. Furthermore, this urine spectral marker correlated with the degree of interstitial fibrosis, tubular atrophy and Scr (p<0.05). There was significant elevation of the plasma 1545 cm⁻¹ marker in all the disease groups compared with healthy volunteers.

**Conclusions:** Our results show the use of the specific urine and plasma FTIR biomarkers will be a novel approach to investigate progressive kidney diseases, including GN and DN, without chemical manipulation of samples.

**Funding:** Private Foundation Support

**FR-PO387**  
**Omics Investigation of Urine Samples with and without Addition of a Protease Inhibitor**  
Claire Boulanger, Ilse M. Roed, Petra Züriég, Manuja Kaluarachchi, Elaine Holmes, Franz S. Schaefer, John C. Lindon, Jack F. Wetzels, Jeroen Deegens. Metabolomers Ltd, London, United Kingdom; Dep of Nephrology, RadboudUMC, Nijmegen, Netherlands; Mosaïques Diagnostics GmbH, Hannover, Germany; CSM, Dep of Surgery & Cancer, Imperial College London, London, United Kingdom; Dep of Nephrology, Univ of Heidelberg, Heidelberg, Germany.

**Background:** Urine is an ideal biofluid for biomarker discovery. To conserve the protein profile integrity, samples are stored with a protease inhibitor (PI). It is unknown whether the PI alters the metabolomic and proteome profiles. This study aimed to test the influence of the PI on metabolomic and proteomic analysis of urine samples.

**Methods:** We collected 10 urine samples from normal controls (NC, n=4) and membranous nephropathy patients (MN; n=6) and the samples were aliquoted. A PI (mini complete, Roche) was added to an aliquot of each sample. Urine samples were stored at -80°C. For metabolomics, samples were analyzed by 1H NMR spectroscopy and HILIC-UPLC-MS. Multivariate analysis (MVA) was used to elucidate any PI effect in normal urine and proteinuria. For peptidomics, capillary electrophoresis-coupled mass spectrometry was used to profile the low molecular weight proteome in urine.

**Results:** Unsupervised MVA of urine metabolic profiles showed clear discrimination between NC-PI, NC+PI, MN-PI and MN+PI. Supervised MVA of PI+ and PI- samples revealed subtle changes in metabolite levels and the presence of intense signals between 3.63 to 3.91 ppm in the PI+ samples, obscuring endogenous metabolite peaks. Unsupervised MVA of HILIC-UPLC-MS data showed discrimination between MN-PI and NC-PI. Supervised MVA of PI+ and PI- samples showed no detectable difference between the two sample types. For peptidomics, MVA between PI+ and PI- resulted in no statistically significant peptide differences. Further validation with a proteome classifier for CKD (CKD273) showed no statistical significant difference between samples with and without PI.

**Conclusions:** The PI addition did not affect the distinction between MN and NC in the metabolome and proteome analysis. However, PI may affect the analysis of metabolic subcategories using UMR. Therefore, samples with PI can be used, but with caution.

**Funding:** Other NIH Support - The research leading to these results has received funding from the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 305608 (EURenOmics).

**FR-PO388**  
**The Application of Potential Label-Free Mid-Infrared Biomarkers in Patients with Biopsy-Proven Kidney Diseases**  
Met-Ching Yu, Peter R. Rich, Vinod Sathyananarayana Dibbur, Jennifer Smith, Frederick W.K. Tam. PaeDiatric Nephrology, LingKou Chang Gung Medical Centre, Taiwan; ‘Imperial College Kidney & Transplant Centre, Hammershmit Hospital, United Kingdom; ‘Structural and Molecular Biology, Univ College London; ‘UCL Centre for Nephrology, Univ College London, Royal Free Hospital.

**Background:** We have previously discovered novel spectral markers, the urinary 1545 cm⁻¹ & plasma 1460 cm⁻¹ peaks, indicating proportion of experimental GN using Fourier transform infrared spectroscopy (FTIR) (2013 & 2014 ASN). In this study, the aims were to investigate these spectral markers in patients with different biopsy-proven kidney diseases, and the correlations between the spectral markers with clinical features.

**Methods:** The urine and plasma samples were collected at the time of renal biopsy from 50 patients at Imperial College Renal & Transplant Centre, London, UK and compared with healthy volunteers. All samples were measured by FTIR spectrometer and analysed by the established method. The biochemistry results such as urine protein/creatinine ratio (uPCR), Scr and renal histopathology were collected.

**Results:** In comparison with healthy volunteers, patients with GN, diabetic nephropathy (DN), membranous nephropathy and FSGS exhibited significantly higher levels of the urine 1545 cm⁻¹ marker. Furthermore, this urine spectral marker correlated with the degree of interstitial fibrosis, tubular atrophy and Scr (p<0.05). There was significant elevation of the plasma 1460 cm⁻¹ marker in all the disease groups compared with healthy volunteers.

**Conclusions:** Our findings indicate that HyperCube is a valuable analytical method for the description of CKD severity phenotypes.

**FR-PO389**  
**CNVkit – Software Tools for Analyzing Genomic Structural Variants**  
David Fasel, Miguel Verbitsky, Simone Sanna-Cherchi. Medicine, Columbia Univ Medical Center, New York, NY.

**Background:** Copy number variations (CNVs) are increasingly recognized as genetic susceptibility factors for kidney disease. Determining whether CNVs are pathogenic or associated with a specific phenotype is challenging and few tools exist to aid in this process. Here we describe new software tools that provide semiautomated and flexible annotation and interpretation of CNVs, including array CGH, DNA SNP microarrays, and NGS, and to perform joint analyses. It was also used to identify copy number variant regions by using a sliding window approach to detect regions or genes that are enriched for deletions or duplications.

**Results:** CNVkit was recently used as a key component of a study (Verbitsky, JCI 2015), which compared CNVs in 419 children with chronic kidney disease against those found in 21,575 controls, and against predefined coordinates of known genomic imbalances. The software was used to homogenize results and output from different detection platforms, including array CGH, DNA SNP microarrays, and NGS, and to perform joint analyses. It was also used to identify copy number variant regions by using a sliding window approach to detect regions or genes that are enriched for deletions or duplications.

**Conclusions:** Structural variants are major susceptibility factors to congenital kidney malformations and pediatric kidney disease, and should be considered when investigating the cause of genetic disorders. CNVkit provides freely available and easy-to-use tools to help CNV annotation and interpretation.

**Funding:** NIDDK Support, Private Foundation Support
FR-PO398
Quantifying Uropathogenic Bacteria Infection in 3D  Neal A. Paragana,1 Alexander Klose,a,2 1Medicine, Univ of Washington, Seattle, WA; 2In Vivo Analytics, Inc, New York, NY.

Background: Urogenital tract infection is a disease that annually affects more than 250 million people worldwide; however, the number of antibiotic resistant strains have been increasing while newly validated antibiotics have been lagging behind. We have developed a method to monitor and quantify a uropathogenic bacterial infection with multispectral bioluminescence tomography (BLT) of a novel bioluminescent uropathogenic E. coli (UPEC-lux).

Methods: We modeled pyelonephritis by transurethral injection of UPEC-lux. First, we acquired bioluminescence images with a bioluminescent optical imaging at four different spectral windows centered at 575, 655, 695 nm and with bandwidth of 50 nm. The multi-orientation images were acquired using a mirror gantry for simultaneous imaging of the dorsal and ventral view. The animal was placed in a fixed position into a novel body shape conforming animal mold, placed onto the mirror gantry and spectral images were acquired. In vivo bacterial quantification, a novel calibration device using tissue mimetic material was used. The light intensity imaging data became input to a novel BLT reconstruction algorithm based on an expectation-maximization (EM) method and the simplified spherical harmonics (SPH) equations for modeling in vivo light propagation. Post reconstruction, we calculated the total photon emission density of a volume of interest (VOI). We then calculated the in vivo organ bacterial load by registering it to a novel organ probability map.

Results: The EM method reconstructed the 3D photon emission density of the UPEC-lux and mapped the signal to a novel organ probability map. We analyzed these UPEC-lux in a model of pyelonephritis and we were able to determine the bacterial load in the kidney by BLT which correlated to CFUs from serial dilution of kidney homogenate (Pearson correlation coefficient R2=0.92). For the first time, we could demonstrate the feasibility of determining the bacterial burden in the kidneys.

Conclusions: The ability to monitor bioluminescent signal non-invasively will be a powerful tool to understand the pathophysiology of urinary tract infections and a new method to test novel antibiotics.

Funding: NIDDK Support

FR-PO390
Public Engagement of Kidney Related Health Information on the Internet Samir Sulaiman, Joseph A. Vassalotti, Vijay Lapsia. Medicine, Icahn School of Medicine, New York, NY.

Background: The National Kidney Disease Education Program (NKDEP), a part of the National Institutes of Health (NIH) provides an authoritative, up-to-date and trusted consumer health information resource for patients with kidney disease. We hypothesized that the US government (GOV) supported websites would have the highest consumer engagement of kidney related health information on the internet.

Methods: We used traffic rank based on publicly available data obtained from alexa. We modeled pyelonephritis in the genitourinary disorders group. The NKDEP had fewer unique US visitors (59,408) compared to Davita. We hypothesized that the US government (GOV) supported websites would have the highest consumer engagement of kidney related health information on the website.

Results: In the general health category, the NIH website ranked at the top; however, the NIH website was the only kidney related website. Cancer was the only disease category with more than 1 website in the top 25 (7 total). The NKDEP ranked 8th in the genitourinary disorders group. The NKDEP had fewer unique US visitors (59,408) compared to Davita. We modeled pyelonephritis by transurethral injection of UPEC-lux. First, we acquired bioluminescence images with a bioluminescent optical imaging at four different spectral windows centered at 575, 655, 695 nm and with bandwidth of 50 nm. The multi-orientation images were acquired using a mirror gantry for simultaneous imaging of the dorsal and ventral view. The animal was placed in a fixed position into a novel body shape conforming animal mold, placed onto the mirror gantry and spectral images were acquired. In vivo bacterial quantification, a novel calibration device using tissue mimetic material was used. The light intensity imaging data became input to a novel BLT reconstruction algorithm based on an expectation-maximization (EM) method and the simplified spherical harmonics (SPH) equations for modeling in vivo light propagation. Post reconstruction, we calculated the total photon emission density of a volume of interest (VOI). We then calculated the in vivo organ bacterial load by registering it to a novel organ probability map.

Results: The EM method reconstructed the 3D photon emission density of the UPEC-lux and mapped the signal to a novel organ probability map. We analyzed these UPEC-lux in a model of pyelonephritis and we were able to determine the bacterial load in the kidney by BLT which correlated to CFUs from serial dilution of kidney homogenate (Pearson correlation coefficient R2=0.92). For the first time, we could demonstrate the feasibility of determining the bacterial burden in the kidneys.

Conclusions: The ability to monitor bioluminescent signal non-invasively will be a powerful tool to understand the pathophysiology of urinary tract infections and a new method to test novel antibiotics.

Funding: NIDDK Support

FR-PO391
Media Awareness and Reporting of Dialysis Disruptions and Death from Natural Disasters in the United States Samir Sulaiman, Lindsay E. Jebult, Vijay Lapsia. Medicine, Icahn School of Medicine, New York, NY.

Background: Patients receiving in-center hemodialysis are particularly vulnerable during and after disasters. Evidence of morbidity/mortality from disruption to dialysis in a disaster is limited and is so far based on statistical inference. We investigated media awareness and reporting of dialysis disruptions and death during natural disasters in the US.

Methods: We identified all major disaster declarations by the US Federal Emergency Management Agency. Disasters since 2000, excluding man-made and wildfires, with at least 1 known death were included. We then conducted a systematic Google News search to identify articles within 30 days of each disaster in the electronic mass media (media).

Results: Of 887 natural disasters from 2000-2015, 120 had at least 1 reported death (total 4,383 deaths). Of 19 hurricanes incidents, 13 articles referred to dialysis, reporting 7 dialysis disruptions, 4 dialysis deaths and 12 instances of potential disruptions to dialysis. Only 1 of the 61 deaths reported during 3 winter storms was dialysis related, with 2 instances of dialysis disruptions and 3 instances with potential for dialysis disruption. Tornadoes, which occurred most often and resulted in the second highest mortality had no coverage in the media during its aftermath.

Conclusions: Based on media reports, hurricanes and winter storms are major contributors of treatment disruption and mortality in patients on dialysis. Media reports can help identify the magnitude of disruption to dialysis operations as well as deaths.

FR-PO392
A Comparison of Physician Reporting versus Computer Algorithms for CMS Data Reporting on Form CMS-2728 Mohammed Said Malas,1,2 Ranjani N. Moothi,1 Jon D. Duke,2 Sharon M. Moe,1 1IU, Indianapolis, IN; 2RI, Indianapolis, IN.

Background: The CMS-2728 form (ESRD Medical Evidence Report) assesses 23 comorbidities chosen to reflect poor outcomes and increased mortality risk. Previous studies have questioned the validity of physician data entry on forms CMS-2728 and the relationship to hard outcomes. We hypothesize that reporting of comorbidities by a computer algorithm identifies more comorbidities and therefore is superior to physicians’ completion of the forms.

Methods: We collected data from CMS-2728 forms for all 296 patients who had included an ESRD diagnosis and received chronic dialysis between 2005 and 2014 at Indiana University outpatient dialysis centers. We analyzed patients’ data from electronic records systems that collated information from multiple sources. Previously utilized computer algorithms or natural language processing was used to extract data on 10 comorbidities (Table) for a period of up to 10 years prior to ESRD incidence. These algorithms incorporate billing codes, prescriptions, and other elements that are relevant to each comorbidity. We compared the presence of these comorbidities on the forms to the determined presence according to the algorithms.

Results: The computer algorithms had higher reporting of comorbidities compared to physician completion of the forms (Table). This remained true when decreasing the data span to one year and using only single health center data sources.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Deaths</th>
<th>Articles with dialysis disruptions</th>
<th>Instances of dialysis death</th>
<th>Instances of dialysis disruptions</th>
<th>Potential Dialysis Disruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurricanes</td>
<td>19</td>
<td>2,702</td>
<td>13</td>
<td>4</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Tornadoes</td>
<td>84</td>
<td>1,454</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Earthquakes</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Floods</td>
<td>11</td>
<td>162</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
</tr>
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<td>Winter Storms</td>
<td>3</td>
<td>61</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>4,383</td>
<td>18</td>
<td>5</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

*Estimates as of 05/15/2015
NA: Not available

Conclusions: In terms of consumer engagement, the kidney specific NIH website - NKDEP, as well as the non-profit kidney.org supported by the National Kidney Foundation were out performed by Davita.com, a publicly listed for-profit company by an unexpectedly wide margin.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO393
Kidney Dashboard: An Integrated Support Tool for Clinical Care and Research Involving Kidney Patients
Jamie S. Hirsch, 1, 2 Hojat Salmasian, 2 Amy Y. Chan, 3 David Vawdrey, 1 Matthew Fred, 3 Krzysztof Kiryluk, 1 1 Div of Nephrology, Dept of Medicine, Columbia Univ, New York, NY; 2 Dept of Biomedical Informatics, Columbia Univ, New York, NY; 3 NewYork-Presbyterian Hospital, New York, NY.

Background: Large amounts of data are contained in electronic health records (EHR), and retrieval of relevant information for nephrology patients is cognitively complex and time-consuming. This results in inefficiencies, missed opportunities to improve care, and difficulty adhering to complex clinical guidelines. We developed a Kidney Dashboard, an integrated tool that gathers and analyzes information to facilitate the care and research of kidney patients.

Methods: Relevant clinical data were catalogued and categorized, including visit history, billing data, vital signs, labs, imaging, pathology, and medications. We automated generation of derived data, such as estimation and trend of eGFR, proteinuria, and automated CKD-staging. We implemented a comprehensive rule-based alert system based on KDIGO guidelines to provide real-time clinical decision support.

Results: The Dashboard was created within the clinical information system at NewYork-Presbyterian Hospital, incorporating inpatient and outpatient data from multiple sources. It uses a tile layout, where each tile represents a relevant section of data that matches clinician workflow, e.g., renal function, anemia, bone and mineral metabolism, glomerulonephritis, etc. Repeat eGFR and proteinuria data are presented as interactive timelines. The Kidney Dashboard aims to improve care and facilitate research by consolidating all relevant EHR data at the point-of-care and generating phenotypic decision support and creates a portable phenotypic patient profile for genetic and epidemiologic research in kidney disease.

Conclusions: The Kidney Dashboard aims to improve care and facilitate research by consolidating all relevant EHR data at the point-of-care and generating phenotypic profiles of kidney patients. This project promotes precision nephrology, exemplifying the new generation of “smart” EHR tools. Following its public release, effectiveness of the Dashboard will be studied in focus groups and by time-motion studies and audit log analyses. The improvement in adherence to KDIGO guidelines will be tested prospectively.

FR-PO394
Forecasting a Renal Prognosis of IgA Nephropathy Using Machine Learning: Validation Study
Haejoong Lee, 1 Junhyung Noh, 1 Hyosang Kim, 1 Won Seok Yang, 1 Yong Su Kim, 1 Dong Ki Kim. 1 Internal Medicine, Seoul National Univ Hospital; 2 Computer Science and Engineering, Seoul National Univ College of Engineering; 3 Internal Medicine, Asan Medical Center.

Background: We aimed to develop and validate individual outcome prediction models in IgAN patients using machine learning.

Methods: We included adult IgAN patients from Seoul National University Hospital (SNUH, n = 1,540) and Asan Medical Center (AMC, n = 1,044) at the time of renal biopsy. They were divided into development (followed up >10 years) and prediction (follow up <10 years) sets, respectively. The outcome was 10-year renal survival (10YRS) probability. We developed predictive models from SNUH test set by using logistic regression (LR) with Lasso method, a classification and regression tree (CART), and neural network (NN) using 16 clinico-pathologic variables. We also used bagging, random forest (RF) and boosting for ensemble learning. Finally, those models were validated internally in SNUH prediction set and externally in AMC development and prediction sets.

Results: Considering missing data, 1,514 and 847 patients were included from SNUH and AMC cohorts. In the LR model, eGFR, hemoglobin, proportions of GS and SS, interstitial fibrosis (IF) were selected as predictors for 10YRS. The CART model, eGFR 53.3 ml/min/1.73m2 was proved to be a watershed for 10YRS, followed by proportion of GS and SS, IF, hemoglobin and proteinuria, sequentially. In addition, the ensemble learners showed good performance (accuracies of bagging, 0.868; RF, 0.874; boosting, 0.882). These individual learners were validated internally with good performance (sensitivities of LR, 0.855; CART, 0.921; NN, 0.952; bagging, 0.857; RF, 0.921; boosting, 0.921). And finally, we proved the robustness of those models from external validation. Good performances of both development (sensitivities of LR, 0.847; CART, 0.867; NN, 0.855; bagging, 0.852; RF, 0.872; boosting, 0.851) and prediction sets (sensitivities of LR, 0.980; CART, 0.929; NN, 0.941; bagging, 0.882; RF, 0.902; boosting, 0.922) were showed.

Conclusions: We developed robustness of prediction models using machine learning for the individual’s likelihood of 10YRS in IgAN with both internal and external validation.

FR-PO395
Quantifying the Gender Reimbursement Gap in Nephrology
Sadeen Ali, Xiangming Fan, Pankaj Jawa, Tejas P. Desai. Nephrology, East Carolina Univ; Greenville, NC.

Background: 2015 Medscape Compensation Report suggests that female providers earn less than male providers but the sample size was 1695; only 1% Nephrologists. To analyze the financial disparities, we compared total Medicare reimbursements paid to males & females.

Methods: We obtained reimbursement data from 2014 Medicare Provider Utilization & Payment Data Physician Public Use File. We consolidated all reimbursements by NPI number & categorized them by specialty & sex. We adjusted reimbursement differentials against number of Medicare beneficiaries seen & services provided. Linear regression models were used to compare reimbursements.

Results: We analyzed 246,996 providers in 13 specialties; 5% were Nephrologists. Female Nephrologists were reimbursed less $41,776.96 (unadjusted); the 6th worst female-reimbursement differential. In the adjusted analysis, female Nephrologists had the worst reimbursement differential: less $17,971.66.

Female Reimbursement Deficits ($). Lower & Upper Refer To 95% Confidence Interval Bounds.

Conclusions: When adjusted for the number of beneficiaries seen & services provided, female Nephrologists endure the largest reimbursement gap by sex in any specialty. Steps should be considered to close his gap.

FR-PO396
Protein Engineering for Renal Delivery of Molecular Therapies
Pan Liu, Jing Jin. Dept of Medicine-Nephrology/Hypertension, The Feinberg School of Medicine, Chicago, IL.

Background: Targeted delivery of therapeutic enzymes to the kidney is desirable for treatment of renal diseases and beyond. Previously, approaches that exploit the renal excretion of low-molecular weight proteins (LMWP) have been attempted. However, these carriers can only deliver chemical compounds, and their efficiency is further hampered by in vivo clearance. In order to deliver enzyme cargos, we designed carrier proteins for specific and long-lasting renal delivery. We engineered a fusion protein comprised of a kidney-targeting polybasic tag (PBT) and an Fc segment for extended stability.

Methods: PBT-Fc and Fc-only control were produced as recombinant proteins. We used in vitro parameters as an ULMWP control for alternative means of renal targeting through excretion. The probes were then separately labeled with a radionuclide 111In-Technetium (**In-Tc) tracer. Following i.v. injection of the probes to rats, we performed SPECT in whole body scanning. Radiograms were obtained in a time series for up to 1 hour. In parallel, we performed histology studies of kidney sections to determine the sub-anatomical patterns of the injected probes.

Results: Prominent and sustained kidney localization of **In-PBT-Fc (>95%) was observed by SPECT, a pattern in contrast to that of the **In-Fc control that was mainly in blood circulation during the course of observation (only <5% is in the kidney). **In-Tc-
Duramycin reached the kidney quickly and then followed through urinary excretion to the bladder in less than 20 minutes, leaving only 5% remaining in the kidney. The imaging results were consistent with IHC findings from mouse kidney following probe injections, which shows the PBT-Fc, but not FC-alone, binding the glomeruli and tubule basement membrane shortly after injection. PBT-Fc sustained in the kidney for at least 10 days.

Conclusions: Our engineered PBT-Fc carrier exclusively targets kidney through binding to the glomeruli and tubule basement membrane. This recombinant probe also achieves long-lasting kidney retention (days as compared to minutes for LMWP), yet another desirable property for targeted therapeutic delivery. This vehicle potentially be useful for delivery of molecular therapies, particularly enzyme proteins, to the kidney.

FR-PO397

Dynamic Culture on an Orbital Shaker Alters the Phenotype of Primary Human Renal Tubular Epithelial Cells
Nicholas J. Ferrell, Jin Cheng, Siemng Miao, William Henry Fissell,1 Nephrology, Vanderbilt Univ Medical Center, Nashville, TN; 2Biomedical Engineering, Vanderbilt Univ, Nashville, TN.

Background: Primary cells cultured in vitro gradually lose features characteristic to the in vivo cell type, variously termed “senescence” or “culture stress.” Culture conditions that help maintain cell-specific phenotype are advantageous for cell biology and tissue engineering. Here we evaluated the phenotype of primary renal tubular epithelial cells after applying apical fluid shear stress using an orbital shaker.

Methods: Human renal tubular epithelial cells were isolated from donor kidneys not suitable for transplant. Cells were cultured on Transwell inserts under static conditions or on an orbital shaker at a frequency producing fluid shear stresses of 2 dyn/cm². Transphesitapillary resistance was measured daily. After 2 weeks in culture, cell density was analyzed by counting DAPI stained nuclei, and expression of tubule-specific markers was measured by PCR and western blotting.

Results: Dynamic culture significantly increased steady state transphesitapillary resistance from 344±31 to 544±32 Ω·cm² (p<0.001) and resulted in a 21.5±2.1% (p<0.001) increase in cell density. Gene expression of tubule epithelial cell markers (GTG1, COL4A1, COL4A2, NHE3, and NAPP2) increased with fold changes in expression of 4.3 ± 0.4, 3.1 ± 0.2, 2.1 ± 0.4, and 1.9 ± 0.2, respectively. Cells grown under shear also showed increased protein expression of gamma-glutamyl transpeptidase.

Conclusions: Primary renal tubular epithelial cells grown on an orbital shaker with physiological levels of fluid shear stress appear to express proximal tubule markers more than cells grown in static conditions. This may be due to increased nutrient delivery and waste removal with improved mixing at the apical brush border, or due to specific gene regulation related to mechanotransduction. Further mechanistic insight may allow investigators to develop improved in vitro culture systems for cell biology and tissue engineering and more accurate in vitro models of disease.

Funding: NIDDK Support

FR-PO398

CRISPR/Cas9-Mediated Site-Specific Mutation in Rat Angiomotin Gene via Direct Injection of One-Cell Embryos
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Background: Genetically modified animals represent a crucial tool for understanding gene function in development and disease. The recently developed CRISPR/Cas9 system is an efficient gene-targeting technology to generate genetically modified animals. We have performed exome sequencing in a Singapore Chinese family with X-linked recessive membranous nephropathy associated with Fanconi syndrome and anti-tubular basement antibodies, and identified AMOT, coding for angiomotin, as a novel candidate gene with a putative disease-causing mutation p.S50G in the N-terminal of the p130-AMOT isoform. Preliminary work confirmed the expression of angiomotin in renal tubular cells. This study aimed to introduce the mutation into rat genome via direct injection of CRISPR/Cas9 into one-cell embryos, establishing rat models for downstream pathological studies.

Methods: The tracrRNA:crRNA fused single guide RNA (sgRNA, 20ng/µl) and a single-stranded oligonucleotide (ssODN, 3ng/µl), which encodes the p.S50G mutation of angiomotin and serves as template for HDR-mediated repair, was introduced into the rat pronucleus via microinjection. Pups produced from the injected one-cell embryos, establishing rat models for downstream pathological studies.

Funding: Government Support - Non-U.S.

FR-PO399

Double Transduction of a Cre/LoxP Lentiviral Vector: A Simple Way to Generate Cell-Specific Knockdown Mice
Shin-Wook Kang, Bo Young Nam, Meiyan Wu, Tae-Hyun Yoo. Brain Korea 21 PLUS, Severance Biomedical Science Inst, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Genetically engineered mice have been used to elucidate the function of specific genes. Transgenic mice via conventional knockout techniques using oocytes or embryonic stem cells are most commonly used to downregulate genes, but this method has certain limitations. Therefore, a novel method to knock down specific genes in a cell specific manner in adult mice was devised by lentivirus (LV)-assisted transfer of short hairpin RNA.

Methods: In vitro, the LV suspension containing LV-Hoxb7 Cre and/or LV-Aquaporin 3 shRNA (LV-AQP3) was added to primary mouse renal collecting duct cells (CDs) and mouse mesangial cells (MMCs). In vivo, first, LV-Hoxb7 Cre was injected into the intrapleural injection site to check the Hoxb7 promoter efficiency. Second, LV-loxP shAQP3 was injected into the Hoxb7 Cre transgenic mice to check shAQP3 function. Third, consecutive injections of LV-Hoxb7 Cre and LV-loxP shAQP3 were made to C57BL/6J mice.

Results: In vitro, LV-Hoxb7 Cre worked only in CDs due to the presence of Hoxb7 in CDs but not in MMCs. Furthermore, combined injection of CDs with LV-Hoxb7 Cre and LV-loxP shAQP3 significantly inhibited the protein expression of AQP3 with the disappearance of EGFP protein expression, suggesting that LV-Hoxb7 Cre and LV-loxP shAQP3 used in this study worked together effectively. In vivo, kidney CD-specific AQP3 knockdown mice were generated by consecutive injection of LV-Hoxb7 Cre and LV-loxP shAQP3 in adult C57BL/6J mice. In mice treated with LV-Hoxb7 Cre alone, mCherry protein expression occurred only in CDs, while LV-loxP shAQP3 injection alone led to an increase in EGFP expression in all cells. In the kidney, AQP3 expression in mice injected with LV-Hoxb7 Cre or LV-loxP shAQP3 alone did not differ, but consecutive injection of LV-Hoxb7 Cre and LV-loxP shAQP3 significantly reduced AQP3 expression. However, the expression of AQP3 in other organs did not differ between the groups.

Conclusions: Double transduction of Cre- and loxP-based LV can be a simple way to generate cell-specific knockdown mice, and this method may also be applicable to other species.

FR-PO400

Local Delivery of Interleukin-10 via Injectable Hyaluronic Acid Hydrogels to Prevent Local and Systemic Injury in Ischemic Acute Kidney Injury
Danielle Soranno,1 Chris Altmann,2 Sarah Faubel,2 Ana Andres-hernando,2 Pediatrics & Bioengineering, Nephrology, Univ of Colorado, Aurora, CO; 2Medicine, Nephrology, Univ of Colorado, Aurora, CO.

Background: AKI is pro-inflammatory and causes systemic complications via IL-6. Here, we use injectable hyaluronic acid (HA) hydrogels to deliver IL-10, an anti-inflammatory cytokine, to improve local and systemic outcomes of AKI.

Methods: Four treatment groups were followed for 28 days following AKI (15 µL of therapy delivered 3 days status-post AKI), and compared to healthy and untreated AKI controls (n=5): IL-6 in saline delivered under the kidney capsule (LK IL-6); IL-10 suspended in HA delivered subcutaneously (SQ gel IL-10); HA with or without IL-10 injected under the left kidney capsule (LK gel, LK gel IL-10); HA hydrogels were developed as previously reported. Serial measurements of blood urea nitrogen and creatinine were followed for 4, 14, and 28 days. Serum IL-6 was measured at sacrifice. Immunohistochemistry (IHC) was performed to identify collagen type III deposition. Positive cells were quantified (20 images/section, in cortex). ANOVA with Dunnett’s posthoc was used to determine significance.

Results: All treatment groups normalized BUN, Cr and serum IL-6 by day 28 while the untreated AKI cohort had a persistent increase in BUN, Cr and IL-6. All treatment groups showed a significant reduction in collagen deposition in both left and right kidneys compared to untreated AKI, with variable effect depending on the mode of HA/IL-10 delivery.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO401

Substrate Stiffness Regulates Renal Epithelial Cell Cilia Formation via Autocrine TGFβ Signaling

Mingfang 2

Shuvo Roy, 1

Dong Ki Kim. 1, 2

Background: The primary cilium senses the extracellular environment. Malformation of primary cilia has been shown to result in kidney disease. Although much is known regarding ciliogenesis, the role of mechanical features of the microenvironment in cilia formation is poorly understood.

Methods: Human primary proximal tubule epithelial cells (HRECs) and LLC-PK1 cells were plated on collagen-coated polyacrylamide gels with different stiffness (0.5 kPa, 1 kPa, 10 kPa and 40 kPa) and grown for 5 to 7 days. Cilia formation was analyzed by immunofluorescence staining of AC-tubulin followed with microscopy imaging. Protein expression was measured by immunoblotting. Recombiant TGFβ 1 and an inhibitor of TGFβRII SB431542 were used for TGFβ signaling modulation. LiCl was utilized to stimulate P-GSK3b.

Results: Stiff gels (10 kPa and 40 kPa) gave rise to higher ciliary density than compliant gels (0.5 kPa and 1 kPa) did (60% vs 20%). Furthermore, this phenotype could be altered by manipulation of transformation growth factor beta (TGFβ) signaling: addition of TGFβ 1 could increase the cilia frequency even when the cells were on compliant gels; similarly, inhibition of TGFβ receptor II impairs cilia formation in the context of stiff substrates. Further supporting a role for TGFβ, substrate stiffness was associated with increased SMAD2 and GSK3B phosphorylation. Incubation with LiCl also increased GSK3B phosphorylation and cilia formation independent of TGFβ.

Conclusions: Substrate stiffness determines cilia formation through TGFβ signaling via downstream GSK3β phosphorylation. This work highlights that substrate mechanical properties have a strong influence on markers of differentiation. This has relevance for tissue engineering efforts and also suggests a mechanism of disease progression in the scurvy kidney. This may broaden researches on kidney disease and contribute to disease therapy.

Funding: Other U.S. Government Support

FR-PO402

An Additive Role of Microfluidics on KLF 15-Induced Differentiation of Human Primary Podocyte

Seung Hoe Yang, 1

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Yon Su Kim, 1, 2

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Background: Podocyte de-differentiation is one of major problems during the process of primary podocyte culture. Recently, much interest has been focused on the topic, yet length and technical process hinder a progress. Kringel-like factor (KLF 15) was reported to be a novel transcriptional regulator of podocyte differentiation and its expression was increased by retinoic acid (RA) which promotes the differentiation of podocytes. But, the duration of podocyte differentiation process remains long. Here, we present a novel in vitro protocol to induce podocyte differentiation.

Methods: To mimic in vivo biological environment of glomerulus, a polydimethylsiloxane (PDMS) microfluidic device was used. The human primary podocytes were cultured in the 500 mm by 130 mm microfluidic channel and were stimulated with a laminar fluidic shear stress of 0.5 dyn/cm2 for 5 days. Various dose of RA was used to promote podocyte differentiation.

Results: In this research, we were able to reduce the time required for podocyte differentiation with higher shear stress and higher dose of RA. A couple of tests were conducted to verify the podocyte differentiation through the protocol. First, the phenotype of podocytes changed from cobblestone like shape to arborized cells. Through immunofluorescence staining, the increased expression of cytosplasmic synaptopodin and intercellular junction ZO-1 was confirmed. Moreover, KLF 15 expression was also increased. These molecules were also quantified with mRNA expression through real-time PCR. The size of podocytes became larger and the height of podocytes increased by a factor of 2.3 fold. Lastly, the podocytes aligned with the direction of flow.

Conclusions: In conclusion, we were able to promote podocyte differentiation in the shorter processing time with microfluidics and RA. Yet, more effort to mimic biological aspects of kidney such as complex structure with multiple cell layers and round surface is necessary.

Funding: Private Foundation Support

FR-PO403

CCL18 Correlates with Disease Activity in ANCA-Associated Neutrophilic Glomerulonephritis

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Background: Microarray analysis of renal tissue from patients with antineutrophil cytoplasmatic antibody (ANCA)-associated neutrophilic glomerulonephritis (GN) revealed the CC chemokine ligand 18 (CCL18) as the highest up-regulated chemokine. The renal production of CCL18 was associated with fresh glomerular lesions and impairment of renal function. The cellular sources of CCL18 were identified as macrophages and dendritic cells. CCL18 serum levels were elevated in patients with newly diagnosed ANCA GN as well. In order to test whether CCL18 might serve as a biomarker of relapsing renal ANCA disease, we prospectively analyzed CCL18 serum levels.

Methods: Hundred thirty-five patients with biopsy proven ANCA GN were prospecively analyzed for CCL18 serum levels. Patients included in the study were in remission on maintenance therapy (n=117) or without immunosuppressive treatment (prednisolone 5mg or less was accepted) (n=18). Serum levels of CCL18 were measured by ELISA every three months. Renal relapse was defined as either rising serum creatinine with urinary red cell casts or biopsy-confirmed active ANCA-associated glomerular lesions (i.e. fibrinoid necrosis and/or cellular crescents) accompanied by an intensification in immunosuppressive treatment.

Results: During a mean follow up time of 11.6 ± 8.3 months, 16 patients developed a renal relapse. CCL18 levels were higher in relapsing patients when compared with patients who were in remission (p=0.001; 167.5±34.6 ng/ml vs. 83.17±46.38 ng/ml). CCL18 serum levels increased at the time of relapse and decreased after immunosuppressive therapy was restarted or intensified (n=16; ANOVA; p<0.001).

Conclusions: CCL18 serum levels are associated with disease activity in patients with ANCA GN and might serve as a marker of renal relapses in the surveillance of these patients.

Funding: Government Support - Non-U.S.

FR-PO404

Prognostic Value of Persistent Hematuria and Proteinuria in ANCA-Associated Vasculitis: Data from the European Vasculitis Study Group (EUVAS) Therapeutic Trials

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Background: Renal involvement is frequent ANCA-associated vasculitides (AV), due to crescentic glomerulonephritis (CGN). Hematuria (Hu) and proteinuria (Pu) are detected during the initial and active phase of CGN but the prognostic value of the persistence of these urinary abnormalities during the remission phase of AV is still controversial.

Methods: Data were combined from three EUVAS trials (IMPROVE, RITUXV AS, MUCYCYC), providing data for Hu and Pu at month 6 (M6) following initiation of immunosuppression and patient follow-up until month 18 (M18). Hu was defined as urine protein >0.1 RBC/mm3. Proteinuria was evaluated by protein-to-creatinine ratio (PCR, g/gmml).

Results: Data concerning 337 patients were available for analysis. ANCA specificity (PR3/MPO) was 58.37%, renal involvement was present in 73% of cases and initial mean eGFR was 46.3±2 mL/min/1.73m2. Hu was still positive at M6 in 27% of cases, although 96% of patients were in AV remission. Positivity of Hu at M6 was associated with more severe initial nephropathy but was not predictive of renal dysfunction at last FU (mean eGFR at M18 was respectively of 55.24 and 60.24 mL/min for Hu+ and Hu- patients, p=0.03). Proteinuria at M6 was <0.03 g/mmol in 53% of cases, between 0.03 and 0.1 g/mmol in 25%, >0.01 g/mmol in 22%. Among patients with M6 Pu <0.1 g/mmol, 29% had CKD stage 4 or 5 at M18, vs 3.5% and 11.5% respectively for patients with M6 PCR <0.03 and 0.03-0.1 g/mmol. Multivariate analysis using a mixed effects model demonstrated that the presence of eGFR at M18 and at the marker of renal relapse were independently associated with age (p=0.001), baseline eGFR (p=0.001) and M6 proteinuria (p=0.002), but not with M6 haematuria (p=0.284) nor ANCA specificity (p=0.82).

Conclusions: Persistence of micro-hematuria during the remission phase of AV is associated with more severe initial renal involvement but does not predict poor renal outcome. Degree of proteinuria at M6 reflects more severe kidney damage and is an independent predictor of CKD progression in AV nephropathy.
Methods: Retrospective analysis of AAV pts treated w/ new SI regimen: RTX 1gm Q2wk x 2, doses oral CYC 3mg/Kg/d x 1 wk and 1.5mg/Kg/d x 2, mtx (adj) for eGFR, and pulse pulsedmethylone followed by a rapid prednisone (pred) taper to 15mg pred by 5wk. Remission defined as BV AS-WG 0 and pred dose <7.5 mg/d. Pts received SI alone or SI+ plasma exchange (PE).

Results: 74 pts treated with SI and 35 pts w/SI+PE (table 1). Time to remission in the SI and SI+PE was 117±53 and 122±39 days, respectively (p=0.06). Cumulative incidence plots (Figure 1). Among survivors, 100% of SI and 97% of SI+PE achieved remission. 3 pts (4%) in SI and 1 (3%) in SI+PE died during induction. There were 0.04 treatment-related adverse events/p't month in both groups.

Conclusions: RTX with low-dose bridging CYC allows for successful induction of remission in essentially all AAV pts while attenuating exposure to high dose GC. Treatment-related adverse events were minimal. Our data provide an impetus for a randomized trial comparing this new regimen with the standard of care.

FR-PO408

Pulse Methylprednisolone for Induction of Remission in Severe ANCA Associated Vasculitis Is Associated with an Increase in Adverse Events but No Improvement in Outcome

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Background: Intensive pulse methylprednisolone (MP) is frequently used as part of remission induction in severe ANCA associated vasculitis (AAV). However, there are no studies assessing its efficacy in the setting of AAV, while treatment related complications remain the main source of morbidity.

Methods: We retrospectively analysed outcomes of 114 patients that presented with severe AAV at 5 large centers in the United Kingdom, United States and Denmark between 2000-2013. All patients received high dose oral corticosteroids, cyclophosphamide and plasma exchange. Rituximab treated patients were excluded. The chi square and Mann-Whitney U tests were used for statistical analysis.

Results: Fifty-two patients received MP (median dose 1.5 g over 3 days) in addition to standard therapy while 62 did not. Patient characteristics and disease severity were comparable between the two groups. There was no difference in survival at 3 months (MP: 94.2% vs non MP: 91.9%, p=0.633) or 12 months (84.6 vs 80.6%, p=0.579). Renal recovery amongst survivors (63.5 vs 72.6%, p=0.297) and relapse rates at 12 months (11.6 vs 8.6%, p=0.617) were similar. MP therapy was associated with more infections per patient at 3 months (0.7 vs 0.3, p=0.005) and more new onset diabetes (28.6 vs 6.6%, p=0.002).

Conclusion: Within the limitations of this study we found that the addition of MP to standard therapy for remission induction in severe AAV led to a significant increase in adverse events, with no improvement in survival, renal recovery or relapse rates. Our results question the currently widespread use of MP in severe AAV and suggest that a randomized controlled trial is urgently needed in order to definitively address this issue.

FR-PO409

Serum B Lymphocyte Stimulator (BLYs) Levels as Markers of Disease Activity in Anti-Neutrophil Cytoplasm Antibody (ANA) Associated Vasculitis (AAV)


Background: B lymphocyte stimulator (BLYs) has been implicated in the pathogenesis of AAV. Previous studies have shown elevated levels in active disease, and following anti-CD20 therapy. Antineutrophil cytoplasm antibodies (ANCA) are not reliable predictors of disease activity and relapse and alternative markers are needed in order for immunosuppressive therapy. The aim of this study was to determine the clinical significance of serum BLYs levels in our patients with AAV.

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

Underline represents presenting author.

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Methods: Serum samples were obtained from patients with AAV at our centre, and BlyS levels detected using sandwich ELISA. Clinical data were obtained by review of patient records.

Results: Samples were collected from 68 patients with AAV and 13 healthy controls. Thirty one patients were male, 44 Caucasian and 21 Indoasian. Fifty patients had granulomatosis with polyangiitis, 13 patients had microscopic polyangiitis and 5 had eosinophilic granulomatosis with polyangiitis. Significantly higher BlyS levels were found in patients with active disease than those in remission and healthy controls.

Thirty seven patients who had been treated with Rituximab had significantly higher BlyS levels (p<0.0001). Eighteen patients had relapsed at 1 year following recruitment. These relapsing patients had significantly higher BlyS levels than those patients who did not relapse (p<0.0016).

Conclusions: This study supports the role of BlyS in the pathogenesis of AAV. BlyS levels could be used as markers of disease activity and predictors of relapse. With increased use of rituximab in AAV, further studies are needed to assess the impact of B cell depletion on B cell survival factors. These findings highlight the potential role for BlyS in the maintenance of remission of AAV.

Funding: Government Support - Non-U.S.

FR-PO410

Predictors of Renal Histopathology in Antineutrophil Cytoplasmic Antibody Associated Glomerulonephritis Sophia Lionaki, 1 Clio Marvagni, 2 George Liapis, 1 George Somarakis, 4 John N. Boletis, 3 Alexandros Drosos, 4 Athanasios Tzioufas, 3 Haralampos Moutsopoulos, 2 *Nephrology, Laiko Hospital, Athens, Greece; 2Pathophysiology, Univ of Athens, Greece; 3Pathology, Laiko Hospital; 4Rheumatology, Univ of Ioannina.

Background: Prompt, aggressive therapy is vital foranti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN) asdelays in diagnosis of renal histopathological changes may compromise patient outcomes. We aimed to identify predictors of distinct renal histopathological classes 6 months after diagnosis.

Methods: A single-centre cohort of patients with biopsy-proven ANCA-associated GN was studied retrospectively. Demographics, clinical, laboratory, serological and radiological parameters were analyzed. Patients were classified on the basis of renal histopathology, according to the report by Berden et al (JASN 2010) for ANCA-associated GN by a renal pathologist into: focal class, crescentic class, mixed class and sclerotic class. A risk score was developed for each histopathological class using univariate and logistic regression analyses. Patients were classified on the basis of renal histopathology.

Results: Variables independently associated with focal class included disease duration up to diagnosis < 8 weeks, absence of red blood cell (RBC) casts by urine microscopy and eGFR > 49ml/min/1.73m2; with crescentic class > 40 erythrocytes/hpf, identification of RBC casts in urine, ear nose and throat (ENT) involvement and eGFR < 49ml/min/1.73m2; with mixed class age > 54 years, male gender, and absence of ENT involvement. In the presence of 2 or 3 risk factors a predictive risk score of each histopathological class was calculated: odds ratio (OR), 95% confidence intervals (CI), for focal class (2 risk factors) 17.5 (95% CI [4.9-62.9]), 38.0 (6.8-213.7) for crescentic class (3 risk factors), and 8.3 [1.0-67.5] (2 risk factors) for mixed class.

Conclusions: We propose a predictive algorithm of specific histopathological classes of ANCA-associated GN, which might provide a crude estimation of the disease activity in the glomeruli at presentation. This tool might assist the clinician in making decisions regarding the level of intensity of inductive immunosuppressive therapy at clinical diagnosis.

FR-PO411

Rituximab as a Cyclophosphamide Sparing Agent for Patients with Multi-Relapsing ANCA-Associated Small Vessel Vasculitis Sophia Lionaki, 1 George E. Fragoulis, 2 Alice Venetanapouloou, 2 John N. Boletis, 3 Panagiotis Vlachogiannopoulos, 3 Haralampos Moutsopoulos, 2 Athanasios Tzioufas, 3 *Nephrology, Laiko Hospital, Athens, Greece; 2Pathophysiology, Univ of Athens, Greece.

Background: To evaluate the clinical efficacy and outcomes, of patients with multi-relapsing ANCA-associated Vasculitis (AAV), who received induction therapy with rituximab for a new disease relapse.

Methods: We retrospectively studied all patients with biopsy proven AAV, who were treated with rituximab upon a new relapse. A control group consisted of patients from the era prior to the initiation of rituximab in the treatment of AAV, was selected using the following criteria: i/history of relapse, ii/organ involvement at relapse, iii/treatment with the standard regimen. Patients and controls were matched for age, gender, and disease duration. Comparisons of disease outcomes along with the frequency and severity of adverse events were performed between groups. Rituximab was used with high dose glucocorticoids and depending on the organ involvement a short course of cyclophosphamide was added.

Results: Of 147 patients with AAV and a mean total follow up time of 78.2 months, 18 patients (12.2%) received induction treatment with rituximab for disease relapse. Time to 1-relapse from the 1st diagnosis of AAV was shorter in the rituximab group and the mean number of relapses per patient was significantly higher in this group. The mean BVAS score was similar between groups at study entry while 13/18 patients received a 3-month course of cyclophosphamide in addition to rituximab.

Conclusions: Rituximab was shown efficacious in patients with multiple relapsing AAV including cases with renal and pulmonary involvement. It allowed us to minimize the ultimate exposure to cyclophosphamide in these patients, which is crucial, as they accumulate remarkable toxicity in long-term.

FR-PO412

Differences Between Patients with Definite and Suspected ANCA-Associated Vasculitis in a Secondary Care Hospital Eline Houwen, 1 Willem A. Bax, 3 Walentina A. Sliker, 2 Bastiaan Van Dam, 1 Femeneke C.P. Frerichs, 1 Gideon Verhave, 1 Dept of Nephrology, MCA-Gemini Group, Alkmaar, Netherlands; 2Laboratory of Clinical Chemistry, Hematology and Immunology, MCA-Gemini Group, Alkmaar, Netherlands.

Background: ANCA-associated vasculitis (AAV) is a rare disease with a broad spectrum of symptoms. Therefore, diagnosing AAV is often challenging. In an effort to provide guidance for clinicians, we aimed to identify differences between ANCA positive patients with a definite and suspected diagnosis of AAV.

Methods: In this retrospective study, all patients that tested positive for MPO and/or PR3 ANCA between 2005 and 2015 in a secondary care hospital in the Netherlands were analyzed. Patients were divided into subgroups according to clinical diagnosis and the Birmingham Vasculitis Activity Score (BVAS). Possible predictors for AAV, such as patient characteristics, clinical symptoms and ANCA titers were identified. Patients were also screened for commonly used exclusion criteria in trials.

Results: We included 240 patients with a positive MPO and/or PR3 ANCA, of which 120 patients were clinically diagnosed with AAV (group 1); all had a BVAS ≥ 3. Of the patients without the diagnosis AAV, 50 had a BVAS ≥ 3 (group 2) and 70 had a BVAS < 3 (group 3). In group 2, 29 patients had an alternative diagnosis, including other rheumatic diseases and infection. In a multivariable linear regression model, higher ANCA titers, higher BVAS and Ear Nose Throat (ENT) symptoms were predictive for AAV (all p<0.001). Of the patients diagnosed with AAV, 21 (18%) would have been excluded from most trials, based on a malignancy (n=13) or drug use associated with vasculitis (n=8). Notably, characteristics of these patients did not differ significantly from the other AAV patients.

FR-PO413

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FR-PO413
Rituximab and Low-Dose Cyclophosphamide Therapy for Renal ANCA-Associated Vasculitis: Long-Term Follow-Up
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Background: The previously reported study of rituximab (RTX) and low-dose cyclophosphamide (CYP) followed by azathioprine maintenance for ANCA-associated renal vasculitis (AAV), suggested it was efficacious in inducing remission and has an acceptable side-effect profile (N Mansfield et al 2011). We have followed the cohort for over seven years and report the regimen’s efficacy and safety profile.

Methods: Long-term outcomes were retrospectively ascertained from all 23 previously treated patients.

Results: Mean time since starting the treatment regimen was 83 months; twenty-one patients started the regimen more than five years ago. All patients achieved clinical remission within six weeks, with depletion of circulating CD19-positive B cells and significant reduction in median anti-PR3-MPOANCA titre. After 84 months follow-up, five renal and four non-renal relapses were observed and treated in five patients. Median eGFR improved from 28 ml/min (range 11-63) at presentation to 49 ml/min (range 1.87) after one year and was maintained at 50 ml/min (8-90) at five years (n=21) and 46ml/min (22-76) at seven years follow-up (n=9). To date, three infections requiring hospital admission and four malignancies have been recorded.

Conclusions: This rituximab-based low-dose cyclophosphamide regimen followed by maintenance therapy provides safe and effective long-term treatment at more than five years follow-up.

FR-PO414
The Histopathologic and Clinical Determinants of the Change in GFR During the 1st Year of Treatment in ANCA-Associated Vasculitis
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Background: Identifying the predictors of the change in GFR in ANCA-associated vasculitis (AAV) is helpful to avoid prolonged immunosuppression in those where no benefit exists and to consider modifying therapy in those who should improve but fail to do so.

Methods: We retrospectively reviewed cases of AAV with a renal biopsy in 3 hospitals to determine predictors of the change in GFR (deltaGFR) during the 1st year of treatment. We considered demographics, pathology findings, treatments and complications incurred. In particular, we addressed the histopathologic classification (Berden JASN 2010) proposing focal, crescentic, mixed and sclerotic subsets.

Results: Of 120 patients with AAV, 71 had a renal biopsy and received immunosuppression. They presented at an age of 59±13 with 48% female, 49% anti-MPO+ and a GFR of 32±30 ml/min including 22 patients on dialysis. Induction consisted of cyclophosphamide (93%), rituximab (6%), plasma exchange (27%) and pulse methylprednisolone (69%) in addition to oral corticosteroids. During the first year, patients recovered 15±20 ml/min/1.73m2 with 11 no longer requiring dialysis. The deltaGFR increased up until 6 months, although it varied greatly individually. Age, hypertension, MPO positive serology, the extent of crescentic and sclerotic glomeruli, tubular atrophy and the histopathological classification were associated with a lower GFR at diagnosis. However, at one year only the histopathologic classification and the number of admissions for treatment-related complications predicted a lower deltaGFR. The focal, crescentic, mixed and sclerotic subsets experienced a 19±5, 20±10, 26±10 and ±2±2 ml/min deltaGFR respectively (p=0.026, trend test).

Conclusions: The change in GFR during the 1st year of treatment in AAV increased 15±20 ml/min. It appeared maximal at 6 months into therapy. The histopathologic classification helped predict the deltaGFR at 12 months, with a reduced benefit of therapy in the sclerotic subset.

FR-PO415
Analysis of Clinical Features in ANCA-Associated Vasculitis: 30 Years Single Center Experience – Relationship Between RPGN and Renal Prognosis
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Background: The clinical features of AAV, with respect to rapidly progressive glomerulonephritis (RPGN), have been changing, but were not well examined in Japan, where MPO-ANCA-associated vasculitis (MPO-AAV) are dominant in contrast to the Western countries. Thus, we retrospectively analyzed the clinical database of the 179 patients with AAV who were admitted to our hospital for the last 30 years.

Methods: At the onset, all patients fulfilled the Chapel Hill Consensus Conference (CHCC) classification criteria for MPA, GPA and EGPA. We divided the AAV patients into the 4 groups based on the presence or the absence of RPGN and hemodilution and compared the clinical features and renal prognosis. Among 179 AAV patients, 166 cases (92.7%) were MPO-ANCA positive and 14 cases (7.8%) were PR3-ANCA positive.

Results: RPGN was observed in 100 (55.9%) of the 179 patients, including 49 cases of maintenance hemodialysis group (A), 2 cases of temporary dialysis group (B) and 49 cases of non-dialysis group (C), in addition to 79 cases without RPGN and dialysis (D). Significant differences were observed in BVAS, CRP, eGFR and serum Cr concentration. There were no differences for treatment choice, rate of kidney biopsy and frequency of relapses among the groups. Comparison among the different periods for every 10 years show the tendency of an increase in age of onset and the downward trend of serum Cr concentration, rate of RPGN and maintenance hemodialysis, BVAS scores, and frequency of relapses and mortality.

Conclusions: These results have clearly shown the changing features of AAV in Japan, with an earlier detection and the improvement of renal and patient survival during the periods.

FR-PO416
The Effect of Race on 5-Year Survival Outcomes in ANCA-Associated Renal Vasculitis
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Background: Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is a multi-systemic autoimmune disease characterized by inflammation of microscopic vessels. Renal involvement occurs in 70% of patients, with 1 year mortality rates exceeding 15%. With a prevalence of two cases per 100,000 populations there is a significant preponderance to Caucasians (C). Little is known about the outcomes in patients from Indo-Asian (IA) and Afro-Caribbean (AC) race despite an increasing number of cases seen with the disease.

Methods: We performed a single center, retrospective study, observing 5-year survival outcomes and relapse rates between C, IA and AC in ANCA-associated renal vasculitis. Electronic case notes over a 10-year period (2004-2014) were used collect data to include age at time of diagnosis, Birmingham vasculitis activity score (BVAS) at presentation, race, presence of diabetes and renal function. 5-year survival outcomes were analyzed using a cox proportional hazard model.

Results: In total 121 patients were included in the study, there were 84 (70%) C’s, 31 (25%) IA’s and 6 (5%) were of AC background. Median age was 66 years, 56% were men, 20% were diabetic and average BVAS score at presentation was 5. One-year relapse rates were low with 8 (6%) relapses seen. No significant difference in 5-year survival outcome was found between the races. Age at presentation significantly affected survival outcomes (p=0.007).

5-year survival outcomes dependent on race

Caucasian
Afro-Caribbean
Indo-Asian

Conclusions: We conclude that survival outcomes for IA and AC are not worse compared to those of C origin. Age remains to be a significant predictor in determining mortality outcomes. This study provides valuable clinical information in an area that has not been well studied.

FR-PO417
Possibility of Increasing Prevalence of Otitis Media with ANCA Associated Vasculitis in Japan
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Background: A new disease concept, otitis media with ANCA associated vasculitis (AAV), has been advocated.

Methods: One hundred and fifty seven patients (74 males and 83 females) with AAV (81 microscopic polyangiitis, 54 granulomatosis with polyangiitis (GPA), and 22 eosinophilic GPA) were admitted to Niigata University Hospital from 1989 through 2014. Twenty seven patients (17%, 13 males and 14 females) with AAV were reviewed. Their clinical presentation was compared to those of C origin. Age remains to be a significant predictor in determining mortality outcomes. This study provides valuable clinical information in an area that has not been well studied.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 450A
Conclusions: OMAAV is increasing. Chest X ray, urinary test, and measuring ANCA should be considered in refractory otitis media.

FR-PO418
Temporal and Spatial Clustering of Anti-Glomerular Basement Membrane Disease
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Background: An environmental trigger has been proposed as an inciting factor in anti-glomerular basement membrane (anti-GBM) disease. We aimed to define country-wide incidence of anti-GBM disease, investigate clustering of cases in time and space and to assess the impact of spatial variability in incidence on outcomes.

Methods: National multicentre observational study of anti-GBM disease cases diagnosed in Ireland 1.6.2003-31.5.2014. We ascertained cases by screening immunology laboratories for instances of positive anti-GBM antibody and the national renal histopathology registry for biopsy-proven cases. We defined the population at risk using census figures. A variable-window scan statistic was used to detect temporal clustering. A Bayesian autoregressive spatial model was used to provide standardised incidence ratio (SIR) estimates for each county. Patient and renal survival were assessed using Kaplan-Meier and log-rank test.

Results: Seventy-nine cases were included. National incidence was 1.64 (95% CI 0.82-3.35) pmp/year. A temporal cluster was identified (n=10) in a 3 month period in early 2013; 6 (60%) were resident in the southeast. Spatial analysis revealed wide regional variations in SIR (fig 1A) and a cluster (B,C) in the northwest (n=7, SIR 1.71, 95% CI 1.02-3.06).

However, being in a cluster or distance from diagnosis site to treating center did not significantly impact on patient (HR 1.8, 95% CI 0.9-3.8) or renal survival (HR 0.7, 95% CI 0.4-1.1).

Conclusions: Country-wide incidence of anti-GBM disease is higher than reported by single centre studies. We detected clustering of cases in time and space supporting the hypothesis of an environmental trigger. Wide regional variation in incidence highlights the need for country-wide epidemiological studies of anti-GBM disease to further our understanding of its aetiology.

Funding: Government Support - Non-U.S.

FR-PO419
Venus Thromboembolism in ANCA Vasculitis Is Associated with Elevated Microparticle Tissue Factor Activity
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Background: Venous thromboembolism (VTE) is a severe complication of ANCA vasculitis (AAV). Mechanisms of VTE are not known, but tissue factor (TF)-bearing microparticles (MPs) from activated or apoptotic cells may play a role. We hypothesized that elevated microparticle tissue factor activity (MPTFa) is associated with VTE in AAV.

Methods: Patients without VTE (VTE-) were enrolled prospectively during active disease. Patients with VTE (VTE+) were included whether active or in remission at the time of VTE. Longitudinal platelet-free plasma (PPP) samples from 28 patients and 16 healthy controls (HC) were assayed for MPTFa. All patients had >3 samples spanning 112 months. MPs (mean ± SD) were enzymatically derivatized with Factor Xa inhibitor X. Absorbance was measured after addition of Factor Xa chromogenic substrate. Recombinant relipidated human TF was used as a standard. Values were expressed as a percent of MPTFa from a positive control (FFP from LPS-stimulated HC blood). Fisher’s exact tests and Wilcoxon tests were used to compare categorical and continuous variables, respectively.

Results: Demographics were similar among patients and HC. VTE+ and VTE- patients did not differ in ANCA serotype or titer, BVS, D-dimer, other laboratory data, or organ involvement. VTE+ patients had significantly higher peak MPTFa than VTE- (HR 10.5 (95% CI 2.8, 40.5) p<0.001) most strongly associated with peak D-dimer (HR 2.1, 95% CI 1.0-4.5, p=0.03) (fig 1, 2). All VTE+ patients had peak MPTFa above normal (mean ± 2SD of HC = 6.5) versus 2/20 VTE- patients (p<0.0001).

Conclusions: Patients with AAV who develop VTE have a notable propensity for increased MPTFa at times both near and remote from VTE. Conversely, those without VTE rarely exhibit MPTFa significantly higher than healthy controls during their disease course. Further study is needed to determine if elevated MPTFa can identify AAV patients at high risk for VTE and whether MPTFa contributes to thrombogenesis.

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FR-PO420
C9B0 and Angiopoietin-like 4 in Glomerulopathies
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Background: Proteinuria in MCD is thought to be due to an increased C9B0 podocyte expression. Recently, podocyte angiopoietin-like 4 (Ang4) has been suggested to induce proteinuria in MCD. Objective: To determine the pattern of C9B0 and Ang4 in MCD and other glomerulopathies.

Methods: 34, 30 and 32 patients with biopsy-proven MCD, FSGS and MN respectively, were enrolled. Urinary and serum C9B0 and Ang4 were measured by Elisa. Differentiated human podocytes were incubated for 6 h with 15% of serum from MCD patients in relapse or in remission. Podocyte expression of C9B0 and Ang4 was measured by Western-Blot analysis. Urinary Ang4 pl was measured by 2D electrophoresis Statistical analysis: Mann-Whitney U test, Wilcoxon matched-pairs signed rank test for comparison of paired groups, and Spearman correlation.

Results: Urinary C9B0 was increased in MCD patients during relapse, but not in patients with FSGS or MN, or normal controls. Serum C9B0 was lower in patients with glomerulopathies during relapse compared to normal controls. Urinary Ang4 pl was increased in patients with glomerulopathies compared to normal controls, whereas serum Ang4 pl was higher in normal controls compared to patients with glomerulopathies. Both urinary C9B0 and Ang4 pl correlated with proteinuria in MCD, FSGS and MN. Podocytes exposed to sera from MCD patients in remission showed a significant increase in C9B0 expression but not Ang4 pl when compared to MCD patients in remission. Urinary Ang4 pl was 5.4.

Conclusions: 1) Decreased serum C9B0 and Ang4 pl in nephrotic syndrome is likely due to increased urinary losses. 2) Increased urinary C9B0 was only observed in MCD patients in relapse while increased urinary Ang4 pl was seen in all the glomerulopathies. 3) Podocyte C9B0 but not Ang4 expression was increased by serum from MCD patients in relapse. 4) Urine Ang4 pl in MCD has a pl of 5.4, suggesting no role on Glomerular Basement Membrane charge. 5) While C9B0 seems to play a role in proteinuria in MCD, Ang4 detected in urine in MCD and other glomerulopathies is likely the result of an increased glomerular permeability.

FR-PO421
Apol I Polymorphism Determines HIV Boarding in Human Podocytes
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Background: Patients of African ancestry with untreated HIV infection, carrying the G1 or G2 kidney disease risk variant (Vs) at the APOL1 gene are at a >10-fold greater risk for developing HIV-associated nephropathy (HIVAN) compared to patients of other races. Although the association of APOL1 alleles with kidney disease risk variants. Although podocyteopathy in HIVAN has been attributed to the direct effect of HIV infection, the mechanistic contribution to kidney injury of the APOL1 allelic state remains to be elucidated.

Methods: We evaluated the priming effect of IL-1β on human podocyte (HP) APOL1 expression. To evaluate the effect of IL-1β on HIV-1 processing in podocytes, HPs were pre-stimulated with human recombinant IL-1β for 6h and then incubated with HIV-1 followed by analysis for the HIV-1 strong stop DNA by qPCR analysis. HPs treated under similar conditions were evaluated for Nef receptor knockdown and expression of TLR-4 (VR-1 entry) expression. To determine the effect of over expression of APOL1 (G6) and APOL1 variants (G1/G2) HPs were either transfected with APOL1G6/G1/G2 plasmids, or HPs were pre-stimulated with 10 ng/mL of IFNγ and then incubated with HIV-1 and analyzed for HIV-1 strong stop DNA concentration at various time points and also measured for their lysosomal bioactivity.

Results: APOL1 expression increased after incubation of podocytes with the HIV. In turn, APOL1 expression was further enhanced in response to augmented entry of virus compared to controls, demonstrating enhanced expression of TLR-4 and IL-1β treatment, consistent with viral load dependency. Podocytes over-expressing the non-risk APOL1 gene (G0), either through
FR-PO424

Use of Spot Urine Protein Creatinine Ratio to Predict Proteinuria in Nephrotic Syndrome in NEPTUNE. Marie C. Hoogan, 1 Jonathan P. Troost, 2 Peter J. Nelson, 3 Heather N. Reich, 4 Sharon G. Adler, 5 Daniel C. Catran, 5 Gerald B. Appel, 6 Debbie S. Gipson, 4 Wenjun Ju, 2 Matthias Kretzler, 2 John C. Lieske. 1

Background: Random urine protein creatinine ratio (UPC) is used to estimate 24 hr protein excretion (24P) yet little data are available wrt sensitivity & specificity, especially in pts with glomerular proteinuria.

Methods: The Nephrotic Syndrome Study Network (NEPTUNE) studies newly diagnosed patients with MCD, FSGS, & MN. Total protein, alb & creat are measured in random & 24 hr urine collections at a central biobank at postbiopsy baseline & subsequent visits within 2 yrs of dx.

Results: Of 603 participants, 302 have same day spot & 24 hr ur samples with a total of 827 samples across all visits eligible for this analysis. Urine protein excretion (g; median; 25, 75%); was higher in adults (1.0, 0.3, 2.3) than peds (0.2, 0, 0.7); Spot UPC correlated better with 24 hr UPC than 24P in both adults (r=0.79 vs 0.66) & peds (r=0.84 vs 0.67). Using these data we derived equations to predict 24P from spot UPCs: for adults 24P = [10−0.88(log10 [Spot UPC])]; & for peds was 24P = [10−0.16(log10 [Spot UPC])]. The efficiency (AUC) of spot UPC to accurately predict 24P values above thresholds of 0.5, 1.0, 2.0, 3.0, 6.0 & 10.0 ranged from 0.83-0.97 in adults & peds.

In subgroup analysis the correlation between log-transformed UPC and log-transformed 24P was similar in all age ranges & diseases, but stronger in obese vs. normal wt subjects (bMean=0.78 (0.69, 0.88); bMedian=0.85 (0.78, 0.93); bT25=0.93 (0.85, 1.0) p<0.001).

Conclusions: Among MCD, FSGS, & MN pts UPC correlates only moderately with 24P. 24P is best derived from spot UPC using a non-linear estimating equation. Wu influences reliability of spot UPC. Our data also suggest UPC can be used with caution to identify those pts with 24P above clinically relevant cut points. As 24P is susceptible to collection errors & implications of threshold values may be dependent on patient size, additional studies to evaluate spot UPC vs 24P and clinical outcomes are warranted.

Funding: NIDDK Support, Other NIH Support - The Nephrotic Syndrome Study Network Consortium (NEPTUNE); U54-DK-083912, is a part of NCATS Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, and the National Institute of Diabetes, Digestive, and Kidney Diseases. RDCRN is an initiative of ORD, NCATS. Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, NephCure Kidney International and the Halpin Foundation., Private Foundation Support

FR-PO423

Podocyte Depletion in Alport Syndrome Complex. Larvya T. Wielman, 1 Jeffrey B. Hodgkin, 1 Su Qing Wang, 1 Farsad Afshininia, 1 David B. Keshaw, 1 Roger C. Wiggins. 1 Univ of Michigan.

Background: Increasing evidence suggests that podocytes may play a role in Alport Syndrome Complex (ASC) progression of renal disease. We previously reported that podocyte detachment rate measured in urine is increased in ASC, suggesting that podocyte depletion could play a role in causing progressive loss of kidney function. This result therefore raised the question as to whether progression in ASC could be due to progressive podocyte depletion from glomeruli.

Methods: To address this question we measured podocyte nuclear number, density and cell area (Glepp1 positive) in the same 3m thick formalin-fixed paraffin-embedded histologic section. Twenty six kidney biopsies from 21 patients were collected. Of these 20 were designated as ASC including both classic Alport Syndrome (with thin and thick GBM segments and lamellated lamina densa [n=20]) and Thin GBM [n=6]. Twenty protocol biopsies from deceased kidney transplant donors were used as age-matched controls.

Results: When compared to controls, podocyte number per glomerulus, % podocyte depletion, nuclear density and cell area density were all decreased in the ASC cohort (P<0.01). The mean podocyte volume (MPV) was correspondingly larger for ASC than control (P<0.05) representing podocyte hypertrophy to compensate for reduced podocyte number and density. Podocyte depletion was present in ASC biopsies prior to detectable histologic abnormalities. No abnormality was detected by light microscopy at <5% podocyte depletion, minor pathologic changes (mesangial expansion and adhesions to Bowman’s capsule) were present at 30-50% podocyte depletion, and FSGS was progressively present above 50% podocyte depletion. Estimated GFR did not change measurably until >70% podocyte depletion. Low level proteinuria was an early event at about 25% podocyte depletion and increased in proportion to podocyte depletion.

Conclusions: These data support the concept that progressive podocyte depletion occurs from an early stage in ASC leading to FSGS-like pathologic changes and eventually to End Stage Kidney Disease. Early intervention to reduce podocyte depletion is projected to prolong kidney survival in ASC.

FR-PO425

Rituximab in Steroid Dependent and Calcineurin Inhibitor (CNI) Dependent/Intolerant Adult Idiopathic Minimal Change Disease and Focal Segmental Glomerulosclerosis. Harbir Singh Kohli, 1 Raja Ramachandran, Vivekanand Jha, Krishan L. Gupta. 1 Dep of Nephropathy, Post Graduate Inst of Medical and Research, Chandigarh, India; 2 Dep of Nephrology, Post Graduate Inst of Medical and Research, Chandigarh, India.

Background: Steroid dependent (SD) nephrotic syndrome (NS) is managed with CNIs but the long-term results are limited by CNI nephrotoxicity and dependence. This prospective study was done to evaluate the effect of rituximab in those SD-NS who were either CNI dependent or had CNI induced nephrotoxicity.

Methods: This prospective study was undertaken in patients of SD MCD/FSGS patients were given initially CNI ( tacrolimus). Of these, who were either tacrolimus (TAC) dependent (relapse NS on tapering or stopping after 1 year at least) or had TAC induced nephrotoxicity (rise in serum creatinine >2 times the baseline) were enrolled for rituximab administration during Oct 2013 to Oct 2014. Patient with at least 6 months follow-up were analysed. After achieving remission with oral prednisolone the steroids were tapered to stop in 8 (66.7%). Mean age was 21.8±1.57 gm/day, 2.52±0.78 gm/dl and <2 gm/day or <50% of baseline with normal serum albumin (³3.5 gm/dl).

Results: A total of 12 cases, 10 Tac dependent (duration of TAC-35±12 months) and 2 with nephrotoxicity were studied. Basic disease was MCD in 4 (33.3%) and FSGS in 8 (66.7%). Mean age was 21.8±1.57 yrs. Mean proteinuria, serum albumin and serum creatinine prior to enrollment in the study were 3.24±1.57 gm/day, 2.52±0.78 gm/dl and 0.79±0.15 mg/dl respectively. All achieved target CD-19 (<1%) with single infusion and 4 (33.3%) cases had risen in their CD 19 at 3 months and were given second dose. At 6 months, CR and PR was achieved in 9 (75%) and (8.3%) respectively. There were 2 non-responders (16.6%). Of the 10 responders,3 have completed 1 yr of follow-up and are in remission.

Conclusions: Rituximab appears to be a promising agent in the management of adult CNI dependent or intolerant NS due to MCD/FSGS with minimal short-term adverse events.
FR-PO426

Treatment and Outcomes in Minimal Change Disease: Experience of a Single UK Centre

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Background: Minimal change disease (MCD) accounts for 10–25% of nephrotic syndrome in adults. We retrospectively reviewed the treatment and outcomes of MCD patients in our centre.

Methods: We identified adults who had undergone renal biopsy between June 1996 and March 2012 which was reported as being consistent with MCD, and who had at least 12 months of follow-up. Electronic hospital records were used for data collection.

Results: There were 78 cases, with median follow-up of 72 months. Baseline and treatment details are shown in the table (averages are mean, or median where distribution is skewed). 27% had a history of nephrotic syndrome in childhood. All but one patient (who entered remission spontaneously) were treated with prednisolone, and 97% achieved complete remission at a median time of 33 days (6–309), although 12% needed a second-line agent to do so. Mean number of relapses during the first 24 months was 1.0. 88% experienced at least one relapse, and 45% patients required second-line agents at some point. Regarding complications: 12% developed thromboembolic disease, 14% had an admission-requiring infection, and 41% had at least one episode of AKI. Mean follow-up creatinine was 91 mmol/L, but significantly higher in those who had had AKI (104 vs 85 P=0.04) and those who had received an ACEI (99 vs 78 P=0.01). Of 16 patients who underwent subsequent biopsy (all of whom had received a CNI), 8 showed evidence of CNI damage, and 5 were consistent with FSGS. Diabetes mellitus developed in 12% cases, and 8% patients died during follow-up.

Conclusions: Almost all treated adult MCD patients enter remission, although second-line agents are frequently required. Despite therapy, complications remain common, including AKI which is associated with residual reduced excretory function.

FR-PO427

Predictors for Relapse in Adult Minimal Change Disease

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Background: Minimal change disease (MCD) is well-known benign primary glomerulonephritis in adults because of their distinct rare renal progression to end-stage. However, their relapse-associated morbidity has been underestimated. In this study, we aimed to explore the predictors of relapse in adult MCD patients. Methods: We reviewed clinical and pathologic characteristics of adult primary MCD patients from Seoul National University Hospital from 1979 to 2013. Patients who were presented by nephrotic syndrome and followed up more than 12 months were included. Patients were classified as either relapsers or non-relapsers. Initial treatment regimens, their response, and complication were also reviewed. The number of relapse were classified as follows, no relapse, 1-2 relapses (relapse group 1), and ≥ 3 relapses (relapse group 2).

Results: A total of 195 patients were included in the final analysis. Among them, median age at the time of diagnosis was 38 (23–53) years and 113 (57.9%) were men. During median follow up of 81 (44–153) months, more than 90% of patients reached to remission after initial treatment. However, only 64 (32.8%) patients did not experience any relapse. Remaining 131 patients, 69 (35.4%) relapsed once or twice and 62 (31.8%) relapsed more than three-times. The younger, the more relapse was found. In addition, severity of nephrotic syndrome data were shown in the table. Multivariate analyses found that younger age, lower serum albumin, mesangial proliferation and treatment duration remained as independent risk factor for relapse.

Conclusions: We proved that patients with younger age, severe nephrotic syndrome, lower mesangial proliferation and shorter treatment duration were prone to relapses. Moreover, relapse is morbidity due to higher thromboembolic events in adult MCD patients.

FR-PO428

Rituximab in Relapsing Minimal Change Glomerulonephritis: Clinical Outcomes and Financial Analysis

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Background: Minimal change disease (MCD) accounts for 10-15% of adult nephrotic syndrome, with frequent relapses or steroid-dependency occurring in 25-30%. Glucocorticoids and calcineurin inhibitors are the mainstay of treatment, but can be associated with significant toxicity. Rituximab holds potential to induce long term remission in these patients, but in the United Kingdom is currently not funded based on perceived excessive cost.

Methods: Nine patients with frequently relapsing MCD (histologically confirmed) were given total dose Rituximab 1g – 2.4g divided into two - four doses from 2012 - 2014. Time from diagnosis to first Rituximab dose was 140 months (10 – 336). Cost effectiveness of Rituximab was assessed based on comparing annual relapse rates; inpatient/outpatient attendances and immunosuppressant medication in the two years prior, and one year post Rituximab. Data was obtained retrospectively using hospital finance records, NHS standard tariff and the British National Formulary (2015) respectively.

Results: In all patients Rituximab induced complete remission. All steroid-sparing agents were discontinued. Four patients remain on low dose prednisolone (less than 4mg). Mean follow-up was 15 months (6 – 30) with only one relapse at 19 months. Annual relapse rates fell from 1.83/year (0.5 – 6.0) to 0.12/year (0.0-0.57). Inpatient days fell from a mean of 4.2 days/year (0-9.6) to 1.7 days/year (0-4.5). Outpatient consultations fell from 12.5/year (5-26.4) to 7.3/year (4.5-28). Mean annualised pre-Rituximab costs were £172 and post Rituximab, £5046, in 6/9 patients with sufficient length of follow up for comparison. No major complications were noted following treatment.

Conclusions: In patients with relapsing MCD, Rituximab proved to be cost effective and well tolerated. Burden of medication with attendant side effects, as well as inpatient and outpatient attendance were significantly reduced. Annualised costings showed a modest saving post Rituximab. Further randomised studies are required to confirm and extend these findings.

FR-PO429

Long-Term Outcomes of Nephrotic Syndrome, from Childhood into Adulthood

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Background: Steroid Resistant Nephrotic Syndrome (SRNS) is known to have several long term sequelae including chronic and End Stage Kidney Disease (CKD and ESKD). However there are few studies on the long-term outcomes of steroid sensitive nephrotic syndrome. Presented here is a single center, retrospective case series from an urban, ethnically diverse population in the Bronx.

Methods: We utilized a medical record data mining tool to identify patients by ICD-9 code (1) with a diagnosis of nephrotic syndrome prior to age 18 (2) with a documented albumin <3.5 g/dl or random urine protein >1 g/dl and (3) with at least one hospital encounter after age 18. Patients with a history of renal biopsy or who received immunosuppressant medication other than steroids were termed complicated nephrotic syndrome (CNS). All others were termed simple nephrotic syndrome (SNS). Patients with a diagnosis of asthma prior to age 18 with at least one hospital encounter after the age of 18 were used as controls. Each cohort was evaluated for diagnosis of hypertension, osteoporosis, cataracts, infertility and malignancy. Their last height, weight and creatinine were used to evaluate their height and weight percenttile, BMI and estimated GFR by the MDRD equation.

Results: All three groups – SNS (n=173), CNS (n=169) and control (n=18225) had similar age at diagnosis, length of follow-up. Both the SNS and CNS groups had a greater proportion of short stature, cataracts, infertility and malignancy (Chi square statistic p < 0.05) [table 1]. In addition they had a greater percentage of patients with CKD by eGFR than the controls. Mean BMI of patients with SRNS and CNS were similar to the controls.

Conclusions: Our results show that even patients with uncomplicated nephrotic syndrome are at risk for significant outcomes, including chronic kidney disease. Further study is needed, however it implies that all patients with a diagnosis of nephrotic syndrome will need to be counseled regarding the risks associated with their diagnosis and should have long term monitoring for these outcomes, including worsening renal function, hypertension and malignancy.

Funding: Other NIH Support - NIH T32 Training Grant

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO430

Apolipoprotein CI Levels Are Associated with the Urinary Protein/Urinary Creatinine Levels in Pediatric Idiopathic Steroid-Sensitive Nephrotic Syndrome

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Background: Various humoral factors have been proposed as causal agents of idiopathic steroid-sensitive nephrotic syndrome (ISSNS). In the present study, we analyzed serum proteins using mass spectrometry (MS) in a search for proteins that might be related to ISSNS pathophysiology.

Methods: We collected serial serum samples from 33 children with ISSNS. The serum samples were collected in each phase as follows: Phase A1 [the acute phase prior to steroid treatment (STx)], Phase A2 [remission with STx], and Phase A3 [remission without any medication]. We also included two control groups comprised of children with normal urinalysis (Group B) and children with a nephrotic syndrome other than ISSNS (Group C). The urinary protein/urinary creatinine (UP/UCr) ratios were not statistically different between Phase A1 and Group C. We used surface-enhanced laser desorption/ionization time of flight MS to analyzed samples.

Results: A total of 207 peptide ion peaks were detected in the range of m/z 2000–10000. Four peptide ions (m/z 6444, 6626, 8695, and 8915) were significantly correlated with UP/UCr levels. The m/z 6626 was identified as apolipoprotein CI (Apo CI).

A1 compared with Phase A2, Phase A3, and Group C. The intensities of m/z 6626, 8695, and 8915 were significantly correlated with UP/UCr levels. The m/z 6626 was identified as a protein associated with the UP/UCr levels in pediatric ISSNS. Our findings provide new insight into elucidating the pathophysiology of ISSNS.

Conclusion: Apo CI was detected as a protein associated with the UP/UCr levels in pediatric ISSNS. Our findings provide new insight into elucidating the pathophysiology of ISSNS.

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FR-PO431

Ofatumumab in Two Nephrotic Syndrome Children

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Background: Rituximab (RTx), an anti-CD20 monoclonal antibody, is an effective treatment in patients with frequently-relapsing or steroid-dependent nephrotic syndrome (Ravani, JASN 2015). However, some patients develop adverse reactions. We describe the use of a humanized anti-CD20 monoclonal antibody, ofatumumab (OFA), as a viable alternative.

Methods: Patient 1 is a 3-year-old boy who presented at 18 months with NS initially resistant to treatment with oral prednisone. He was then treated with 3 iv boluses of methylprednisolone followed by cyclosporinaA, with remission. Upon steroid discontinuation, NS relapsed. Prednisone was restarted and a single dose of RTx was planned, but was never completed as at start of infusion a severe allergic reaction (urticaria, dyspnea) occurred. Patient 2 is a 14-year-old boy with SDNS since the age of 2 years treated with oral prednisone, cyclosporinaA and micophenolate mofetil (MMF), with the development of severe obesity. A first infusion of RTx at age 12 was well tolerated and allowed prednisone discontinuation for over 2 years. Then a prolonged (>30 days) relapse occurred under treatment with oral prednisone, MMF and cyclosporinA. Therefore, a second RTx infusion was attempted, but the child presented severe dyspnea and it was interrupted. The use of OFA at 1.5 g/1.73 m2, described in steroid-resistant NS children (Basu, NEJM 2014), was attempted. In patient 2 OFA was preceded by three boluses of iv methylprednisolone to induce remission.

Results: In pt 1, OFA infusion was uneventful. In pt 2, a mild allergic reaction was observed and treated. Remission was maintained during the follow-up period (9 months for pt 1, 5 months for pt 2), despite the interruption of prednisone treatment in both patients, and in pt 1 of cyclosporinaA, while in pt 2 of MMF with ongoing cyclosporinaA at last follow-up. After OFA infusion, CD19+ B cells reappeared at 7 months in pt 1, while remained depleted (0%) at 5 months in pt 2.

Conclusions: OFA could be a therapeutic option in managing severe forms of drug-resistant nephrotic syndrome in patients who have developed intolerance to RTx.

Funding: Private Foundation Support

FR-PO432

Population-Based Identification of Children with Primary Nephrotic Syndrome: Kaiser Permanente Nephrotic Syndrome Study

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Background: Few population-based data exist about children with primary nephrotic syndrome (NS) in the US. We identified a cohort of children with primary NS in a large integrated healthcare system.

Methods: Kaiser Permanente Northern California cares for >750,000 children. We identified members age<18 yrs between 1996-2012 who had nephrotic range proteinuria (UACR>3500 mcg/mg, PCR>3 mg/mg, 24-hr protein>3500 mg, dipstick>300 mg/dL) or diagnosed NS (ICD-9 581.x) in electronic records and lab databases. Nephrologists reviewed records for clinical presentation, lab and biopsy results to confirm primary NS.

Results: We identified 179 children with NS due to minimal change disease (72%), focal segmental glomerulosclerosis (23%) or membranous nephropathy (5%). Incidence was 1.47 per 100,000 (95% CI 1.27-1.70). Biopsies were available in 40% of cases. Baseline features at diagnosis are shown by cause of NS.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Overall</th>
<th>Minimal Change Disease</th>
<th>FSGS (N=42)</th>
<th>Membranous Nephropathy (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) age, yr</td>
<td>6.9 (3.7-12.9)</td>
<td>5.9 (3.6-9.9)</td>
<td>11.4 (6.3-16.2)</td>
<td>14.5 (3.3-16.5)</td>
</tr>
<tr>
<td>Female, N(%)</td>
<td>77 (43)</td>
<td>58 (45)</td>
<td>16 (38)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Race, N(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>46 (26)</td>
<td>31 (24)</td>
<td>12 (29)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Black</td>
<td>23 (13)</td>
<td>15 (12)</td>
<td>7 (17)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>31 (17)</td>
<td>29 (23)</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Other/unk</td>
<td>79 (44)</td>
<td>44 (41)</td>
<td>21 (49)</td>
<td>4 (49)</td>
</tr>
<tr>
<td>Hispanic ethnicity, N(%)</td>
<td>57 (32)</td>
<td>37 (29)</td>
<td>17 (41)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Baseline lab results</td>
<td></td>
<td></td>
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<tr>
<td>Median (IQR) serum creatinine, mg/dl</td>
<td>0.4 (0.3-0.7)</td>
<td>0.4 (0.3-0.6)</td>
<td>0.7 (0.4-1.3)</td>
<td>0.4 (0.4-0.9)</td>
</tr>
<tr>
<td>Missing, N(%)</td>
<td>67 (37)</td>
<td>46 (36)</td>
<td>20 (48)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Median (IQR) serum albumin, mg/dl</td>
<td>1.7 (1.5-2.2)</td>
<td>1.6 (1.5-2.1)</td>
<td>2.0 (1.6-2.7)</td>
<td>2.1 (1.7-3.8)</td>
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<td>Missing, N(%)</td>
<td>86 (48)</td>
<td>56 (43)</td>
<td>26 (62)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl, N(%)</td>
<td>&lt;=240</td>
<td>10 (5)</td>
<td>8 (6)</td>
<td>2 (5)</td>
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<tr>
<td>Missing</td>
<td>113 (63)</td>
<td>78 (61)</td>
<td>30 (71)</td>
<td>5 (62)</td>
</tr>
</tbody>
</table>

Conclusions: Leveraging electronic health records and linked data sources, we identified a population-based cohort of children with primary NS that will provide a unique platform for describing the natural history of NS and identifying predictors of adverse outcomes.

Funding: Private Foundation Support

FR-PO433

Abatacept Treatment and B-1 Immunostaining in Patients with Primary and Post-Transplant FSGS

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Background: Podocyte B7-1 expression has been implicated in the pathogenesis of idiopathic nephrotic syndrome for many years. Recently, podocyte B7-1 was described as a potential therapeutic target by demonstrating efficacy of B7-1 blocking agent abatacept in five patients with primary and post-transplant FSGS (Yu et al. New Engl J Med 2013). The authors speculated that patients who will respond to abatacept can be identified by positive B7-1 immunostaining on kidney biopsy. Here, we report our experience with abatacept and B-1 staining in patients with FSGS.

Methods: Patients with no or partial proteinuria remission after plasmapheresis for treatment of FSGS received abatacept (2 or 3 doses of 10 mg/kg). After several trials of unsuccessful immunofluorescence staining, we performed B7-1 immunohistochemistry on paraffin embedded tissue with a primary antibody mouse anti CD80 (R&D systems).

Results: Three patients with post-transplant FSGS, and one patient with FSGS in the native kidney (Table, Patient 4) were treated with abatacept. All transplant patients had developed nephrotic proteinuria immediately after transplantation. Patient 1 had been treated with plasmapheresis for many years, and was previously unresponsive to B7-1 blocking agent belatacept. None of the patients had proteinuria remissions after abatacept, nor did we observe positive podocyte B7-1 immunostaining.

Conclusions: In our hands B7-1 staining was absent in patients with FSGS. Our data caution against too much optimism regarding the efficacy of abatacept.
Steroid Resistant Nephrotic Syndrome: A Prospective, Open Label Study of the Safety and Efficacy of Combination Tacrolimus and ACTH

**Background:** Steroid resistant nephrotic syndrome (SRNS) in adults is associated with increased risk for progression to ESRD. Tacrolimus is a calcineurin inhibitor (CNI) that is an alternative to steroids, but is associated with progressive fibrosis and loss of GFR. ACTH gel has shown benefit in the treatment of SRNS. To investigate additive effects, we followed 23 SRNS patients receiving combination therapy with Tacrolimus and ACTH Gel.

**Methods:** 23 patients with SRNS (IMGN 8, 11 FSGS and 4 other) receiving ACEi/ARB and 8 weeks of oral steroids prior to combination therapy of ACTH and Tacrolimus. Eleven patients received 2 or more drug therapies. Of the 23, 17 (71%) initially received IMGN therapy followed by Tacrolimus. Duration of ACTH/TAC therapy averaged 6.2 months (range 1-12 months). Complete or partial responses were defined as UP/Cr ratio of < 0.30, <0.5, <1.0, <2.0, <5.0, and <10.0, respectively (all p<0.0001). After adjustment, differences were attenuated but remained statistically significant for demographic, socioeconomic, and comorbidity differences.

**Results:** Of the 23 patients, 6 (26%) achieved a complete response; a partial responses were observed in 11 (48%) for an overall response of 74%. Proteinuria levels (expressed as a UP/Cr ratio) before and after treatment are listed in the Table. There was no difference in the rate or time to complete or partial remission between IMGN and FSGS (IMGN: 82%; 6.1 ± 0.8 mths; FSGS: 75%; 7.0 ± 1.5 mths). Complete or partial remission was achieved in 92% (21) of patients with IMGN. Of the 23 patients, 6 (26%) achieved a complete response; a partial responses were observed in 11 (48%) for an overall response of 74%. Proteinuria levels (expressed as a UP/Cr ratio) before and after treatment are listed in the Table. There was no difference in the rate or time to complete or partial remission between IMGN and FSGS (IMGN: 82%; 6.1 ± 0.8 mths; FSGS: 75%; 7.0 ± 1.5 mths). Complete or partial remission was achieved in 92% (21) of patients with IMGN.

**Conclusions:** In the Tac cohort a higher remission rate was demonstrated and a suggestion of fewer adverse events although numbers are small. However the baseline parameters show the GFR was significantly lower in the prednisolone group. Patients treated with Tac had a longer duration of treatment but appeared to have a better adverse event profile overall. A randomised controlled trial is required to investigate this further.

**FR-PO436**

**Differences in Initial End Stage Renal Disease (ESRD) Treatment Modality Across Glomerulonephritis Subtypes**

Michelle M. O’Saughnessy,1 Maria E. Montez-Rath,2 Richard A. Lafayette,2 Wolfgang C. Winkelmayer3

**Background:** Kidney transplantation (Tx) is the treatment of choice for end-stage renal disease (ESRD). Hemodialysis (HD) and peritoneal dialysis (PD) outcomes are largely equivalent. Whether access to these modalities is equal across glomerulonephritis (GN) subtypes has not been established.

**Methods:** We identified all patients in the US Renal Data System 18-75 years who initiated ESRD treatment with Tx, HD, or PD (1996-2011) and had ESRD attributed to 6 GN subtypes [focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranous nephropathy (MN), membrane-proliferative GN (MPGN), lupus nephritis (LN), vasculitis]. Odds ratios (ORs) for PD vs HD and for Tx vs HD were computed using multinomial logistic regression (IgAN as reference group), with multivariate adjustment for demographic, socioeconomic, and comorbidity differences.

**Results:** Among 75,278 patients studied, demographic, socioeconomic, and comorbidity characteristics differed considerably across GN subtypes. In unadjusted analyses, patients with FSGS, MN, MPGN, LN, and vasculitis were significantly less likely to receive Tx or PD as a first ESRD treatment modality than patients with IgAN: OR for Tx 0.52, 0.35, 0.48, 0.23, and 0.13, respectively; OR for PD 0.77, 0.66, 0.59, 0.48, and 0.30, respectively (all p<0.0001). After adjustment, differences were attenuated but patients with secondary GN subtypes (LN, vasculitis) remained significantly less likely to receive Tx or PD as compared to patients with IgAN (figure).

**FR-PO435**

**Treatment of Nephrotic Syndrome Secondary to Primary FSGS – Prednisolone or Tacrolimus? A Two Centre Experience**

Hannah R. Wilson,1 Thomas M. Connor,2 Tom Cairns,2 Mona Saleh Wahba,2 Marie B. Condon,1 Megan Griffith.3

**Background:** Focal segmental glomerulosclerosis (FSGS) is a significant cause of end-stage renal failure. Patients with nephrotic syndrome have a worse prognosis. Current guidelines advise prolonged prednisolone (pred) at 1mg/kg. Tacrolimus (Tac) is an alternative for patients, but long-term therapy is often necessary, and there are concerns about toxicity.

**Methods:** Retrospective review of all patients with nephrotic syndrome secondary to primary FSGS treated with a minimum of 12 mths follow-up at 2 centres. All patients received standard therapy with max tolerated ACEi +/- ARB. Complete remission (CR) was defined as normal serum albumin with PCR <50; partial remission (PR) as proteinuria ≤50% baseline. Results described as Median (Range); p value <0.05 significant.

**Results:**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Pred n=15</th>
<th>Tac n=23</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 (19-75)</td>
<td>45 (19-78)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>8M, 7F</td>
<td>12M, 11F</td>
<td>ns</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Follow up (mths)</td>
<td>45 (12-257)</td>
<td>45 (12-86)</td>
<td></td>
</tr>
<tr>
<td>Baseline parameters</td>
<td>Creatinine umol/L</td>
<td>167 (61-480)</td>
<td>101 (52-312)</td>
</tr>
<tr>
<td></td>
<td>%creatinuria</td>
<td>87%</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>UP/Cr ratio</td>
<td>906 (478-1910)</td>
<td>1033 (602-3626)</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>23 (10-30)</td>
<td>16 (9-27)</td>
</tr>
</tbody>
</table>

**Results:**

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Age</th>
<th>Baseline</th>
<th>Peak</th>
<th>ACTH</th>
<th>ACTH+TAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responder</strong></td>
<td>17</td>
<td>6-2</td>
<td>11.0±1.1</td>
<td>3.3±1.0</td>
<td>1.4±0.4</td>
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</tr>
<tr>
<td>IMN</td>
<td>6</td>
<td>58±2</td>
<td>13.7±2</td>
<td>4.9±1.2</td>
<td>1.2±0.5</td>
<td></td>
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<tr>
<td>FSGS</td>
<td>9</td>
<td>6±7</td>
<td>10.4±1.4</td>
<td>2.6±0.5</td>
<td>1.7±0.9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>58±2</td>
<td>12.4±2.0</td>
<td>0.3±0.2</td>
<td>0.6±0.7</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Responder</strong></td>
<td>6</td>
<td>52±2</td>
<td>11.6±1.5</td>
<td>5.7±1.5</td>
<td>7.8±1.5</td>
<td></td>
</tr>
<tr>
<td>IMN</td>
<td>3</td>
<td>46±7</td>
<td>11.6±2.9</td>
<td>7.6±2.5</td>
<td>9.2±4.3</td>
<td></td>
</tr>
<tr>
<td>FSGS</td>
<td>3</td>
<td>52±8</td>
<td>11.8±2.5</td>
<td>7.4±2.6</td>
<td>7.3±1.6</td>
<td></td>
</tr>
</tbody>
</table>

Of the 23 patients, 6 (26%) achieved a complete response; a partial responses were observed in 11 (48%) for an overall response of 74%. Proteinuria levels (expressed as a UP/Cr ratio) before and after treatment are listed in the Table. There was no difference in the rate or time to complete or partial remission between IMGN and FSGS (IMGN: 82%; 6.1±0.8 mths; FSGS: 75%; 7.0±1.5 mths). Complete or partial remission was achieved in 92% (21) of patients with IMGN. Of the 23 patients, 6 (26%) achieved a complete response; a partial responses were observed in 11 (48%) for an overall response of 74%. Proteinuria levels (expressed as a UP/Cr ratio) before and after treatment are listed in the Table. There was no difference in the rate or time to complete or partial remission between IMGN and FSGS (IMGN: 82%; 6.1±0.8 mths; FSGS: 75%; 7.0±1.5 mths). Complete or partial remission was achieved in 92% (21) of patients with IMGN.

**Conclusions:** In the Tac cohort a higher remission rate was demonstrated and a suggestion of fewer adverse events although numbers are small. However the baseline parameters show the GFR was significantly lower in the prednisolone group. Patients treated with Tac had a longer duration of treatment but appeared to have a better adverse event profile overall. A randomised controlled trial is required to investigate this further.
FR-PO437
Non Collapsing Focal and Segmental Glomerulosclerosis in Patients with HIV

**Background:** With the improvement of the treatments against HIV, non collapsing focal and segmental glomerulosclerosis (FGS) has become more frequent than HIV associated nephropathy (HIVAN). However, the pathophysiology of non-collapsing FSGS among HIV patients remains poorly understood. We thus aimed to compare patients with HIV and non-FSGS patients with HIVAN and with non HIV patients with FSGS.

**Methods:** HIV patients with a kidney biopsy in our center between 2000 and 2012 (24 non collapsing FSGS and 13 HIVAN) and two control groups (10 primary and 12 secondary FSGS) were included. Clinical and biological data were collected; viral load in serum and urine was assessed, and patients underwent anticoagulation.

**Results:** Clinical and biological features of HIV patients with non-collapsing FSGS were close to those of controls with secondary FSGS. Among HIV patients, the prevalence of cardiovascular risk factors was greater in those with non collapsing FSGS than in those with HIVAN (79% vs. 38%, p=0.01) but was comparable to the one in controls with secondary FSGS (100% vs. 79%, NS). HIV patients with non collapsing FSGS and controls with secondary FSGS had more frequently arteriolosclerosis on the biopsy than patients with HIVAN (75% and 82% vs 36%, p<0.01). Visceral epithelial cells expression of PCNA showed that, despite a stronger staining in collapsing lesions, it can be found among all patients groups and in any FSGS lesion type. The majority of HIV patients with non collapsing FSGS had undetectable viral load in serum and urine.

**Conclusions:** Major clinical, biological and histological differences between HIV patients with non collapsing FSGS and HIVAN support the hypothesis that the diagnosis of HIVAN needs to be excluded among patients at risk for FSGS. An association between idiopathic FSGS and HIVAN is suggested, and the risk of collapsing FSGS should be considered among patients with HIVAN.

**Funding:** Private Foundation Support

FR-PO438
Diabetic Glomerulosclerosis or Idiopathic Nodular Glomerulosclerosis – Role for Insulin Resistance

**Background:** Diabetic nephropathy (DN) is characterized histologically by nodular mesangial sclerosis, a thickened glomerular basement membrane, and hyalinized arterioles. Differential diagnoses by light microscopy (LM) include membranoproliferative glomerulonephritis, amyloidosis, monoclonal immunoglobulin deposition disease, and fibrillary or immunofluorescent glomerulopathy. These can readily be excluded by special staining, immunofluorescence (IF) and electron microscopy (EM). Idiopathic nodular glomerulosclerosis (ING) is the term used to denote classic DN confirmed by LM, IF, and EM, but in the absence of diabetes mellitus (DM). Case reports suggest insulin resistance (IR) as a possible cause.

**Methods:** Data was collected retrospectively on 21 cases of diabetic glomerulosclerosis or ING biopsied due to proteinuria (>1 g on urinalysis to 12.3 g/days), or with or without renal insufficiency (creatinine 0.6-4.4 mg/dL).

**Results:** 13 patients were male with majority of patients being African American (10) and non-Hispanic white (7). 1 patient was post renal transplant and another post liver transplant. None of these patients were diagnosed with DM, although some had intermittently elevated blood glucose and borderline HbA1c. All patients had hypertension, but only 5 were active tobacco users and 8 were former smokers. BMI range was 21-43kg/m². Hemoglobin A1c range was 4.6-6.1% in 10 patients and 6 patients denied DM by telephone survey. The remaining 5 patients had no history of DM per records with few elevated random plasma glucose levels found on 24h iodixanol. None of them fulfilled current diagnostic criteria for DM. Metabolic syndrome (MS) defined by Adult Panel III criteria was evident in 11 patients.

**Conclusions:** The pathogenesis of ING remains unclear. It involves the interplay of hypertension, obesity, and heavy smoking. We feel that IR is critically important, whether evident as subtle, prediabetic elevations of blood glucose, MS, or elevated HOMA-IR score being the only manifest feature. Insulin sensitivity assessed by HOMA-IR score is possibly an important predictive factor in pathophysiology of ING and needs to be tested routinely.

**Funding:** NIDDK Support, Veterans Administration Support

FR-PO439
Association of Serum Albumin Level and Venous Thromboembolic Events in Seven-Thousand Patients with Nephrotic Syndrome

**Background:** Prior studies have shown that low serum albumin in patients with nephrotic syndrome (NS) is associated with an increased risk of venous thromboembolic (VTE) events. This is based on small studies with a low number of thromboembolic events and short term follow-up.

**Methods:** From a nationally representative cohort of over 3 million US veterans with baseline estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m², we identified 7037 patients with NS based on ICD-9 codes. Association between serum albumin level and risk of incident VTE events (based on ICD9 codes) was assessed using Cox regression analysis with adjustments for age, gender, race, comorbidities, eGFR, BMI, and anticoagulant treatment.

**Results:** Mean age was 57±11 years, and patients were 96% male, 32% African-American and 60% diabetic. There were a total of 158 VTE events over a median follow-up was 8.1 years (16 events (4.1%, event rate (ER): 8.5/1000 patient-years(PY)) in patients with albumin < 2.5 g/dl, 18 events (3.4%, ER: 5.7/1000 PY) in patients with albumin 2.5-2.99 g/dl, 89 events (2.5%, ER: 3.4/1000 PY) in patients with albumin 3-3.99 g/dl and 55 events (1.4%, ER: 1.9/1000 PY) in patients with albumin ≥ 4 g/dl. Compared to patients with albumin < 2.5 g/dl, those with albumin levels of 3-3.99 g/dl (adjusted HR: 1.51; 95%CI: 1.01-2.26), 2.5-2.99 g/dl (2.24, 1.24-4.05) and < 2.5 g/dl (2.79, 1.45-5.37) experienced a linearly higher risk of VTE events.

**Conclusions:** Lower serum albumin is a strong incremental risk factor for VTE events in NS. The risk increases proportionately with declining albumin levels. Our finding may have important clinical implications regarding initiation and duration of prophylactic anticoagulation.

**Funding:** NIDDK Support, Veterans Administration Support

FR-PO440
Hypercoagulopathy Is Directly Correlated with Disease Severity in Nephrotic Syndrome

**Background:** Nephrotic syndrome (NS), a leading cause of end stage kidney disease, is characterized by massive proteinuria, hypoalbuminemia, and an increased risk for venous thromboembolism (VTE). We recently reported that hypercoagulopathy is proportional to the severity of both proteinuria and hypoalbuminemia in two animal models of NS. This study was designed to determine if this relationship translates to human NS.

**Methods:** Aliquots of plasma anticoagulated with 0.32% (final concentration) sodium citrate were obtained from the NEPTUNE biorepository (n=147 patients), along with corresponding clinical lab data (e.g. urine protein/creatinine (uPC), serum albumin (sAlb)). Samples collected from a local patient cohort (n=21) were used to validate biorepository

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
specimen integrity. Endogenous thrombin potential (ETP) was determined using the
Technochromin TGA kit and RC Low reagent after 2.1 dilution with buffer. Plasma antithrombin
(pAT) activity was measured by the amidolytic method.

Results: As expected, NEPTUNE patients exhibited a wide range of proteinuria values
(median (range) uP:C: 1.85 mg/mg (0-17.6)). Hypoalbuminemia and proteinuria severity were
proportional to ETP (R=-0.252 & 0.128, respectively, P<0.001). These correlations were stronger in
the subset of patients with uP:C>2 (R=-0.331 & 0.157, respectively, P<0.001). Plasma AT activity
was also significantly correlated to hypoalbuminemia and proteinuria severity (R=(-0.125 & 0.031, P<0.03, respectively). There was no correlation between TA AT activity and ETP. Results were similar in the validation cohort.

Conclusions: Both hypoalbuminemia and proteinuria severity in humans with NS is
significantly, albeit weakly, correlated to ETP (an established marker of thrombotic risk).
Adjusting these data for clinical variables (e.g. smoking status, BMI, etc.) may aid in the modeling and development of evidence-based cut-offs to guide indications for prophylactic anticoagulation.

Funding: NIDDK Support

FR-PO441

Successful Social Media Recruitment into the NephCure Kidney Network, a Rare Disease Patient Registry

Laura Hay, Jennifer H. Mariani, Joanna Dauber, Chelsey Fix, Alyssa Fisher, Jane Shen, Lalita Subramanian, Marilyn Hairperin, Elizabeth L. Cope, 1 Arbor Research Collaborative for Health, NephCure Kidney International.

Background: Participation in clinical research for primary nephrotic Syndrome (NS) has been
limited by the rarity of the disease. There is growing interest in leveraging social media to expand
geographic and demographic reach for recruitment. Because of the妮志ing nature of rare
diseases, patients turn to social media for support, creating online communities that, if accessible, could potentially serve as a resource for recruitment.

Methods: The NephCure Kidney Network (NKN) is a web-based patient opt-in registry for
recruiting patients into clinical trials. Participation is in whole, including kidney disease history, demographics and research participation preferences. Recruitment efforts launched in March 2014 relied on email campaigns to contacts of the patient advocacy group, NephCure Kidney International (NKI), but then expanded in September 2014 to include social media. Weekly posts were made to NKN’s Facebook page, with analysis of performance based on impressions (# of people reached) and engagements (likes, clicks, shares, comments). Relationships with other closed Facebook kidney disease groups were established and posts made to their sites.

Results: 45,151 impressions and 2,927 engagements were made from 9/2014-6/2015. Of
patients who participated, 54% were recruited through social media.

Conclusions: A recruitment strategy which includes social media is an efficient, cost-
effective opportunity to engage rare disease patients across a wide geography, including
those who have not previously participated in research.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO442

The Expression of Podocyte Protein PREX2 in Glomerular Diseases

Anna Levin, 1 Julia Wijkström, 1 Jenny Hulko, 1 Jenny C. Nystrom, 2 Kerstin Ebefor, 3 Annette Bruchfeld, 1 Jaakko Patrakk, 4 Kjell Hultenby, 1 Anniika Wernerson, 3 CLINTEC, Karolinska Inst (KI), Stockholm, Sweden; Dept of Physiology, Sahlgrenska Academy, Gothenburg, Sweden; 2 Dept of Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg, Sweden; 3 Dept of Medicine, KI, Stockholm, Sweden; 4 LabMed, KI, Stockholm, Sweden.

Background: Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor
(PREX2) is a 183 kDa protein that functions as a RAC guanine nucleotide exchange factor (GEF), activating Rac proteins. It has been discovered in several tissues, e.g. brain, lung, liver and kidney. The specific function of PREX2 in the kidney is unknown. The aim of the present study was to investigate the localization of PREX2 in the kidney and the possible role in renal disease.

Methods: RT-PCR, Western Blot and immunohistochemistry (IHC) was used to identify the
localization of PREX2 in renal tissue. The mRNA expression in diseased kidney was
analyzed by microarrays on isolated glomeruli from patients with IgA Nephropathy (IgAN), Membranous Nephropathy (MN) and normal tissue. Immuno electron microscopy (IEM) was used to semiquantify PREX2 in renal biopsies from patients with IgAN (n=6), Minimal Change Nephropathy (MCN, n=5) and control tissue from healthy kidney donors (n=5).

The morphology was correlated to proteinuria at time of biopsy.

Results: RT-PCR and Western Blot showed the presence of PREX2 in glomerulus, IHC and IEM revealed that PREX2 was localized to podocyte foot processes. In disease samples, mRNA levels were not changed in IgAN and MN. Semi-quantitative IEM showed a significantly lower expression of PREX2 in IgAN and MCN compared to controls. A tendency towards a negative association between PREX2 and proteinuria was seen, although this was not significant.

Conclusions: We found that PREX2 is a new podocyte-associated protein. Although no difference in mRNA levels were found, the expression of PREX2 was significantly
lower in IgAN and MCN compared to controls. The function of PREX2 in the glomerular formation is still unknown but it will now be further investigated in an extended patient cohort and in genetically modified animals.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO443

Urinary and Serum Soluble Urokinase Receptor Levels Predict the Therapeutic Response of Nephrotic Syndrome

Kohei Fujimoto, Yuki Matsui, Norifumi Hayashi, Junko Imura, Hiroki Adachi, Hideki Yamaya, Hitoshi Yokoyama. Div of Nephrology, Kanazawa Medical Univ, Uchinada, Ishikawa, Japan.

Background: It is necessary to develop noninvasive biomarkers to predict the treatment response for nephrotic syndrome (NS), and to differentiate their histological types in the initial phase.

Methods: The subjects were 32 patients with primary NS [8 with focal segmental
glomerulosclerosis (FSGS), 12 with minimal change nephrotic syndrome (MCNS), 10 with membranous nephropathy (MN), and 2 with membranoproliferative glomerulonephritis]. Using ROC analysis, we examined whether or not it is possible to differentiate refractory NS from non-refractory NS, and MCNS from FSGS based on the pretreatment values of clinical markers [urinary protein (UP), serum/urinary soluble urokinase receptor (su-) uPAR, urinary L-FABP, and eGFR], and values and changes (Δ) after 2 months (2M).

We also examined the renal expression of activated b3 integrin (AP-3) by immuno-staining in
primary NS and normal tissues.

Results: The following parameters were useful for differentiating refractory NS from
non-refractory NS: 2M (AUC=0.968, p=0.001), 2Ms-suPAR (AUC=0.913, p=0.002), D2Ms-suPAR (AUC=0.906, p=0.007), D2Ms-suPAR (AUC=0.881, p=0.005), and D2MUP (AUC=0.833, p=0.014). On the other hand, D2Ms-suPAR (AUC=0.905, p=0.007) and D2Ms-suPAR (AUC=0.816, p=0.048) were useful for differentiating MCNS from FSGS. In addition, u-suPAR before treatment was positively correlated with UP (p=0.501, p<0.003) and urinary L-FABP (p=0.427, p=0.017). The expression of activated b3 integrin was primarily strong in the proximal tubular epithelial cells in FSGS or MN, but, weak in MCNS and normal tissues. Otherwise, there was no expression of activated b3 integrin on podocytes in both normal and diseased tissues.

Conclusions: It may be possible to evaluate the treatment response of NS and to
differentiate MCNS from FSGS based on changes in u-suPAR within 2 months after the start of treatment. As a mechanism involved in proteinuria in NS patients, u-suPAR may inhibit protein reabsorption in the proximal tubules through the activation of b3 integrin.

FR-PO444

Turkish Atypical Hemolytic Uremic Syndrome Registry: Initial Pediatric Results

Nesrin Besbas, 1 Oguz Soylenmezoglu, 2 Bora Gulhan, 1 Z birsin Ozcaner, 3 Emine Korkmaz, 4 Fatih Ozatins. 1 Pediatric Nephrology, Faculty of Medicine Hacettepe Univ, Ankara, Turkey; 2 Pediatric Nephrology, Faculty of Medicine Gazi Univ, Ankara, Turkey; 3 Pediatric Nephrology, Ankara Univ Faculty of Medicine, Ankara, Turkey; 4 Nephrogenetics Laboratory Dept of Pediatric Nephrology, Hacettepe Univ, Ankara, Turkey.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, genetic, life-
threatening disorder of chronic complement activation leading to systemic thrombotic
microangiopathy and end-organ damage. The national aHUS registry was initiated in November 2013 and collects information on the progression and treatment of disease.

Methods: A clinical diagnosis of aHUS is required for inclusion. Demographic, medical histories, treatments, efficacy and safety outcomes data are collected initially and every 3 months.

Results: By May 15, 2015, 122 pediatric patients (55.8% female and 44.2% male) were
enrolled from 22 centers covering all the country. Mean age at diagnosis was 4.38±4.23 years. A total of 90 patients (74.6%) had oliguria or anuria at the time of diagnosis. Serum complement 3 was low in 49 patients (40.2%). Neurologic system involvement was present in 34 patients (27.2%). Renal biopty was performed in 37 patients (30.7%). Renal replacement therapies (RRT) were initiated in 61.5 % of the patients at administration where only 10% of the patients were discharged with RRT. Genetic studies including the complement pathway, DGKE and factor H antibodies were studied in 73% of patients. Plasma infusion or plasma exchange was the initial treatment in 82% of patients and 59% of patients (n=72) had eculizumab treatment. At the time of discharge after initial management, 78 patients (63.9%) and 92 patients (75.4%) achieved renal and hematological remission, respectively. Four patients died at the acute stage of the disease. Mean duration of follow-up was 2.28±2.30 years. During follow-up, eculizumab was stopped in 18 patients and re-started in four of them due to relapse.

Conclusions: The pediatric aHUS Registry will provide data to help increase our
knowledge of the aHUS patient with different genetic background and also evaluate the
long-term safety and efficacy of treatment options including the eculizumab.
FR-PO445

Long-Term Outcomes of Thrombotic Microangiopathy Treated with Plasma Exchange – A Systematic Review

Background: The adoption of plasma exchange as standard treatment for thrombotic microangiopathy, more patients are surviving and longer-term outcomes have greater relevance.

Methods: We conducted a systematic review of observational studies between 1980 and 2013 that reported outcomes of adults with thrombotic microangiopathy at least 6 months after initiating plasma exchange. We searched several databases from 1980 to 2013 for eligible articles published in any language. We abstracted data in duplicate and assessed the methodological quality of each study using an assessment tool developed based on recommended validity criteria.

Results: We screened 6672 articles, reviewed 213, and included 34 studies totaling 1182 patients (study median range, 24 [10-118]). The (mean or median) follow-up ranged from 6 months to 13 years. The cumulative incidence of relapse and mortality was highly variable and ranged from 3 to 84% and 0 to 61%, respectively. The incidence of other outcomes across 10 studies also varied (outcomes included hypertension, kidney disease, preeclampsia, stroke, seizure, severe cognitive impairment, and depression); in 3 other studies long-term neurocognitive function and health-related quality of life were significantly lower than the general population.

Conclusions: In summary, patients who survive an episode of thrombotic microangiopathy may be susceptible to long-term vascular complications including chronic kidney disease, but the magnitude of this risk and how to mitigate it remains unclear from prior studies.

FR-PO446

Eculizumab Prevents Thrombotic Microangiopathy in Atypical Hemolytic Uremic Syndrome Patients: Long-Term Follow-Up

Background: In previous studies of patients (pts) with aHUS, ECU effectively treated and prevented thrombotic microangiopathy (TMA) and improved renal function and hematological parameters for up to 2 yrs.

Methods: An observational, multicenter, long-term follow-up study of aHUS pts treated with ECU in 5 prior clinical studies. The primary endpoint was exposure/follow-up TMA event rate post-parent study on-(ON) and off-treatment (OFF; among pts who were treated and prevented thrombotic microangiopathy (TMA) and improved renal function and hematological parameters for up to 2 yrs.

Results: 85 pts enrolled (Table); of these, 74 pts had ON and 37 pts had OFF treatment periods with median follow-up of 24.6 and 16.6 months, respectively. The TMA event rate was 6.7 per 100 pt-yrs for ON pts, and 23.5 per 100 pt-yrs for OFF pts. The rate of TMA events while on or off-label and standard dose and quality of life were significantly lower than the general population.

Conclusions: In summary, patients who survive an episode of thrombotic microangiopathy may be susceptible to long-term vascular complications including chronic kidney disease, but the magnitude of this risk and how to mitigate it remains unclear from prior studies.

FR-PO447

An Update on Tailored Eculizumab Maintenance Treatment in Patients with Atypical Haemolytic Uremic Syndrome

Background: Atypical hemolytic uremic syndrome (aHUS) is a severe, systemic thrombotic microangiopathy often related to mutations in the genes encoding complement regulatory proteins. Since 2009, Eculizumab (ECU) has been successfully used in patients (pts) with aHUS. The standard maintenance treatment suggests ECU administration every two weeks (wks), life-long but the best treatment schedule is not yet defined. To update on our experience on individualized ECU treatment schedule for preventing relapses based on drug biological activity, with the rational of improving the patient’s quality of life, reducing the risk of adverse reactions and reducing the heavy costs of the treatment.

Methods: Pts undergoing ECU treatment at our Center were addressed to a progressive extension of the interval between ECU doses from the standard 2 wks to 3 or 4 wks with a strict monitor of global complement activity. APS0 was routinely determined before each ECU administration and the interval between doses was adjusted with the target of maintaining APS0<25%. Strict monitoring of indicators of disease reactivation, namely blood in the urine with home dipstick, was regularly performed.

Results: The interval between doses was extended in 33 pts (13 ≤ 18 yrs) with a median age of 28.1 yrs (5-62), 17 F, 21 with native kidney and 12 with graft. Identified mutations were: CFI-15, CFI-2, CD46-1; MCP-1; CFI-3; C9H2; CFB1; CFBH1 homoz. deletion with (3) or w/o (1) antiFHAb;4; multiple mutations;3; Idiopathic:7. In 19 pts the optimal interval between ECU doses was 4 wks while in 14 pts it was 3 wks. No relapses was observed after discontinuation of ECU compared with 748 mos (mean 23 mos/pt).

Conclusions: In patients with aHUS, our experience supports the possibility of tailoring ECU maintenance treatment schedule based on global complement activity. In a cohort of 10 adult pts the described novel approach leads to an average estimated saving >2 million USD/yr.

FR-PO448

Chemokines as Potential Biomarkers of Renal Involvement in Scleroderma

Background: Renal disease in scleroderma (SSc) remains a major clinical challenge. Previous studies showed up to 50% of SSc patients have CKD. We sought to gain insight into the progression of SSc renal disease by examining markers of disease in serum and urine.

Methods: We collected urine and serum from 80 SSc patients, with or without renal disease, for comparison with patients with CKD of other causes (n=10) and healthy controls (n=12). We performed multiplex analysis of candidate markers of disease activity or severity in SSc and renal injury: MCP-1, MCP-3, IL-6, IL-18, TNF-a, and VEGF.

Results: 40 SSc patients had CKD defined by eGFR and urinalysis. Serum MCP-1 was increased in SSc compared with controls, with SSc-CKD significantly lower than SSc without CKD. Mean serum MCP-1 was 132 pg/ml (95% CI 105-162) for SSc with normal renal function compared with 65 pg/ml in SSc-CKD (p<0.001 for this comparison).

Conclusions: MCP-1 was not increased in CKD of other causes (mean 47 pg/ml, 23-85) compared with

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controls (mean 53 pg/ml, 25-85, p=0.848). Conversely, urine MCP-1:creatinine ratio was higher in SSc-CKD (mean 64, 32-111) than in SSc with normal renal function (mean 23, 18-28, p=0.046). MCP-3 was upregulated in the urine of patients with SSc with or without CKD (mean MCP-3:creatinine ratio 3.6, 2.5-4.6) compared with healthy controls (mean 0.9, 0.5-1.4, p=0.016). There was no difference between groups in serum MCP-3.

**Conclusions:** This is the first study to measure MCP-1 and MCP-3 in the urine of SSc patients. Elevated urine MCP-1 in SSc-CKD suggests increased expression in the renal tract and may help define organ-specific effects of this potential pathogenic mediator that has previously been reported to be increased in serum in association with pulmonary complications. In contrast to MCP-1, other markers of SSc severity (e.g. IL-6) or renal injury (e.g. IL-18) did not differentiate between groups. Our findings support further investigation of urine concentrations of chemokines MCP-1 and MCP-3 as markers or mediators of CKD in SSc.

**Funding:** Government Support - Non-U.S.

**FR-PO449**

Towards a Deeper Understanding of Fibrillary Glomerulonephropathies: Clinicalopathologic Analysis of Patients in a Long-Term Inception Cohort

Caroline J. Poulton, Yichun Hu, Harsharan Kaur Singh, Volker Nickeleit, William Franklin Pendergraft, UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC; UNC Pathology, UNC Chapel Hill, Chapel Hill, NC.

**Background:** Fibrillary glomerulonephritis is an uncommon primary glomerular disease. Accordingly, there are no clinical trials to guide treatment making this a challenging disease to manage. Here, we report clinical characteristics and treatment outcomes of patients with fibrillary glomerulonephropathies diagnosed and/or treated at UNC or through the Glomerular Disease Collaborative Network and compare them to a previously published cohort from Mayo clinic.

**Methods:** Patients were identified through the UNC Division of Nephropathology database. Clinical data were extracted from the electronic medical records starting at the time of initial diagnosis.

**Results:** There were 31 patients with fibrillary glomerulonephritis who were treated at UNC and another 245 patients who were diagnosed by the UNC Division of Nephropathology.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Race</th>
<th>Age</th>
<th>Serum creatinine (mg/dl)</th>
<th>Serum albumin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (61%)</td>
<td>18 (60%)</td>
<td>6.0</td>
<td>6.5</td>
<td>3.0</td>
</tr>
<tr>
<td>12 (39%)</td>
<td>8 (27%)</td>
<td>3.5</td>
<td>4.0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Conclusions:** This clinicopathologic analysis of patients with fibrillary glomerulonephritis is the largest study of its kind in the literature to date. The patients in our cohort were more ethnically diverse than the Mayo clinic group but presented with similar degrees of kidney impairment and nephrotic range proteinuria. Fibrillary mesangiocapillary is an understudied glomerular disease that portends a poor prognosis warranting the need for prospective multi-center treatment studies to determine durable therapeutic avenues.

**Funding:** NIDDK Support

**FR-PO450**

Clinical, Histologic, and Genetic Predictors of Response to MMF in C3 Glomerulopathy


**Background:** Membranoproliferative glomerulonephritis C3 Deposits: Clinicopathological study. Uriel A. Gaviria, Luis A. Castilla, Eduardo I. Navarro, Ismael Lopez, Kelly Camacho, Maia Olivero, Ismael Lopez, Gustavo Arcoa Martinez, Henry J. Gottlieb, Janet Raul Gonzalez, Marianella, Clínica de la Costa, Barranquilla, Atlántico, Colombia; Medicine, Univ Simón Bolívar, Barranquilla, Atlántico, Colombia.

**Results:** Membranoproliferative glomerulonephritis (MPGN) is a pattern of damage characterized in the light microscopy by mesangial hypercellularity, thickening of the glomerular basement membrane and mesangial interposition in the capillary wall. Recent advances in the understanding of its underlying pathogenesis led to a classification scheme based on the findings in the immunofluorescence. Alteration complement regulation has proven to be a risk factor for the development of MPGN.

**Funding:** Cross-sectional study. The data were extracted from NefroRed®, a software platform that contains the socio-demographic, anthropometric, clinical and laboratory data of 1200 patients with kidney biopsies from 2008 to 2014. It was selected for the study those patients that showed the pattern of glomerulonephritis and membranoproliferative and C3 deposits only or preponderant. Each biopsy was studied by light microscopy and immunofluorescence, light microscopy included hematoxylin-eosin, PAS, and Jones for basement membrane. Immunofluorescence was performed using antibodies directed against IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, Lightweight Kappa and Lambda chains.

**Results:** Mean age of men was 42.3 years and women was 36.7 years. The minimum age was 18 years. The maximum age was 69 years; 51.8% (n = 14) of patients were women. 1200 biopsies showed 58 injuries MPGN (5%) of these 58 cases only 27 (32%) lesions showed C3 deposits only or preponderant.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: 30% of patients with GMP have as pathogenic mechanism the complement activation with complement C3 deposition in the glomerulus. Our research group has found C3 deposition causally related to GMP. The most common clinical presentation is nephrotic syndrome.

FR-PO453
Steroids Alone for the Treatment of C3 Glomerulonephritis with Monoclonal Gammopathy
Sanjeev Sethi,1 Insara Jaffer Sathick,1 Ladan Zand,1 Samih H. Nasr,2 Sanjeev Sethi,2 Fernando C. Fervenza,1 Nelson Leung,1,2 1Div of Nephrology and Hypertension, Mayo Clinic; 2Div of Anatomic Pathology, Mayo Clinic.

Background: C3 glomerulonephritis (C3GN) is a rare disease with no trial data to direct treatment. In patients with C3GN with monoclonal gammopathy, steroids alone may be a viable treatment option.

Methods: We present our experience in managing C3GN with monoclonal gammopathy with prednisone.

Results: 5 patients presented to our institution from 2011 to 2014 with biopsy proven C3GN and underlying monoclonal gammopathy. Median age of this cohort was 63 years. Median estimated GFR by MDRD equation was 35.4 ml/min1.73m2 and median proteinuria was 2 g/day at presentation. All patients had IgG kappa monoclonal gammopathy. Patient 5 required renal replacement therapy but recovered renal function. All patients were treated with Prednisone 60mg/day tapering to zero in all except one. Patient 2 and 4 continue on 2.5-5mg/day. Median duration of follow up was 26.9 months. Median estimated GFR at presentation was 40.16 ml/min1.73m2. All patients showed improvement in proteinuria. 3/5 patients showed improvement in proteinuria. 3/5 patients showed improvement in kidney function.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>eGFR at presentation (MDRD) ml/min1.73m2</th>
<th>Proteinuria g/day</th>
<th>Serum M spike (g/dl)</th>
<th>Bone Marrow Biopsy</th>
<th>Presenting features</th>
<th>Alternative complement pathway evaluation</th>
<th>Proteinuria on follow up (g/day)</th>
<th>eGFR on follow up (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>M</td>
<td>24.6</td>
<td>1.87</td>
<td>0.6</td>
<td>&lt;5% kappa restricted cells</td>
<td>CKD, hematuria</td>
<td>C3 nephritic factor negative</td>
<td>0.14</td>
<td>24.6</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>26.2</td>
<td>2.2</td>
<td>0.5</td>
<td>10% kappa restricted cells</td>
<td>CKD, hematuria</td>
<td>Elevated soluble membrane attack complex (SMAC)</td>
<td>0.55</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>F</td>
<td>48.2</td>
<td>2.8</td>
<td>0.5</td>
<td>Normocellular</td>
<td>AKI, nephritic syndrome</td>
<td>No abnormality</td>
<td>0.82</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>M</td>
<td>37.6</td>
<td>2.6</td>
<td>1</td>
<td>&lt;5% kappa restricted cells</td>
<td>AKI with flu like symptoms</td>
<td>C3 nephritic factor positive, elevated SMAC</td>
<td>0.62</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>M</td>
<td>35.4</td>
<td>1</td>
<td>0.8</td>
<td>Hypercellular</td>
<td>AKI with flu like symptoms</td>
<td>Hemozygous for CFH/HDDD/C3G nanosociated allele: C3 nephritic factor positive</td>
<td>0.01</td>
<td>58</td>
</tr>
</tbody>
</table>

Conclusions: Our experience suggests that prednisone alone may be a treatment option in some patients with C3GN associated with a monoclonal gammopathy. Work up should be done to exclude a plasma cell neoplasm and inherited complement abnormalities.
FR-PO456

A Prospective Evaluation of Renal Contrast-enhanced Ultrasound (CEUS) in the Detection of Pyelonephritis

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Background: Contrast-enhanced ultrasound (CEUS) has been described as a promising method for detecting acute pyelonephritis (PN) and its complications. We evaluated its value in diagnosis and risk stratification in the setting of a randomized controlled trial (RCT).

Methods: Immunocompetent adults with community-acquired urinary tract infection (UTI) presenting in the emergency department of Kantonsspital Aarau were enrolled in a RCT designed to evaluate the performance of a PCT/pyuria guided algorithm versus standard guidelines (Drozdov et al. BMC Medicine 2015). Outcomes included antibiotic exposure, duration of therapy, persistent infections and recurrences/re-hospitalizations.

As part of the protocol, all hospitalized UTI patients with fever and/or flank pain were to undergo renal CEUS in addition to standard greyscale and Doppler examination within 48 hours of admission. CEUS findings were defined as: uncomplicated UTI; hyoperfused areas (HAs); or renal perfusion abnormalities (RPA).

Results: Of 70 UTI study patients hospitalized with fever and/or flank pain, 41 (59%) underwent the ultrasound study. Dropout reasons included missing consent (5%), early discharge (6) or technical (18%). Examined and non-examined patients did not differ significantly in baseline characteristics or outcome. Findings suggestive of PN were found in 5/41 (12%). In 3 patients, this was evident in greyscale/Doppler already, in 2 additional patients, critical findings were only present in CEUS. The presence of PN-suggestive findings was not predictable from any baseline clinical characteristic. Patients with and without PN-suggestive findings did not appear to differ in outcome.

Conclusions: Ultrasound evidence of pyelonephritis is rare in patients hospitalized for UTI. Adding CEUS to base greyscale and Doppler ultrasound may substantially increase the number of positive findings.

Funding: Government Support - Non-U.S.

FR-PO457

ISN 0by25 AKI Global Snapshot Project: AKI Disposition

Michael V. Rocco,1 Ravindra L. Mehta,1 Giuseppe Remuzzi,2 Jing Zhang,3 Melanie Godin,4 Michael V. Rocco,5 U Sao Paulo; 6U California San Diego; 7Mario Negri Inst; 8Sherbrooke U; 9Wake Forest U.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web-based survey tool was used to obtain data from individual clinicians on AKI pts who had a confirmed diagnosis of AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Reasons: A web based survey tool was used to obtain data from individual clinicians about AKI pts with AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Nephrology management of AKI was more common in LLMIC (85.1%) versus HIC (59.4%) or UMIC (59.8%). Location of pts 7 days after AKI diagnosis varied by GNI category. Death rate was significantly different in dialyzed (17%) vs. non-dialyzed (9%) pts (p<0.0001). Among dialyzed pts, the mortality rate was similar in countries of different GNI categories. The main reason to start dialysis was solute control, with a similar distribution among country categories.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belloc (Mirandola, Italy), Private Foundation Support

FR-PO458

ISN 0by25 AKI Global Snapshot Project: Indications for Initiating and Withholding Dialysis in AKI Worldwide

Etienne Macedo,1 Ravindra L. Mehta,1 Giuseppe Remuzzi,2 Jing Zhang,3 Melanie Godin,4 Michael V. Rocco,5 U Sao Paulo; 6U California San Diego; 7Mario Negri Inst; 8Sherbrooke U; 9Wake Forest U.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians on AKI pts who had a confirmed diagnosis of AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC). We analyzed the frequency of AKI requiring dialysis and the reasons for starting or withholding dialysis.

Results: Of 3855 pts, 768 (20%) were dialyzed. Mortality rate was significantly different in dialyzed (17%) vs. non-dialyzed (9%) pts (p<0.0001). Among dialyzed pts, mortality rate was similar in countries of different GNI categories. The main reason to start dialysis was solute control, with a similar distribution among country categories.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Belloc (Mirandola, Italy), Private Foundation Support

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Underline represents presenting author.

461A
FR-PO459

INS 0by25 AKI Global Snapshot Project: Differences in Location and Process of Care Among AKI Patients Around the Globe

Etienne Macedo,1 Rudvinda L. Mehta,2 Giuseppe Remuzzi,3 Jing Zhang,4 Melanie Godin,4 Michael V. Rocco,5 1U Sao Paulo; 2U California San Diego; 3Mario Negri Inst; 4Sherbrooke U; 5Wake Forest U.

Background: The Global Snapshot (GSP) was a prospective cross-sectional study designed to capture standardized information on incidence, causes and treatment of AKI in all health care settings throughout countries of diverse economic status. Methods: A web based survey tool was used to obtain data from AKI based on KDIGO criteria in 72 countries. Detailed methodology is found in the ISN GSP abstract on provider characteristics. We analyzed the characteristics of patients and process of care by gross national income (GNI) country levels. Countries were defined as: Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Based on GNI, 23 countries were classified as LLMIC, 20 as UMIC and 29 as HIC. In LLMIC, 58% of patients were classified as AKIN stage 3 at AKI diagnosis. sCr was significantly higher in these patients (3.26 mg/dL) compared to 2.43 in patients from HIC and 2.3 in patients from UMIC.

Conclusions: BS cr was often present in patients from HIC and UMIC, where 1/3 of AKI cases occurred in CKD patients. Absence of BS cr was a common issue in LLMIC, associated with higher levels of sCr and KDIGO stage at AKI diagnosis. UO is often not computed in patients who develop AKI. Systematic assessment of urine output in high-risk patients could help identify AKI earlier.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO461

INS 0by25 AKI Global Snapshot Project: Risk Factors for AKI

Ravindra L. Mehta,1 Giuseppe Remuzzi,2 Jing Zhang,3 Melanie Godin,3 Michael V. Rocco,4 Jorge Cerda,5 John Feehally,6 Fredric O. Finkelstein,7 Nathan W. Levin,8 Marcello Tonelli,9 1U California San Diego; 2Mario Negri Inst; 3Sherbrooke U; 4Wake Forest U; 5Albany Med Coll; 6Yale U; 7Renal Research Inst; 8U Calgary.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalence survey of AKI pts seen in health care facilities throughout the world. Methods: A web based survey tool was used to obtain data from individual clinicians about AKI patients with AKI based on KDIGO criteria. Detailed methodology is found in the ISN GSP abstract on provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Participants were distributed from North East Asia 26.4%, South Asia 18.9%, Latin America/Caribbean 14%, Africa 13.4%, North America 7.3%, Western Europe 6.2%, Oceania/South East Asia 4.3%, Russia/Commonwealth Independent States 3.9%, Middle East 3.4%, Eastern/Central Europe 2.2%. Ethnic groups included 53% Asian, 19% Caucasian, 9% Hispanic, 8% African, 7% Middle Eastern and 1.5% Native/Aboriginal. Causes of AKI varied by GNI and were compared by Kruskal-Wallis test.

Risk factors for AKI

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
<th>HIC</th>
<th>UMIC</th>
<th>LLMIC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>1536</td>
<td>38.2</td>
<td>39.1</td>
<td>32.3</td>
<td>45.6 &lt;0.0001</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>1615</td>
<td>40.2</td>
<td>44.8</td>
<td>38.2</td>
<td>38.2 0.0003</td>
</tr>
<tr>
<td>Cardiac</td>
<td>905</td>
<td>22.5</td>
<td>24.3</td>
<td>27.9</td>
<td>13.1 &lt;0.0001</td>
</tr>
<tr>
<td>Liver</td>
<td>331</td>
<td>8.2</td>
<td>7.7</td>
<td>9.2</td>
<td>7.5 0.18</td>
</tr>
<tr>
<td>Acute kidney disease</td>
<td>488</td>
<td>12.2</td>
<td>11.1</td>
<td>9.4</td>
<td>17.2 &lt;0.0001</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>320</td>
<td>8.0</td>
<td>7.9</td>
<td>6.9</td>
<td>9.5 0.0421</td>
</tr>
<tr>
<td>Infection</td>
<td>1291</td>
<td>32.1</td>
<td>28.8</td>
<td>32.2</td>
<td>35.7 0.0013</td>
</tr>
<tr>
<td>Pregnancy related</td>
<td>56</td>
<td>1.4</td>
<td>0.4</td>
<td>0.9</td>
<td>3.1 &lt;0.0001</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>322</td>
<td>8.0</td>
<td>9.4</td>
<td>9.4</td>
<td>4.6 &lt;0.0001</td>
</tr>
<tr>
<td>Nephrotic agents</td>
<td>980</td>
<td>24.4</td>
<td>29.0</td>
<td>21.7</td>
<td>23.1 &lt;0.0001</td>
</tr>
<tr>
<td>Poisoning</td>
<td>73</td>
<td>1.8</td>
<td>2.1</td>
<td>1.4</td>
<td>2.0 0.32</td>
</tr>
<tr>
<td>Envenomation</td>
<td>35</td>
<td>0.9</td>
<td>0.3</td>
<td>0.7</td>
<td>1.7 0.0005</td>
</tr>
<tr>
<td>Post-surgical</td>
<td>269</td>
<td>6.7</td>
<td>9.2</td>
<td>6.8</td>
<td>3.8 &lt;0.0001</td>
</tr>
</tbody>
</table>
Other organ failures present were pulmonary 16.4% (more common in HIC), cardiovascular 23.1% (less common in LLMIC), neurologic 8.3%, hepatic 10.4%, hematologic 9.5% (more common in LLMIC) and none 53.9%.

Conclusions: Hypotension was the most common cause of AKI in HIC and UMIC; dehydration was most common in LLMIC. Acute kidney disease, pregnancy and hemorrhage were more common in LLMIC.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO462

ISN 0by25 AKI Global Snapshot Project: Evaluation and Treatment

Jorge Cordeira,1 Rodrigo G. da Cunha,2 Giuseppe Remuzzi,3 Jing Zhang,4 Melanie Godin,5 Michael V. Rocco,6 Emmanuel A. Burdman,7 Guillermo Garcia-Garcia,7 Vivekanand Jha,7 Andrew J.P. Lewington,8 Raul Lombardi,9 Albert M. Hsue,10 U’California San Diego; 11 Mario Negri Inst; 12 Sherbrooke U; 13 Wake Forest U; 14 U Sao Paulo; Hosp Civil de Guadalajara; 15 George Inst Global Health; 16 Leeds Teaching Hosp; 17 Servicio Medico Integral.

Background: The 0by25 AKI Global Snapshot Project (GSP) was a point prevalent survey of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Detailed methodology may be found in the ISN GSP abstract or provider characteristics. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC).

Results: Initial evaluation of AKI included urinalysis in 73.6%, ultrasound in 55% and renal biopsy in 4.1%, with all three more commonly being performed in LLMIC. Initial treatment of AKI included fluids in 74.3%, vasoressors in 23.8%, diuretics in 41.4%, antibiotics in 63.8% and urinary diversion in 19.5%. The receipt of dialytic therapy occurred in 790 of 4018 pts (19.7%), with use in 18.8% in HIC, 14.3% in UMIC and 28.0% in LLMIC. In 244 instances where dialysis was recommended but not performed, futility was cited in 58.6% and cultural beliefs were cited in 25.4%. Unavailability of staff or material resources to perform dialysis was reported in 1.4% of HIC, 3.8% of UMIC and 16.4% of LLMIC. Inability to afford therapy was 1.4% in HIC, 1.9% in UMIC and 16.4% in LLMIC (p<0.001). The ratio of pts not able to receive dialysis by those that did receive dialysis was 0.21 in HIC, 0.25 in UMIC and 0.18 in LLMIC. There were significant differences in the renal modality used.

Treatment (n=790) Frequency Percent HIC UMIC LLMIC

<table>
<thead>
<tr>
<th>Modality</th>
<th>N</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID</td>
<td>516</td>
<td>65.3</td>
<td>63.3</td>
<td>58.3</td>
</tr>
<tr>
<td>PD</td>
<td>41</td>
<td>5.2</td>
<td>4.6</td>
<td>3.0</td>
</tr>
<tr>
<td>CRRT</td>
<td>157</td>
<td>19.9</td>
<td>31.7</td>
<td>29.1</td>
</tr>
<tr>
<td>UF</td>
<td>10</td>
<td>1.3</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>SLED</td>
<td>103</td>
<td>13.0</td>
<td>3.4</td>
<td>10.9</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>1.0</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Conclusions: Lack of resources, staff or finances to perform dialysis was most prevalent in LLMIC. When dialysis was provided, it was less likely to be CRRT and more likely to be SLED in LLMIC.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO463

ISN 0by25 AKI Global Snapshot Project: Provider Characteristics

Melanie Godin,1 Rodrigo G. da Cunha,2 Giuseppe Remuzzi,3 Jing Zhang,4 Michael V. Rocco,6 Nathan W. Levin,5 Andrew J.P. Lewington,7 Etienne Macevedo,7 Marcello Tonelli,9 Sherbrooke U; U’California San Diego; Mario Negri Inst; Wake Forest U; Albany Med Coll; George Inst Global Health; Renal Research Inst; Leeds Teaching Hosp; U Sao Paulo; U’ Calgary.

Background: The ISN 0by25 AKI Global Snapshot Project (GSP) was designed to determine the spectrum of AKI pts seen in health care facilities throughout the world.

Methods: Health care providers joined the GSP after gaining approval from their local IRB. Providers chose one “index” day between 9/29/2014 and 12/7/2014 to provide data on AKI pts under their care. De-identified data on pts who met criteria for AKI by modified KDIGO criteria were entered through a secure website using a standard questionnaire developed by the 0by25 AKI workgroup. Data collected included pt demographics, initial clinical data, diagnostic, treatment and outcome information. Countries were grouped into three categories based on gross national income per capita (GNI); high income with GNI >US$12476, low and lower middle income with GNI <US$4035, and upper middle income with GNI between levels 1 & 3.

Results: 324 surveys from 72 countries were received describing 4024 pts with AKI. Providers included 248 nephrologists, 20 nephrology fellows, 14 intensivists, 26 pediatric nephrologists. Location of facilities by region included 52 from Africa, 47 from Latin America & Caribbean, 45 from North America, 45 from South Asia, 40 from North and East Asia, 34 from Western Europe, 19 from Russia/Commonwealth of Independent States, 17 from Oceania & South East Asia, 14 from Middle East and 11 from Eastern & Central Europe. Size of catchment population for each facility was: >5 million in 28%, 0.5-1.5 million in 26%, 0.1-0.5 million in 19% and 1.5-3 million in 11%. Type of facility was institute in 47%, public hospital or health care concern in 37%, private multispecialty group in 14%. Dialysis was available in 97% of facilities.

Conclusions: This project is the first worldwide point prevalent survey of AKI. It demonstrates the feasibility of obtaining data on AKI using a secure website from practitioners in varied health care settings from six continents.

Funding: Pharmaceutical Company Support - Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy), Private Foundation Support

FR-PO464

Postoperative Acute Kidney Injury in Non-Cardiac Surgery

Dong Ki Kim, Kwon-Woon Joo, Yo Sun Kim, Hajeong Lee.

Background: Prevention of acute kidney injury (AKI) and amelioration of its severity remain important issues of improving surgical patient outcomes. Therefore, preoperative renal risk evaluation and patient optimization is crucial for nephrologists. Although there are several studies dealing with postoperative AKI in cardiac surgery, they have been seldom studied in non-cardiac surgery.

Methods: We included adult (age ≥ 18 years) patients who received major non-cardiac surgery in Seoul National University Hospital from 2004 to 2013. We extracted their clinical data from our electronic medical record system. Acute Kidney Injury Network criteria (AKIN) was used to define and classify AKI.

Results: Among a total of 95,266 operations, 1,560 cases (1.64%) developed AKI. Patients with AKIN stage I were 964 (1.01%), stage II, 117 (0.12%), and stage III, 479 (0.50%). AKI was most prevalent in urologic surgery, followed by general surgery, orthopedic surgery, and neurologic surgery. Patients who developed AKI tended to be older (53.7 vs. 58.9 years), and male (45.6% vs. 65.6%). Patients with AKI had higher prevalence of underlying diseases such as liver/heart/hematologic/vascular and neurologic disease than those without. Moreover, they showed higher baseline systolic blood pressure and lower baseline diastolic blood pressure than those without. Baseline renal function was lower in AKI-developed patients than the others (0.90 vs. 1.13 mg/dL, P<0.001). Multivariate logistic regression analyses found that older age, male sex, lower baseline renal function, presence of hypertension, longer duration of surgical time and orthopedic or urologic surgery were significant risk factors for postoperative AKI in noncardiac surgery.

Conclusions: In this study, we demonstrated the incidence of postoperative AKI in non-cardiac major operations. Moreover, we found clinical risk factors for postoperative AKI development. Further investigation of prediction models for postoperative AKI in major non-cardiac surgery should be warranted for development of preoperative renal optimization strategy.

FR-PO465

Impact of Hospital CABG Volume and AKI Needing Dialysis on CABG Hospitalizations

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Background: Acute Kidney Injury (AKI) is common after Coronary Artery Bypass Grafting (CABG) and associated with poor outcome. Increased hospital procedure volume has been associated with better outcomes. We examined (1) impact of number of annual CABG procedures per hospital (CABG-vol) on AKI needing dialysis (AKI-D) and mortality, and (2) if it modifies the relationship between AKI-D and mortality.

Methods: Using Nationwide Inpatient Sample database from 2000-2010 we identified admissions with CABG using ICD-9-CM codes. Those with AKI-D were identified and those with kidney transplant or on maintenance dialysis were excluded. Multivariable logistic regressions were used to assess impact of CABG-vol on AKI-D and mortality. We used restricted cubic splines to account for non-linear relationship between CABG-vol and mortality. A priori interaction term between CABG-vol & AKI-D was assessed in model 2.

Results: Of estimated 3,373,292 (95% CI: 3,103,610-3,570,973) hospitalizations for CABG, 0.7% (24,126) had AKI-D. Those with AKI-D were older, more females (37.5% vs 29.1%; p<0.001) and blacks (7.4% vs 5.5%; p<0.001). On adjusted analysis, CABG-vol was correlated with AKI-D (0.99; 95% CI 0.99-1.00) but was associated with mortality (Fig 1).
AKI-D was a significant predictor of mortality with OR 13.75 (95% CI: 11.37-16.64). Interaction term between CABG-vol & AKI-D was not significant (p=0.8).

**Conclusions:** Lower annual CABG hospital procedure volume is significantly associated with higher mortality but not with higher incidence of AKI-D. AKI-D is associated with higher mortality in those undergoing CABG, however, there is no differential effect of hospital volume on adjusted odds of mortality due to AKI-D.

**FR-PO467**

Changes of Epidemiology and Influencing Factors of Acute Kidney Injury After Cardiac Surgery – A Five-Year Study from 2009 to 2013 Zahouping Zou,1,2 Jiaren Xu,1,2 Wenli Lv,1,2 Bo Shen,1,2 Yi Fang,1,3 Jianzhou Zou,1,4 Jie Teng,1,2 Xiaoping Ding,1,2 1Dept of Nephrology, Zhongshan Hospital, Fudan Univ, Shanghai, China; 2Shanghai Inst for Kidney and Dialysis, Zhongshan Hospital, Fudan Univ, Shanghai, China; 3Shanghai Key Laboratory of Kidney Disease and Blood Purification, Zhongshan Hospital, Fudan Univ, Shanghai, China.

**Background:** Cardiac surgery is a common cause of acute kidney injury (AKI). We collected the epidemiological data of patients with AKI from 2009 to 2013 in order to explore the influencing factors of changes of epidemiology after cardiac surgery. **Methods:** Clinical data of patients undergoing cardiac surgery, which included demographic data of preoperative, intraoperative, postoperative, and laboratory data was collected in our hospital from January 2009 to December 2013. The main endpoint was poor prognosis which included overall mortality and abandonment of treatment. The second point was renal outcome. **Results:** A total of 1,1693 patients enrolled, including 6637 males and 5056 females. The overall AKI incidence was 34.5% (n=4030). The AKI incidence increased during the five years from 34.2% to 36.5% (P<0.05). There was no significantly statistical differences in AKI-RRT incidences during the five years (P=0.360). The hospital mortality of AKI decreased from 6.3% in 2009 to 3.8% in 2013. The incidence of poor prognosis in AKI was 8.3%, 7.5%, 6.8%, 5.1%, 8.0% (P=0.196). The mortality of AKI-RRT decreased from 47.1% to 29.5%, but there was no statistical difference (P=0.230). The incidence of non-progression in RRT decreased from 66.7% to 57.4%, also no significantly statistical difference (P=0.825). Multivariate logistic regression analysis showed that male age (every additional 10 years), body mass index (every additional 5 kg/m²), hypertension, chronic heart failure, pre-operative serum creatinine >115 mmol/L, CPB (every additional 30 min) were the risk factors of AKI after cardiac surgery. **Conclusions:** The incidence of AKI after cardiac surgery increased from 2009 to 2013 and the rate of poor prognosis did not change. The incidence of AKI-RRT and the rate of poor prognosis remained high. The prevention and treatment of AKI still need improvement. **Funding:** Government Support – Non-U.S.

**FR-PO468**

The Very Long-Term Co-Morbidity Adjusted Impact of AKI following Cardiac Surgery: A 15-Year Follow-Up Study Alejandro Ferreiro,1 Raul Lombardi,2 1Nephrology, INCC, Facultad de Medicina, Montevideo, Uruguay; 2Critical Care Medicine, SMI, Montevideo, Uruguay.

**Background:** AKI is a frequent complication of cardiac surgery (CS) associated to high mortality. The co-morbidity adjusted residual impact on very long-term mortality (>12 years) of AKI, excluding the initial catastrophic impact on early mortality has never been addressed before. **Objectives:** To evaluate the net attributable impact of AKI after CS on long-term survival. **Methods:** All adult patients submitted to CS between 1/1/2000 and 31/12/2013 (n=7755) were enrolled. The INCC prospective-collected database with more than 750 variables (demographics, comorbidities, type of CS, intraoperative and postoperative variables, peri-operative support and short time outcomes) was used. Long-term survival (up to 15 year by December 2014) was obtained by systematic telephone survey (minimum 1-year follow-up) and the National Population Registry. AKI stages were defined according to KDIGO definition. Demographics, logistic EuroSCORE (and their single components), type of CS, baseline renal function (Cockcroft-Gault formula) were used for comorbidity risk-adjustment. Statistical analysis: "t" test, Kruskal-Wallis test, Kaplan-Meier curves with long-rank test and Cox regression for multivariate survival analysis. Only patients alive after the first year follow-up entered in the long-term survival analysis (n= 9050). **Results:** AKI incidence: 38.4%. RRT: 1.7%. Long-term (15 years) actuarial survival after 1 year follow-up: no AKI 0.58; AKI I: 0.47; AKI II: 0.39; AKI III: 0.27 (P<0.001). In multivariate Cox regression analysis, AKI stages I, II and III (OR 1.17; 1.24; 1.62 respectively) were independently associated with mortality between 1 year after CS and 15 year follow-up, even after adjustment with logistic EuroSCORE (OR 1.02), age (OR 1.038), diabetes (OR 1.58), pre-operative eGFR (OR 0.996) and no-isolated coronary bypass surgery (OR 1.24). **Conclusions:** AKI and its severity are independently associated with very long-term mortality, even after discarding short term events (1 year), in cardiac surgery. Should AKI be causative or a surrogate marker of late events in the long-term follow up is a matter of concern to be evaluated.

**Funding:** NIDDK Support

**FR-PO469**

Incidence and Influencing Factors of Cardiac Surgery-Associated Acute Kidney Injury Based on the KDIGO Criteria: A Retrospective Cohort Study Changchun Cao,1 Xiangcheng Xie,1 Xin Wan,2 1Nanjing Hospital Affiliated to Nanjing Medical Univ (Nanjing First Hospital); 2Nanjing Hospital Affiliated to Nanjing Medical Univ (Nanjing First Hospital).

**Background:** The incidence and influencing factors of cardiac surgery-associated acute kidney injury (CSA-AKI) based on the KDIGO criteria have not been well studied. This study was aimed to evaluate the incidence, risk or protective factors of acute kidney injury (AKI) in patients after cardiac surgery.

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

Underline represents presenting author.
Methods: A retrospective analysis of 2575 patients undergoing first documented cardiac surgery with cardiopulmonary bypass (CPB) between January 2008 and December 2012 in our hospital was conducted. Perioperative variables were collected and analyzed. Univariate and multiple logistic regression models were used for determining the association between the development of AKI and risk factors.

Results: Of 2575 patients, 931 (36%) developed AKI. A total of 38(1.2%) patients required renal replacement therapy. The overall in-hospital mortality rate was 1.5% (38 of 2575). CSA-AKI was significantly associated with in-hospital mortality (adjusted HR: 2.22, 95% CI 1.16-4.24, P = 0.016), especially in patients needing RRT (adjusted HR: 18.68, 95% CI 8.58-40.68, P < 0.001). The independent risk factors identified by multivariable analysis were shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.14</td>
<td>1.17-1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.29</td>
<td>1.11-1.49</td>
<td>0.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.49</td>
<td>1.21-1.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Inulin-controlled diabetes</td>
<td>1.56</td>
<td>1.06-2.30</td>
<td>0.025</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.88</td>
<td>0.94-3.72</td>
<td>0.074</td>
</tr>
<tr>
<td>Red blood cells transfused(U)</td>
<td>1.08</td>
<td>1.05-1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPB duration (10min)</td>
<td>1.31</td>
<td>1.07-1.61</td>
<td>0.009</td>
</tr>
<tr>
<td>Mechanical ventilation(9h)</td>
<td>1.45</td>
<td>1.20-1.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea</td>
<td>0.69</td>
<td>0.56-0.88</td>
<td>0.006</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>1.23</td>
<td>1.02-1.50</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Conclusions: This study demonstrates that mechanical ventilation duration, erythrocytes transfusion and postoperative body temperature above 38°C in within 3 days were considered independent risk factors for CSA-AKI. Use of urea was associated with lower incidence of CSA-AKI.

Funding: Government Support - Non-U.S.

FR-PO470

Acute Kidney Injury Post-Major Orthopaedic Surgery: A Single Centre Experience

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Background: Given the increasing incidence of AKI and the burden this places on the medical system, there is a clear need to expand the practice of ‘preventative nephrology’ – the optimisation of renal function through minimisation of potential insults. Renoprotection is particularly critical in the perioperative setting, a period of high renal vulnerability. However, there is currently little evidence regarding numerous theoretical risk factors for postoperative AKI.

Methods: All patients undergoing MOS at our centre between 2008 and 2014 were included. Of 2277 surgeries audited for AKI using comparisons of preoperative and postoperative creatinine, 164 cases were identified (per RIFLE criteria) and matched to controls 2:1 for age, sex, procedure and chronic kidney disease stage. Their records were reviewed for established and proposed risk factors for postoperative AKI: diuretic, non-steroidal anti-inflammatory (NSAID) and angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) use. Associations of proven and hypothetical risk factors were estimated using conditional logistic regression.

Results: Controlling for known risk factors, both diuretic and ACEI or ARB use were found to be associated with an approximately twofold increased risk of AKI (diuretic – OR 2.06 95%CI 1.30-3.26, p<0.005, ACEI/ARB – OR 2.09 95%CI 1.31-3.32, p<0.005). A dose-effect model accounting for preoperative, intraoperative and postoperative NSAIAD administration demonstrated a linear relationship between the number of times NSAIADs were given and postoperative AKI risk (OR 1.35 95%CI 1.05-1.73, p<0.05).

Conclusions: Perioperative diuretic, NSAIAD and ACEI or ARB use were shown to be significantly associated with postoperative AKI, indicating that these medications should be used with caution in MOS. Further prospective studies are required to confirm this.

FR-PO471

Incidence of In-Hospital Acute Kidney Injury by Surgery and Invasive Surgical Procedures Among Non-Emergency Hospital Admissions

Joshua Taylor Swan,1,2 Beverly A. Shirley,1 Linda W. Moore,1 Wadi N. Suki,1 A. Osama Gaber,1,3 1Houston Methodist Hospital; 2Texas Southern Univ; 3Weil Cornell Medical College.

Background: This study aimed to identify non-emergency invasive surgical procedures that are associated with the highest burden of in-hospital AKI.

Methods: Urgent and elective admissions to a quaternary teaching hospital in 2012-2013 with a principal procedure within 1 day of admission were included. Principal procedures were categorized using AHRQ’s Clinical Classifications Software (CCS).

<table>
<thead>
<tr>
<th>CCS Category, CCS code</th>
<th>Admissions, n</th>
<th>Any AKI, n (%)</th>
<th>Stage 1 AKI, n (%)</th>
<th>Stage 2 AKI, n (%)</th>
<th>Stage 3 AKI, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ transplantation (other than bone marrow, corneal or kidney)</td>
<td>47</td>
<td>29 (61)</td>
<td>10 (21)</td>
<td>10 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Heart valve procedures</td>
<td>43</td>
<td>32 (74)</td>
<td>19 (44)</td>
<td>9 (21)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Coronary artery bypass graft (CABG)</td>
<td>44</td>
<td>17 (39)</td>
<td>12 (27)</td>
<td>3 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Diabetic nephropathy and biopsy of kidney</td>
<td>27</td>
<td>15 (56)</td>
<td>7 (26)</td>
<td>4 (15)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Other OR procedures on vessels other than head and neck</td>
<td>61</td>
<td>40 (66)</td>
<td>24 (39)</td>
<td>9 (15)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Other OR procedures on coronary artery</td>
<td>70</td>
<td>56 (80)</td>
<td>16 (23)</td>
<td>13 (19)</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Total</td>
<td>265</td>
<td>161 (60)</td>
<td>92 (35)</td>
<td>42 (16)</td>
<td>27 (10)</td>
</tr>
</tbody>
</table>

Conclusions: This study assesses the incidence of AKI after invasive surgical principal procedures, and this data will help prioritize research to prevent in-hospital AKI. Non-kidney transplant, heart valve, and CABG surgical procedures were associated with the highest number of AKI cases at this single center, and non-kidney organ transplants were associated with a high severity of AKI.

FR-PO472

Risk Factors Associated with Post-Operative AKI After General Surgery

Pradeep Pradeep,1,2 Nader Zadeh,1,2 1Div of Nephrology, VAMC, Buffalo, NY; 2Anesthesiology, VAMC, Buffalo, NY; 3Surgery, VAMC, Buffalo, NY.

Background: AKI after cardiac and vascular surgery has been extensively studied. However, there is no study which has evaluated the factors associated with development of stage 1 AKI by AKIN criteria in general surgery patients.

Conclusions: This study assesses the incidence of AKI after invasive surgical principal procedures, and this data will help prioritize research to prevent in-hospital AKI.
Methods: We conducted a cohort study using a prospective database of patients undergoing non-cardiac and non-vascular surgery performed at Mount Sinai Health System which are in part reported to the National Surgical Quality Improvement Program (NSQIP). Demographic, social history, comorbid diseases, including coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive lung disease (COPD), peripheral vascular disease (PVD), cerebrovascular accidents (CVA), hypertension, and diabetes, were prospectively entered into the Veterans Affairs Surgical Quality Improvement Program (VASQIP) database at the time of surgery. Preoperative laboratory data were also entered for each participant. Univariate and multivariate logistic regression were performed to estimate the odds of AKI after surgery.

Results: A total of 13300 patients who underwent non-cardiac and non-vascular surgery whose data was available to define AKI between 2000-2014 were included in this analysis. A total of 1621 patients developed AKI stage 1. In univariate analysis, increasing age, male gender, ASA class, poor functional status, presence of COPD, peripheral vascular disease (PVD), cerebrovascular accidents (CVA), hypertension, and diabetes were prospectively entered into the Veterans Affairs Surgical Quality Improvement Program (VASQIP) database at the time of surgery. Preoperative laboratory data were also entered for each participant. Univariate and multivariate logistic regression were performed to estimate the odds of AKI after surgery.

Conclusions: AKI is associated with increased length of hospital stay and mortality. Efforts to recognize and intervene in preoperative modifiable factors to prevent AKI will improve outcomes in general surgical patients.

FR-PO474

The Comparison of the Incidence of Acute Kidney Injury Post Coronary Artery Bypass Graft versus Percutaneous Coronary Intervention: National Inpatient Sample Experience

We extracted total 485742 cases from National Inpatient Sample (NIS) to create a propensity-score matched cohort of patients who had multivessel coronary disease and underwent first-time CABG or PCI between 2004-2012. Patients received concomitant valvular repair or both CABG and PCI on same admission, history of organ transplant, CKD stage IV or V, or RRT on dialysis were excluded. Both groups were matched for age, gender, race, payer, prior MI, unstable angina, heart failure, CVA, stroke or TIA, peripheral arterial disease, atypical or aortic valve disease, atrial fibrillation/bradycardia, ventricular fibrillation or tachycardia, CKD, diabetes, HTN, dyslipidemia, smoking, cirrhosis, obesity, anemia and in-hospital GI bleeding. The odds ratios were estimated by logistic regression analysis.

Results: The incidence of AKI in CABG group was higher than PCI group (8.41% vs. 0.40%; OR 2.07, 95% CI 2.00-2.15, P< 0.001). The incidence of severe AKI requiring RRT were similar in both groups (0.95% vs. 0.91%, P=0.147). Compared with PCI group, CABG group had higher total in-hospital mortality (1.99% vs. 1.48%, OR 1.34, 95% CI 1.24-1.40, P<0.001). The in-hospital mortality in patients with AKI was higher in CABG (0.92% vs 0.59%, P<0.001).

Conclusions: Patients received CABG were at higher risk of developing AKI and associated with higher total in-hospital mortality. The in-hospital mortality in patients with AKI was higher in CABG.

FR-PO475

Diagnosis-Required Acute Kidney Injury Among Hospitalized Adults with Documented Hepatitis C Virus Infection: A Nationwide Inpatient Sample Analysis

We identified a total of 4,603,718 adult hospitalizations with associated HCV from 2004-2012, of which 51,434 (1.12%) were complicated by AKI-D. The proportion complicated by AKI-D increased significantly from 0.86% in 2004 to 1.28% in 2012. Trend was similar when stratified by cirrhosis and paralleled that in HCV negative hospitalizations.

Figure 1. Temporal Trends in the Incidence of Acute Kidney Injury (AKI) Requiring Renal Replacement Therapy among Hospitalized Adults with and without Documented Hepatitis C Virus Infection

In-hospital mortality was significantly higher in hospitalizations complicated by AKI-D vs. those without (27.38% vs. 2.95%; adjusted odds ratio 2.09, 95% Confidence Interval 1.74-2.51) which remained stable over the study period.

Conclusions: The proportion of HCV hospitalizations complicated by AKI-D increased significantly between 2004-2012. Similar to observations in the general population, AKI-D was associated with two-fold increase in odds of in-hospital mortality. These results highlight the burden of severe AKI in hospitalized adults with HCV infection.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Temporal Trends of Burden of Dialysis Requiring Acute Kidney Injury in Cerebrovascular Accident Hospitalizations

**Methods:** We used the Nationwide Inpatient Sample to evaluate the yearly incidence of AKI-D in AIS and ICH admissions from 2002 to 2011. We also evaluated the trend of impact of AKI-D on in-hospital mortality and adverse discharge utilizing adjusted odds ratios (aOR) after adjusting for demographics and comorbidity indices. Results: We extracted a total of 3927267 AIS and 704648 ICH admissions, AKI-D occurred in 1.5 and 3.5 per 1000 in AIS and ICH admissions respectively. Incidence of admissions complicated by AKI-D doubled from 0.9/1000 to 0.17/1000 in AIS and from 2.1/1000 to 4.3/1000 in ICH admissions.

Conclusions: The proportion of DC hospitalizations with AKI-D increased from 2006-09 & although, this was stable from 2009-12, there was an increase in absolute case number. These results elucidate burden of AKI-D on DC hospitalizations & excess associated mortality as well as highlight the importance of prevention, early diagnosis & testing of novel interventions in this vulnerable population.

**Funding:** NIDDK Support

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**FR-PO478**

Long-Term Healthcare Utilization and Mortality After Acute Kidney Injury in Critically Ill Children

**Methods:** Retrospective cohort study of children admitted to two Montreal, Canada PICUs, 2003-2005 (N=2500). Exclusions: no health number, deceased in PICU. Clinical chart data was merged with provincial administrative health data. AKI (main exposure): by Kidney Disease Improving Global Outcomes serum creatinine (SCr) definition (if no PICU-SCr drawn, non-AKI was assumed). 5-year outcomes: all-cause mortality; healthcare utilization (HCU), defined as the number of hospitalizations, emergency room (ER) and physician visits per 100 person years. AKI-outcome relation was evaluated with multivariate logistic (mortality) and linear regression (HCU), adjusting for gender, age, cardiac surgery, PRISM (mortality) score, vasopressors and infection.

Results: Of 2407 children (mean±SD age=6±5.7 yrs; PRISM = 8.2±5.9); 56% male; 448 (18.6%) developed AKI. AKI (yes/no) was associated with mortality in univariate (p=0.05) but not multivariate analysis. Stage 2 AKI or worse was associated with 5-year mortality (adjusted aOR=1.9, 95% CI 1.1-3.2). AKI (yes/no) was associated with increased 5-year hospitalizations (adj p=0.05) and physician visits (adj p=0.001), but not ER visits (adj p=0.8). There was a graded increase in 5-year HCU with higher AKI severity.

Conclusions: PICU-AKI is associated with long-term increased mortality risk and HCU. Research should evaluate cost-effective interventions to improve child AKI treatment and evaluate effects on late outcomes.

**Funding:** Government Support - Non-U.S.

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**FR-PO479**

Acute Kidney Injury: A 12 Month Follow, the Incidence and Mortality

**Methods:** Patients who were admitted between the time periods of August 2012 until January 2013 were included in this study. Liaising with the biochemistry department, all patients who had a rise in their creatinine based on the Acute Kidney Injury Network Criteria received an e-alert sign on the computer system. Clinical outcomes were obtained from each patient record.

Conclusions: PICU-AKI is associated with long-term increased mortality risk and HCU. Research should evaluate cost-effective interventions to improve child AKI treatment and evaluate effects on late outcomes.

**Funding:** Government Support - Non-U.S.
Results: There were a total of 36,957 patients admitted during that 6 month time period of which a total of 358 cases of AKI were identified. There was total of 183 male patients and 171 female patients. Four of the male patients had a further AKI alert during the same hospital admission. The mean age was 72.18 years. Pre-renal causes were identified as the main contributors to the cases. Majority of the AKI alerts were Stage 1 AKI which was 70.7%, Stage 2 AKI was 25% and Stage 3 AKI was 4.3% of the total cases. The data also revealed that the average length of stay (ALOS) did not differ in each of the stage. A patient ALOS for Stage 1 AKI was 23.3 days, Stage 2 AKI 24 days and Stage 1 AKI 21 days. Of the total number of cases of patients with AKI, 50.6% (179/354) of the patients had died within the 12 months period. Looking into the mortality rate of each individual stages of AKI the mortality rate at 12 months for Stage 1 AKI is 46.5%. For Stage 2 AKI, 62.7% and for Stage 3 AKI, 47.6%.

Conclusions: From the data collected, it shows that the degree of AKI does not affect the length of stay of patients. Despite the different stages of AKI indicating the severity of the injury, mortality rate for Stage 1 and Stage 3 did not differ. This indicates that AKI carries a high mortality rate regardless of the severity of the injury. Early recognition leads to early intervention in the prevention of AKI.

FR-PO480
Acute Kidney Injury: Adding Informatics to Injury – (Electronic Injury Alerts)
Conor Patrick Moran, Ying C. Kuan, Patrick Lm Lynch, Francis Mccarroll. 1 Dept of Nephrology, Altnagelvin Hospital, Londonderry, United Kingdom; 2 Dept of Clinical Chemistry, Altnagelvin Hospital, Londonderry, United Kingdom.

Background: Acute Kidney Injury, (AKI), is common with a variably reported mortality, (15-60%). UK national audit reported that up to 30% of cases were avoidable and that as much as 43-61% of post-admission AKI experienced an unacceptable delay in recognition of insult. There has been a paucity of work with regards to AKI recognition and prevention. National guidelines have recommended the use of electronic alerts (e-alerts) for AKI detection.

Methods: We introduced AKI e-alerts with accompanying electronic guidance in late October 2014 and prospectively collected data on the patients identified with severe AKI. Data collection was carried out for 3 months, (n=110). The demographics of this cohort were compared with a historical cohort of severe AKI (n=89).

Results: Mean age, (72 years vs. 73 years), gender distribution, (M:F: 46% / 54% vs. 47% / 53%), and median time to death, (10 days vs. 9 days), were comparable. Thirty day mortality was similar with regards to hospital acquired AKI, (27.3 % vs. 26.1%). 30 day mortality was significantly lower for community-acquired AKI, (10.7%). Mean and median age was demonstrated to be higher in the group of patient who died, (Mean: 80.1 years vs. 75.7 years), (Median: 82 years vs. 82 years) – negative skew due to outliers.

Conclusions: Although our initial data suggests an electronic AKI alert has a discernable effect on 30 day mortality rate and time to death. We feel that e-alerts with the addition of further Quality Improvement work will eventually result in a steady reduction in AKI mortality.

FR-PO481
Tenofovir Nephrotoxicity Is an Important Cause of Acute Kidney Injury in HIV Infected Inpatients

Background: Tenofovir disoproxil fumarate (TDF) is widely prescribed as a first choice therapy for HIV infection, because of its convenient dosing schedule, efficacy and relatively low side effects. However, renal toxicity may lead to acute kidney injury (AKI), chronic kidney disease (CKD), and proximal tubular injury. Here we describe clinical characteristics and outcomes of AKI associated to TDF.

Methods: In a retrospective cohort (between Mar/2011 to Feb/2015), we have described AKI alerts in patients with TDF nephrotoxicity, defined as an elevation of Cr by ≥ 0.3 mg/dl during a 14 day period after administration of cisplatin (peak Cr) compared with baseline (bl Cr). Patients with bl Cr of >1.5 were excluded.

Results: Of the 1979 patients in our study, 55% were male with a mean ± SD of age of 61.6 ± 12.8. A bl Cr was 0.9 ± 0.2. 241 of 1979 (12.2%) patients developed CaN. However, it ranged from 7.8% in the medium dose group (cisplatin dose 75-130 mg) to 18.2% in the high dose group (>130mg) without a clear dose response relation.

Conclusions: CaN associated to TDF nephrotoxicity was prevalent in the HIV infected inpatients and showed high morbidity, including almost a third of patients requiring dialysis and more than a half not recovering renal function after withdrawing the drug.

FR-PO482
Cisplatin-Associated Nephrotoxicity: Not as Frequent as Previously Reported
Shiveta S. Motwani, Sushrut S. Waikar, Benjamin D. Humphreys, Gary C. Curhan. Nephrology, Brigham and Women’s Hospital, Boston, MA.

Background: Cisplatin-associated nephrotoxicity (CaN) is a frequent problem amongst patients with various cancers. Most older studies have reported 25-30% of patients who receive cisplatin experience acute kidney injury. However, these data have not been re-evaluated systematically recently despite rapid advances in oncologic care. Therefore, we examined the proportion of patients who develop acute kidney injury after exposure to the first cycle of cisplatin in a large patient database. We also examined the frequency of kidney injury stratified by sex and cisplatin dose regardless of cancer type.

Methods: We collected data on patients ≥ 18 years of age who had received cisplatin as a primary, secondary or adjuvant or neo-adjuvant therapy at a tertiary-care medical center (Massachusetts General Hospital) between 2006 and 2014. Detailed data regarding cisplatin dose, demographic characteristics, concurrent medical history and laboratory data including serum creatinine (Cr) and electrolytes were collected. CaN was defined as an elevation of Cr by ≥ 0.3 mg/dL during a 14 day period after administration of cisplatin (peak Cr) compared with baseline (bl Cr). Patients with bl Cr of >1.5 were excluded.

Results: Of the 1979 patients in our study, 55% were male with a mean ± SD of age of 61.6 ± 12.8. A bl Cr was 0.9 ± 0.2. 241 of 1979 (12.2%) patients developed CaN. However, it ranged from 7.8% in the medium dose group (cisplatin dose 75-130 mg) to 18.2% in the high dose group (>130mg) without a clear dose response relation.

In addition, a significantly lower frequency of CaN was noted amongst females compared with males (9.3% vs 14.5%, p<0.001).

Conclusions: Cisplatin-associated nephrotoxicity occurs less frequently than previously reported. This may reflect changes in preventive care such as more aggressive hydration with electrolyte-rich solutions.

Funding: Other NIH Support - T32 training grant
FR-PO483

Characteristics of 681 Patients with Atypical Hemolytic Uremic Syndrome in the Global aHUS Registry

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

FR-PO485

Use of ACEIs and ARBs in Patients with Chronic Kidney Disease and Superimposed Community-Acquired Acute Kidney Injury

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

FR-PO486

Renal and Patient Outcomes of Dialysis Dependent Patients with ATN Who Survive Hospitalization

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

FR-PO484

Long-Term Renal Function After Recovery from Dialysis-Requiring Acute Kidney Injury

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO487

Long-Term Follow-Up of Children with STEC-HUS Caused by E. coli O104:H4 (German HUS Outbreak 2011): A GPN Registry

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Background: In 2011 E. coli O104:H4 caused the largest outbreak of HUS in adults and children. A total of 90 children were affected, of whom 64 (71%) required dialysis for a median of 11 days.

Methods: Currently following data are available from 60 of 90 children (67%), 31 girls from 11 pediatric centers in Germany. Median follow-up is 2.7 range 1.2-3.8 years, median current age of patients is 14.7 (3.4-18.7) years.

Results: Median current serum-creatinine is 0.7 (0.3-8.9) mg/dl. In two patients (2.2%) with CKD stage 3 and 4 at discharge GFR improved and they are now in CKD Stage 2. One patient remained dialysis dependent initially and one reached ESRD after 3.5 years; both underwent successful living-related kidney transplantation. All these 4 patients were treated with eculizumab in the initial phase of STEC-HUS including 2 who also received plasmapheresis. Proteinuria is currently present in 17 (19%) patients and 9 (10%) require treatment for hypertension. Three patients have neurologic symptoms (headache, performance deficit, spasmodic movement disorder) and 3 patients have EEG abnormalities without symptoms.

Conclusions: Long-term follow-up is important after O104:H4 associated STEC- HUS. CKD stage 3-5 at discharge is a risk factor for ESRD, however some children show a spontaneous improvement over time. Patients with proteinuria and hypertension need long-term follow-up. Follow-up studies after STEC HUS should include neurologic investigations.

FR-PO488

SOFA Scores as Predictors of Mortality and Dialysis Dependency in Acute Kidney Injury

V. Shane Pankratz,1 Christos Argyropoulos,1 Khaled Abdel-Kader,2 Kelly V. Liang,3 Paul M. Palevsky,3 Mark L. Unruh.1 1Dept of Internal Medicine, Div of Nephrology, Univ of New Mexico School of Medicine, Albuquerque, NM; 2Dept of Medicine, Div of Nephrology and Hypertension, Vanderbilt Univ School of Medicine, Nashville, TN; 3Dept of Medicine, Renal- Electrolyte Div, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: The Sequential Organ Failure Assessment (SOFA) score measures the severity of organ failure, and baseline SOFA scores have been used to predict mortality in patients with Acute Kidney Injury (AKI). We evaluated whether SOFA scores, either upon initiation of dialysis or clinically updated, predict mortality and dialysis dependency following AKI.

Methods: Data from patients enrolled in the Acute Renal Failure Trial Network (ATN) study, a randomized multicenter trial of the intensity of renal support in AKI, were used in Cox proportional hazards regression and multinomial logistic models to assess the degree to which SOFA scores predict mortality and dialysis dependency.

Results: SOFA scores were associated with increased mortality risk following AKI among the 1,124 ATN participants, but the concordance statistic was low, at 0.651 (standard error [se]=0.014). When time-dependent analyses were used to take advantage of prospectively updated SOFA scores, the concordance statistic increased to 0.753 (se=0.013). When time-dependent analyses were used to take advantage of prospectively updated SOFA scores, the concordance statistic increased to 0.753 (se=0.013).

FR-PO490

Comparison of Clinical Characteristics of Patients with Acute Kidney Injury After Intraoperative Versus Inhaled Colistin Therapy

Hvinnia Yoon,1 In O Sun,2 Kwang Young Lee,1 A young Cho.1 Div of Nephrology, Dept of Internal Medicine, Presbyterian Medical Center, Jeonju, Jeonbuk, Republic of Korea.

Background: The aim of this study is to investigate the incidence and clinical characteristics of intraoperative or inhaled colistin associated acute kidney injury (AKI) using the RIFLE and AKIN criteria.

Methods: From 2010 to 2014, 160 patients were treated with inhaled or intraoperative colistin. Of these, we included 139 patients who received colistin for >72 h, and compared the incidence and clinical characteristics of patients in the inhaled (n=120) and intraoperative (n=19) groups.

Results: The patients included 116 men and 23 women, with a mean age of 68 years (range, 20-91). Patients were infected with either A. baumannii (54%) or P. aeruginosa (46%), and pneumonia (91%) was the most common type of infection. The mortality rate was 43.9%, and AKI occurred in 83 (60%) patients. At the end of therapy, bacteriologic cure rate was 64%. There were no differences in the clinical characteristics between the intraoperative and inhaled groups except for age. In comparison with patients in the intraoperative group, the patients in the inhaled group were older (74 ± 6 vs 67 ± 14 years, p=0.03). The incidence of AKI was not different between the two groups (62% vs 47%, p=NS), and there was no difference in the severity of AKI according to the RIFLE criteria. Of the 83 patients with AKI, 8 and 1 patients underwent renal replacement therapy.

Conclusions: In our study, the incidence of AKI in patients undergoing colistin therapy was 60%, and there was no difference in safety between the intraoperative and inhaled colistin groups. Therefore, it is also important to monitor renal function during colistin therapy regardless of the route of administration.

FR-PO491

Acute Kidney Injury following Coronary Angiography

Dadi Helgason,¹ Jörð E. Long, ¹ Gísl H. Sigurdsson,² Martin I. Sigurdsson,² Olafur S. Indridsson, ³ ¹Dept of Medicine; ²Department of Anesthesia, Landspitali; ³Dept of Anesthesia, Brigham and Women’s Hospital, Boston, MA; ⁴Div of Nephrology, Landspáli - The National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Acute kidney injury (AKI) is a known complication of coronary angiography (CA). The aim was to study the incidence, risk factors and outcome of AKI following CA in a whole nation.

Methods: This was a retrospective analysis of data from all CA in Iceland during a 9 year period. AKI was diagnosed according to the creatinine based KIDGO criteria and survival status for all patients was verified at Statistics Iceland. The epidemiology and clinical outcomes were compared between three 3-year periods using Chi-squared and Kaplan-Meier method, and multivariate logistic regression was performed to find predictors of AKI.

Results: From Jan 1st 2005 to Dec 31st 2013 10713 patients underwent 13890 CA of whom 40% entailed an intervention. Median (range) age was 65 (19-96) years and 70.7% were men. AKI was diagnosed in 214 patients (1.5%; 168 (1.2%), 270(2.2%) and 19 (0.1%) of stage 1, 2 and 3, respectively. There was a trend towards a decreasing incidence of AKI: 1.8% in the first 3 year period, 1.3% in the second and 1.4% in the last (p=0.05). AKI was more common in the intervention group, 2.2% vs. 1.1% (p=0.0011). Patients with AKI were older (p=0.04), had more prior intervention of AKI, more coronary disease and prior eGFR compared to non-AKI patients. In multivariate analyses age over 70 years (OR=1.01, 95% CI=1.007-1.016), angiography with intervention (OR=1.01, 95% CI=1.003-1.019), COPD (OR=1.01, 95% CI=1.003-1.025), liver disease (OR=1.03, 95% CI=1.014-1.058) and prior history of AKI (OR=1.07, 95% CI=1.051-1.080) were independent predictors of AKI after CA. One year survival of AKI patients did not differ between time periods: 67.0%, 63.1% and 69.0% in the first, second and third, respectively, p=0.3.

Conclusions: There is a trend towards a decrease in AKI incidence following CA in recent years. Aged patients with multiple co-morbidities and prior history of AKI need special attention in connection with this fact.

Funding: Private Foundation Support

FR-PO489

Risk Factors of Acute Kidney Injury and In-Hospital Mortality in Adult Patients Receiving Extracorporeal Membrane Oxygenation (ECMO)

Sung Woo Lee,1 Seon Ha Back,2 Jae Yoon Park,2 Shin-Young Ahn,1 Sejoong Kim,1 Ho Jun Chin,1 Dong-Wan Chae,1 Ki Young Na.1 1Seoul National Univ Bundang Hospital; 2Seoul National Univ Hospital.

Background: Although acute kidney injury (AKI) is the most frequent complication in patients receiving extracorporeal membrane oxygenation (ECMO), little has been studied about the risk factors of AKI and in-hospital mortality. Thus we performed the study to identify factors associated with AKI and in-hospital mortality.

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

Underline represents presenting author.

470A
Acute Kidney Injury in the First Hundred Days After Hematopoietic Stem Cell Transplantation: Experience with 222 Transplanted Patients in a Single Center Miguel A. Sols, Sandra Tejedor, Isidro Torregrosa, Carmen Ramos, Isabel Juan, Patricia Tomas, Patricia Zambrano Esteves, Juan José Guzmán Herrera, Maria Jesus Puchades, Alfonso M. Carrasco. Nephrology, Univ Clinic Hospital, Valencia, Spain.

Background: Hematopoietic stem cell transplantation recipients are at an increased risk of Acute Kidney Injury (AKI) or Chronic Kidney Disease (CKD). An earlier diagnosis could dramatically improve the patients’ prognosis. Objective. To analyze the incidence of AKI in the first 100 days of Hematopoietic stem cell transplantation recipients and the relationship with mortality.

Methods: We carried out a retrospective study including 222 adult patients who underwent Hematopoietic stem cell transplantation between 2006 and 2010 at our institution. AKI was defined using the RIFLE criteria in the first 100 days after transplantation. Results: 222 patients were included in the study, 137 males and 85 females. Median follow-up was 30 months, range 1-60 months. In the first 100 days after transplantation AKI developed in 78 patients according to the RIFLE criteria (35.1%). A total of 85 patients died during follow-up vs 47 who had developed AKI (38.2% versus 61%, p<0.05). Detailed patients’ characteristics are summarized in table 1.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male: 137</th>
<th>Female: 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years.</td>
<td>48.9 (SD 13.4)</td>
<td></td>
</tr>
</tbody>
</table>

Type of transplantation.

<table>
<thead>
<tr>
<th>Type of transplantation</th>
<th>Autologous: 117 (52.7%)</th>
<th>Allogeneic: 105 (47.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ablative</td>
<td>57 (25.5%)</td>
<td>48 (21.6%)</td>
</tr>
<tr>
<td>non ablative (miniAllo)</td>
<td>60 (26.8%)</td>
<td>57 (26.9%)</td>
</tr>
</tbody>
</table>

Previous transplantation.

<table>
<thead>
<tr>
<th>Follow-up, months.</th>
<th>37 (16.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30, range 1 to 60</td>
<td></td>
</tr>
</tbody>
</table>

AKI, RIFLE criteria. 78 (35.1%)

<table>
<thead>
<tr>
<th>AKI in Type of Transplantation</th>
<th>Autologous 11.1%</th>
<th>Allogeneic 59.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>miniAllo: 66.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall Mortality 85 (38.2%)

Mortality in AKI 47 (61%)

Conclusions: AKI incidence in hematopoietic stem cell transplantation recipients is very high. There is a statistically significant relationship between AKI and death in these patients. Earlier AKI identification could prevent kidney damage progression and improve patient outcome over time.

FR-PO493

STOP-Acute Kidney Injury (AKI): A Streamline Approach to the Management AKI Leads to Reduction of Mortality Rates Hsu-phen Chong, Thangavelu Chandrasekar. Nephrology, Aintree Univ Hospital, United Kingdom.

Background: Acute Kidney Injury (AKI) has a mortality rate of 30%, greater than common conditions such as myocardial infarction (8%) and stroke (9%). It is estimated that 15% of all inpatients at University Hospital Aintree (UHA), Liverpool, UK, suffer an AKI making it a condition of considerable importance in everyday practice. Through clinical audit, it was found that mortality rate of AKI in UHA was 33% on wards other than renal ward (9%).

Methods: To reduce AKI mortality by 30% and length of stay by 20% over a 12 month period from Oct 2013 using standardised, evidence based approach. Using plan, do, study act (PDSA) methodology, we developed and tested an automated e-alert diagnostics system, an AKI treatment bundle and a patient information leaflet. The STOP-AKI project was launched. Our Primary drivers were early and accurate identification of AKI, effective intervention and monitoring, staff and patient engagement. Initially, trialled at ward level, the project was scaled up to admission areas (Accident and Emergency Department and the Medical Assessment Unit) becoming part of routine management for all admitted patients.

FR-PO494

Race and Risk of Acute Kidney Injury (AKI) in VA Patients Michael Hugue, Diane Steffick, Deidra C. Crews, Neil R. Powe, Sharon Saydah, Meda E. Pavkovic, Kara Zivin, Rajiv Saran. 1Univ of Michigan; 2Johns Hopkins Univ; 3Univ of California San Francisco; 4Centers for Disease Control and Prevention; 5VA Ann Arbor Health System.

Background: African Americans (AA) are at increased risk for AKI compared to Caucasians (C); potential explanations include differences in risk factors, genetic susceptibility and socioeconomic factors. We explored the influence of race on AKI risk in the Veterans Administration (VA), an integrated healthcare system.

Methods: Retrospective cohort analysis of all hospitalizations for VA patients with known AA or C race in 2011. AKI was defined by KDIGO criteria (≥ 0.3 mg/dL increase in serum creatinine from pre-admission baseline). Modified Poisson regression models estimated the effect of AA race on risk of AKI, adjusting for age, sex, baseline eGFR, comorbidities (DM, HTN, coronary heart disease,CHD; CHF), geographic region and severity of illness during hospitalization. Additional models including albuminuria were run for those with available data.

Results: We identified 180,429 VA hospitalizations. Compared to C, AA had higher prevalence of DM (43.1% v. 41.1%, P<.001), lower prevalence of CHD (45.7% v. 58.8%, P<.001), lower Charlson comorbidity scores (1.4 v. 1.6, P<.001) and higher baseline eGFR (89.2 v. 81.7, P<.001). AKI occurred in 19.5% of admissions (35,134) involving 23.2% of AA and 18.5% of C. In adjusted models, AA race remained an independent risk factor for AKI (RR 1.26, 95% CI 1.24-1.28). In the subgroup with albuminuria data (40,668), the risk was slightly attenuated (RR 1.20, 95% CI 1.16-1.24). A similar increased risk of hospital-acquired AKI in AA compared to C (RR 1.19, 95% CI 1.15-1.23) was found.

Conclusions: Although AA Veterans had higher baseline eGFR and lower comorbidity scores compared to C, AA had an increased risk of developing AKI, even after accounting for differences in risk factors & geographic region. This increased risk for AKI in AA persisted when examining AKI that developed during hospitalization. Given that VA patients have similar healthcare access and benefits, our results suggest that the increased AKI risk seen in AA is unlikely to be fully accounted for by disparities in access to care.

Funding: Other NIH Support - Centers for Disease Control and Prevention, Veterans Administration Support

FR-PO495

Mortality Risk Factors in Mexican Patients with Acute Kidney Injury Luis Alberto Evangelista-Carrillo,1 Enrique Rojas-Campos,2 Salvador Mendoza Cabrera,1 Benjamin Gomez-Navarro,1 1Nefrologia y Trasplantados, IMSS, Guadalajara, Jalisco, Mexico; 2Unidad Médica de Investigación en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico.

Background: Acute kidney injury (AKI) data in Latin American is scarce.

Methods: Aim: To determine patient survival, mortality risk factors and treatment in AKI patients from a tertiary hospital. Methods: Prospective cohort Dec 2010-2012 of 275 patients with AKI who need Nephrology consultation. Recollected data at admission, follow-up, months. Results: Fall in mortality rates from a baseline of 24% to 18.5 %, representing an overall reduction in mortality of 23%. Length of stay fell by 11% equating in a 2.0 day reduction in length of stay.

Conclusions: The STOP-AKI project led to the development of an AKI bundle in Oct 2013. This has achieved not only a significant reduction in patient mortality and length of stay but in addition a more structured and streamlined way of approaching the patients with AKI in our hospital. With the bundle being rolled out to primary care and the rest of our inpatient wards, we anticipate a further reduction in mortality.
Nephrologists consultation and 30 days follow up included demographics and biochemical variables, time between AKI onset and Nephrology consultation, fluid balance, mortality scale, treatment and date of death or patient discharge.

Results: The overall mortality was 49%. Mean age 58 years. The principal diagnosis at admission was coronary syndrome. The AKI at the moment of consultation was 3 in the 64%.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CONSERVATIVE</th>
<th>HEMODIALYSIS</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>60.8±17.7f</td>
<td>53.1±19.1</td>
<td>58.3±16.7</td>
</tr>
<tr>
<td>Nephrology consultation (time since first creatinine increase hours)</td>
<td>50.5±48.9</td>
<td>71.7±69.8</td>
<td>61.3±83.5</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>38</td>
<td>52.9</td>
<td>72</td>
</tr>
<tr>
<td>24 hrs urea (L)</td>
<td>2.1±1.4f</td>
<td>1.2±1.4</td>
<td>1.4±1.2</td>
</tr>
<tr>
<td>Fluid gain</td>
<td>3.1±4.4f</td>
<td>4.5±8</td>
<td>6.6±6.2</td>
</tr>
<tr>
<td>Base creatinine (mg/dl)</td>
<td>0.96±0.26</td>
<td>1.01±0.35</td>
<td>1.02±0.30</td>
</tr>
<tr>
<td>Creatinine at nephrology consultation</td>
<td>2.96±2.04f</td>
<td>4.97±3.21</td>
<td>2.92±1.72</td>
</tr>
<tr>
<td>APACHE II</td>
<td>19±8f</td>
<td>28±5</td>
<td>24±5</td>
</tr>
</tbody>
</table>

*p<0.05

Mortality predicted analysis.

Conclusions: This is the first report of epidemiology of AKI in Mexico. The conservative treatment is associated with mortality. The consultation with nephrology was late. Use of diuretic, vasopressor and urea less than 1 liter per day at the nephrology consultation time were associated with mortality.

FR-PO496

Cast Nephropathy versus Acute Tubular Necrosis in Newly Diagnosed Multiple Myeloma: A Comparative Study

Insara Jaffer Satiajik, 1 Samih H. Nasr, 2 Nelson Leung, 1,3

1 Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2 Div of Anatomic Pathology, Mayo Clinic; 3 Div of Hematology, Mayo Clinic, Rochester, MN.

Background: Myeloma cast nephropathy (MCN) and acute tubular necrosis (ATN) are recognized causes of acute kidney injury (AKI) in newly diagnosed multiple myeloma patients. However it is currently not known if there is a difference in outcomes between these two groups. We conducted a retrospective study to compare the clinical characteristics and renal response rates in patients presenting with acute kidney injury at the time of myeloma diagnosis.

Methods: We included all patients with AKI at the time of multiple myeloma diagnosis with biopsy-confirmed diagnosis of MCN or ATN between 1998 and 2013. Patients with chronic kidney disease (estimated GFR by MDRD equation=45ml/min/1.73m2) and relapsed multiple myeloma were excluded. We assessed survival and renal outcomes. Six month landmark survival analysis was done with Kaplan Meier estimates. Renal response was classified according to IKMG consensus criteria.

Results: Out of a total of 51 patients who were included in the study, 42 had MCN and 9 had ATN. Baseline characteristics were not significantly different between the groups except urine albumin percentage of >6% was predictive of ATN.

Conclusions: Our data suggests that AKI due to ATN at the time of myeloma diagnosis is more likely to recover compared to MCN with a faster time to response. However this does not seem to affect overall survival.

FR-PO497

Hospital Manifesting AKI Presents Worst Outcome Than Community Acquired AKI

Xose Luis I. Perez-Fernandez, 1 Florentina E. Siclsen, 1 Joel Sabater Riera, 1 Kathleen D. Liu, 2 John A. Kellum, 3 Servei de Medicina Intensiva, Hospital Univ de Bellvitge, L’Hospital de Llobregat, Barcelona, Spain; 2 Critical Care, Univ Pittsburgh Medical Center, Pittsburgh, PA; 3 Nephrology & Critical Care, Univ California San Francisco Parnassus MC, San Francisco, CA.

Background: The objective of this study was to evaluate outcomes in critically ill patients with severe community-acquired AKI (CA-AKI) and hospital-manifesting AKI (HM-AKI). Secondary objectives were to identify characteristics that differ between patients with CA-AKI and HM-AKI to design future preventive strategies.

Methods: Observational retrospective study conducted at two tertiary care hospitals between 2000-2008 (UPMC, Pittsburgh, USA) and 2006-2012 (HUB Barcelona, Spain). Those with CA-AKI met criteria for KDIGO Stage 3 AKI at hospital admission whereas those with HM-AKI did not have AKI at hospital admission. HM-AKI subjects met KDIGO Stage 3 AKI criteria within 24 hours of ICU admission, with at least 72 hours elapsing between hospital admission and ICU admission. The relationship of type of AKI (CA-AKI, HM-AKI) with 90-day survival was analysed using Cox regression models controlling for differences between survivors and non-survivors.

Results: 354 patients met inclusion criteria. 92.5% of these patients required RRT at some point during ICU admission. 189 (35.4%) patients had AKI manifest while in hospital, especially those who presented with severe comorbidity. HM-AKI remained an independent risk factor for death compared to CA-AKI (HR 1.5; 95%CI (1.1 – 2)). Analysis, HM-AKI remained an independent risk factor for death compared to CA-AKI.

Conclusions: AKI manifesting after hospital admission has significantly worse outcomes compared to AKI present at hospital admission even among patients progressing to stage 3 by ICU admission. Future interventions should be directed to prevent AKI in hospital wards.

FR-PO498

Assessing Patient Awareness in Moderate to Severe Acute Kidney Injury

Sharidan Parr, Marcus G. Wild, Swee-Ling Levea, Talat Alp Ikizler, Edward D. Siew, Kerri L. Cavanaugh, Vanderbilt University Medical Center, Nashville, TN.

Background: We aimed to evaluate awareness and knowledge of kidney disease in patients experiencing moderate to severe AKI, which is important for implementing targeted patient self-care risk-reduction strategies.

Methods: We surveyed 150 hospitalized patients in one academic medical center who experienced KDIGO Stage II or III AKI. We characterized patients’ awareness that AKI is more likely to recover compared to MCN with a faster time to response. However this does not seem to affect overall survival.

Conclusions: AKI due to ATN at the time of myeloma diagnosis is more likely to recover compared to MCN with a faster time to response. However this does not seem to affect overall survival.
Results: Median participant age was 54 years; 53% were male; 81% were white; 90% had high school education or higher; 30% had health literacy scores ≤6; baseline serum creatinine (Scr) was 0.9 mg/dL; peak Scr was 2.9 mg/dL; 50% had Stage 2 AKI and 50% had Stage 3 AKI. In total, 80% of patients were unaware that they experienced AKI, including 7 patients requiring dialysis. Predictors of awareness included female gender (71% vs 41%), peak serum creatinine (4.5 vs 2.7), Stage-III AKI (82% vs 42%); nephrology consultation (68% vs 31%), dialysis (29% vs 6%), duration of injury (6 vs 3 days), discharge Scr (2.2 mg/dL vs 1.5 mg/dL), and reporting a diagnosis of AKI with a provider during the hospitalization (43% vs 21%) (p values <0.05 for all comparisons). We found poor patient recognition of preventable causes of AKI and most patients desired more information [Figure 1].

Conclusions: Most patients with moderate to severe AKI are unaware of their condition, lack understanding of risk factors for future AKI, and desire more information about AKI. Optimizing AKI awareness and understanding to promote patient-centered communication and care will require targeted educational strategies during and after hospitalization.

Funding: NIDDK Support

FR-PO501

Early and Late Auto Kidney Injury in Severely Burned Patients

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Background: Evaluation of factors influencing early and late acute kidney injury (AKI) in severely burned patients and assessment of the relationship between time of occurrence of AKI and mortality.

Methods: Retrospective analysis of severely burned patients with ≥30% total body surface area (TBSA), admitted to two centers for the treatments of burns. We selected and analysed 239 severely burned patients. Renal function was evaluated at three points: admission, critical middle point of hospitalization and the endpoint death or discharge from the center. AKI criteria: decrease in glomerular filtration rate (GFR)<60 ml/min at admission, decrease in GFR<75% compared to baseline, decrease in the daily diuresis<500 ml.

Results: At admission 15.1% of the patients had GFR <60 ml/min. AKI occurred in 38.5%. The occurrence of AKI was associated with: elderly age (p<0.001), female gender (p<0.017), overweight and obesity (p=0.055), extented depth of burns, respiratory failure, low protein concentration (for all p<0.001), low blood pressure (p=0.014) and high white blood cells count (WBC) (p=0.010). Early AKI was detected in 28% Mortality was 100% with the initial GFR<60 ml/min, 100% with the initial GFR<60 ml/min and early development of renal function, 50% with the initial GFR<60 ml/min and early developing, and 60% with the initial GFR<60 ml/min and no worsening. Late AKI was observed in 10% of patients and mortality was 79.2%. Mortality in the group with AKI was 88.0% versus 24.5% without AKI.

Conclusions: The frequent occurrence of AKI, especially early, worsens the prognosis for survival. The assessment of renal function should be included in the prognostic scales for burned patients.

FR-PO502

Acute Kidney Injury and Risk of Incident Heart Failure Among U.S. Veterans

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Background: Acute kidney injury (AKI) is common and associated with poor long-term outcomes. Heart failure (HF) is a leading cause of cardiovascular disease among patients with chronic kidney disease (CKD). The relationship between AKI and HF remains unknown and may identify a novel endpoint and link between kidney and cardiovascular disease.

Methods: We studied a national retrospective cohort of 111,488 U.S. Veterans hospitalized between 2003-2012 without history of HF. AKI was defined as a 0.3 mg/dl or 50% increase in serum creatinine using the difference between peak hospitalization and baseline creatinine (as determined by mean of outpatient creatinine over previous year and staged according to Kidney Disease Improving Global Outcomes (KDIGO) criteria using change in serum creatinine. Incident HF was defined as ≥1 hospitalization or ≥2 visits with a diagnosis of HF, as determined from validated ICD9 codes, through 2012. Propensity score matching of 37 relevant inpatient and outpatient covariates were generated and patients with and without AKI were matched 1:1. Cox proportional hazards were used to determine the association of AKI with risk of incident HF, adjusting for baseline age, eGFR, coronary heart disease and hypertension. Patients who died or had an outcome after the end of the study were censored.

Results: There were 17,272 matched pairs with and without AKI in the study. Patients with and without AKI during the index hospitalization were well matched with median

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Acute Kidney Injury Increases Medical Costs Even in the Pre-AKI Stage

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Background: Early detection of acute kidney injury (AKI) is important to prevent the progression of AKI and to improve clinical outcomes. However the significance of mild increase in serum creatinine below AKI stage is not well established. In this study, we defined pre-AKI as the 25-50% increase in serum creatinine levels from the baseline levels. We aimed to investigate the influence of AKI stage including pre-AKI on clinical outcomes.

Methods: All clinical and laboratory data were retrieved from electronic medical record database.

Results: We enrolled a total of 2816 patients who admitted Seoul National University Bundang Hospital from January 1, 2013 to December 31, 2013. We excluded patients who had not checked serum creatinine levels during admission or who were on dialysis due to end-stage renal disease.

Results: The proportion of patients who had AKI during admission were 21.6% (pre-AKI), 15.8% (AKI stage 1), 5.9% (AKI stage 2), and 3.2% (AKI stage 3). In-hospital mortality increased according to the stage of AKI [log-rank P < 0.001; HRs 1.878 (1.189-2.966) AKI stage 1; 6.039 (3.948-9.239) AKI stage 2; 12.064 (7.992-18.210) AKI stage 3].

Conclusions: We suggest that outpatients should be monitored for AKI, given its unexpected incidence and increased medical costs during admission. Clinical significance of pre-AKI should be paid attention.

Impact of Fluid Overload on Acute Kidney Injury Diagnosis and Associated Outcomes in Critically III Patients: A Retrospective Cohort Study

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Background: Fluid overload/FO changes the volume of distribution of creatinine, which is equivalent to total body water(TBW),this can alter the serum creatinine(sCr) concentrations,higher TBW result in lower sCr leading to underestimation of AKI.

Methods: We made a retrospective analysis of 120 records of pts from 2 centers. We calculated daily fluid balance and divided it by the body weight to obtain a percentage of FO.Pts were divided into 2 groups,A and B,with <2.5% and >5% of FO,respectively.

Results: We made a retrospective analysis of 120 records of pts from 2 centers. We calculated daily fluid balance and divided it by the body weight to obtain a percentage of FO.Pts were divided into 2 groups,A and B,with <2.5% and >5% of FO,respectively.

Conclusions: Fluid overload/FO changes the volume of distribution of creatinine, which is equivalent to total body water(TBW),this can alter the serum creatinine(sCr) concentrations,higher TBW result in lower sCr leading to underestimation of AKI.

Placental Growth Factor (PLGF) is the Novel Predictor of CKD Progression: The Results from NARA-CKD Study

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Background: PLGF plays a critical role in arterio genesis through vascular inflammation. We have already reported an independent association of PLGF with survival and cardiovascular risk in the patients with chronic kidney disease (CKD study), we performed Assessment of Risk management for Atherosclerotic diseases in CKD (NARA-CKD) study; however, the relations between circulating levels of PLGF and the progression of CKD remains unknown.

A prospective cohort study of 402 participants undergoing renal biopsy was conducted to elucidate the predictive value of PLGF on renal prognosis in the patients with CKD.
Results: Histologically, elevated PI GF was significantly associated with the severity of glomerulointerstitial damage and the intimal thickening of small renal arteries. During a median follow-up of 2.7 years, 82 patients reached primary end-points which were defined as the requirement of replacement renal therapy (38 patients) and the decline of eGFR by more than 25% from baseline (44 patients). Although baseline eGFR was not statistically different among patients in all PI GF quartiles, the rate of eGFR decline in the patients with the highest PI GF quartile was significantly faster than those with other quartiles. With adjustment of known confounding factors, PI GF was significantly associated with the risk of deterioration of renal function with the adjusted hazard ratio of 1.75 (1.38–2.26) for each quartile increment of PI GF. The combined use of eGFR and PI GF significantly improved the predictive accuracy for CKD progression compared with eGFR alone (c statistics from 0.689 to 0.772, p<0.001).

Conclusions: Elevated PI GF is a novel and independent predictor of renal prognosis in the patients with CKD.

FR-PO508

Steep Decline in Renal Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study

Methods: Data from the PREVEND study, a population based prospective cohort with median follow-up of 11 years, were used to identify women without and with self-reported HDP (non-HDP, n=1805 and HDP, n=977). A case cohort, 10 years post-partum was created by record linkage, with subgroups: normal pregnancy (control, n=202), pregnancy-induced hypertension (PIH, n=56) and preeclampsia (PE, n=29). Renal function and the prevalence of CKD were compared.

Background: Hypertension in pregnancy can be associated with renal injury which may be masked by gestational change. Postpartum assessment is an opportunity to detect persistent renal abnormalities. However previous studies are small and often exclude those with pre-existing hypertension, a risk factor for CKD. Aim: To determine the postpartum prevalence of renal abnormalities in women with chronic hypertension, pregnancy induced hypertension (PIH) or preeclampsia (PE) in a previous or current pregnancy.

Methods: Women with singleton pregnancies referred to a hypertension pregnancy clinic (Feb 2011-Nov 2014) attending postpartum review (offered to all) were included. Those with previously diagnosed CKD were excluded. Demographics, 24-hour urine protein, estimated GFR (CKD-EPI) and blood pressure after six weeks postpartum were recorded.

Results: Overall 120 (29.7%) of women were found to have features of renal disease postpartum. Subgroup analysis according to hypertensive groups is shown in Table 1.

Conclusions: A substantial proportion of women with hypertension in pregnancy have renal abnormalities after six weeks postpartum. Identification of risk factors for progression of CKD in this population through longitudinal studies is needed.

FR-PO509

Pregnancy Outcomes in Women with Chronic Kidney Disease in South Australia

Methods: Data was obtained from the PREVEND study, a population based prospective cohort with median follow-up of 11 years, were used to identify women without and with self-reported HDP (non-HDP, n=1805 and HDP, n=977). A case cohort, 10 years post-partum was created by record linkage, with subgroups: normal pregnancy (control, n=202), pregnancy-induced hypertension (PIH, n=56) and preeclampsia (PE, n=29). Renal function and the prevalence of CKD were compared.

Results: eGFR was lower at baseline and during follow-up in HDP vs non-HDP (A). In addition, the decline in eGFR was steeper in HDP vs non-HDP (B). At baseline and during follow-up there were more anti-hypertensive drug use, including ACEi in the HDP group. 24-h albuminuria at baseline was higher in HDP vs non-HDP and remained steadily higher in HDP during follow-up. A trend towards increased risk of CKD was observed in HDP. FR-1.13 (1.13-1.16) (C). In the case cohort, eGFR was significantly lower (C) and 24-h albuminuria significantly higher (p<0.003) in the PE vs controls. 7.8% of the controls, 10.6% of the PIH and 12.9% of the PE group met the criteria for CKD.

Conclusions: We report a lower renal function and a steeper renal function decline over time after HDP. Women with severe hypertensive disorders of pregnancy (PE) have the highest risk for renal function loss.

FR-PO511

Changes of Markers of Prothrombotic State in Membranous Nephropathy Complicated with Type 2 Diabetes

Methods: Patients were enrolled if they were diagnosed with MN and T2DM during the time period of 2005-2014. All patients were treated with immunosuppressive therapy and followed up until December 2015. The study population was divided into two groups: (1) MN patients with T2DM (MN+T2DM, n=14); (2) MN patients (pure MN, n=6). Differences in the biomarkers of vascular function and markers of thrombosis were evaluated at baseline and after 6 months of treatment. The primary endpoint was to assess the changes in thrombotic and anti-thrombotic markers.

Results: There were no significant differences in baseline characteristics between the two groups. After 6 months of treatment, there were significant differences in levels of proteinuria (>150 mg/d: MN+T2DM vs pure MN, p<0.05), homocysteine (MN+T2DM vs pure MN, p<0.05), proteinuria (MN+T2DM vs pure MN, p<0.05), and vWF levels (MN+T2DM vs pure MN, p<0.05). The levels of proteinuria, homocysteine, proteinuria, and vWF were significantly lower in MN+T2DM group compared to pure MN group.

Conclusions: The changes in markers of prothrombotic state were significantly different between MN patients with T2DM and pure MN patients treated with immunosuppressive therapy. The changes in these markers may contribute to the pathogenesis of MN in patients with T2DM.

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

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Conclusions: Under NS state, MN+DM patients existed more serious prothrombotic state compared to primary MN+DKD. The mechanism is related to disorders of plasminogen activation function, coagulation function, as well as fibrinolytic function. More attention should be paid to treatment of prothrombotic state in MN+DM patients.

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FR-PO512
Serum C3 and Renal Outcome in Patients with Primary Focal Segmental Glomerulosclerosis
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Background: The role of complement in the pathogenesis or progression of FSGS is uncertain. The aim of this observational cohort study was to identify the clinical implications of serum C3 levels and to investigate their utility as predictor of renal outcomes in patients with FSGS.

Methods: 591 biopsy-proven primary FSGS patients were recruited. Clinical, histological and progression data were recorded. Decreased serum C3 level was defined as C3 <85 mg/dl. The study endpoint was end-stage renal disease (ESRD).

Results: Of the patients, there were 117 patients (21.5%) with low serum C3. At the time-point of renal biopsy, compared to patients with C3 ≥85 mg/dl, those with C3 <85 mg/dl had higher level of serum creatinine, lower levels of eGFR, proteinuria, hemoglobin, triglyceride, cholesterol, IgA, more severe segmental sclerosis, tubular atrophy and total suPAR serum level for the prediction of recurrent FSGS.

Conclusions: Complement activation may occur in patients with FSGS. It is associated with clinical and histological severities. Low serum C3 is an independent risk factor for the decline of eGFR, and is associated with poor renal outcome in patients with FSGS.

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FR-PO513
Role of Proteolytic Fragment suPAR D2-D3 in Prediction and Cause of FSGS
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Background: Primary FSGS is a kidney disorder that leads to end stage renal disease and affects tens of thousands people annually. Several studies suggest the soluble urokinase-type plasminogen activating receptor (suPAR) to be a predisposing circulating factor and prognostic marker of FSGS through its interaction with αvβ3 integrin.

Methods: We collected serum samples from kidney transplant recipients with FSGS. We also analyzed sera from healthy controls and patients with sepsis and on peritoneal dialysis. These sera were used to assess integrin activation in podocytes. Western blot identified a fragment of suPAR containing the D2-D3 only in the subset of sera from patients with recurrent FSGS. In vitro, the EC50 response of D2-D3 for activating integrin αvβ3 was approximately ten fold than for D1-D2-D3. Exposure of podocytes to physiological concentrations of the D2-D3 increased the amount of surface uPAR and facilitated podocyte motility. Injections of the D2-D3, but not full-length suPAR, induced transient proteinuria in mice. Transgenic mice for D2-D3 developed rising serum suPAR levels and a variable degree of proteinuria. A composite risk analysis score was developed that included presence of the D2-D3 in patient serum, podocyte integrin activation capacity, and total suPAR serum level for the prediction of recurrent FSGS.

Conclusions: suPAR D2-D3 fragment is a prognostic marker and risk factor for recurrent FSGS.

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FR-PO514
Prognosis, Survival and Renal Function in Patients with Lupus Nephritis
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Background: Lupus nephritis is the most common glomerulonephritis in the Colombian Caribbean region, despite there is less published information about its evolution and clinico-pathological aspects. Objective: To evaluate prognosis, survival and renal function of patients with LN residing in the Colombian Caribbean region controlled between 2000 - 2014.

Methods: 229 patient study with LN corroborated by histology according to the International Society of Nephrology Classification / Renal Pathology Society (ISN/ RPS. 2003) treated with induction and maintenance therapy and with a systemized following of at least 2 years. The pharmacological treatments included prednisolone, azathioprine, and Cyclophosphamide mycophenolate mofetil in isolation or combined and the clinical laboratory and histopathology variables were correlated as predictive value of therapeutic response. To achieve this as methodology a non-parametric descriptive statistics ANOVA (k-w) was used and canonical correspondence analysis.

Results: 229 patients in total of 34±12 of age, which 88% women, whose evolution were controlled during 24±6 months. The most common form of clinical presentation was nephrotic syndrome and asymptomatic hematuria-proteinuria (68.07%) the type III and type IV patients under 25 years and negative response to treatment. The estimated glomerular filtration rate measured by MDRD showed a significant improvement at 24 weeks with regard the baseline figure of 74.36.

Conclusions: The early detection and reference of NL patients allows an early approach and therapy. Which will prevent chronic kidney disease.

FR-PO515
Association of ABO Blood Group with Progression of IgA Nephropathy
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Background: ABO blood group antigens are major histocompatibility antigens and little is known about its association with progression of IgA nephropathy (IgAN).

Methods: Biopsy-proven primary IgAN patients were retrospectively recruited. Clinical, histological and progression data were recorded. Patients with eGFR<15ml•min^-1•1.73m^-2 at time of biopsy were excluded. Renal tissue was semi-quantitative scored according to the Oxford scoring system. ABO blood group was determined by standard erythrocyte antiserum agglutination method. All patients were divided into B antigen group (type B and AB) and non-B antigen group (type A and O) based on their ABO types.

Results: Among the 752 IgAN patients recruited in this study, 210 patients were type A (27.9%), 221 were type B (29.4%), 72 were type AB (9.6%) and 249 were type O (33.1%). When renal biopsy was performed, patients in B antigen group had higher eGFR (82.44 ± 65.68 ml/min), lower systolic blood pressure (125.36 ± 129.29 mmHg), and uric acid (373.59 vs. 393.93 mmol/l) than patients in non-B antigen group. No significant difference was detected between histological lesions and these two groups. Totally, 100 patients progressed to end-stage renal disease (ESRD) after a median follow-up period of 51.05 months, including 32 (15.2%) type A, 18 (8.1%) type B, 2 (2.8%) type AB and 48 (19.3%) type O patients. Kaplan-Meier analysis showed that median ESRD-free survival time in patients in B antigen group was significantly longer than patients in non-B antigen group (148.2±5.5 months vs. 138.8±7.5 months, p<0.001). Furthermore, patients in B antigen group were associated with a decreased risk of ESRD (HR=0.56, 95%CI 0.33-0.94) after adjusted by age, sex and clinical variables including eGFR, sbp, serum albumin, urine protein and hemoglobin by Cox proportional hazards model.

Conclusions: Our data suggested that B antigen had an independent protective effect against the progression of IgAN.

FR-PO516
The Analysis of the Long-Term Outcomes of Patients with Primary IgA Nephropathy
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Background: Primary IgA nephropathy (IgAN) is one of the most common glomerular diseases in China. In this study we try to investigate the clinical characteristics and the relationship between CKD stages and long-term outcomes of patients with primary IgAN through the retrospective analysis of their clinical data.

Methods: Patients with biopsy-proved primary IgAN from 2002 to 2013 were included in the retrospective analysis. They were older than 18 years old and their follow-up time was more than 12 months. We collected their medical history, laboratory test reports and other clinical data. Then we enrolled 297 patients who were followed up for 5 years for further research. Kaplan-Meier method was used to calculate the renal survival rate of the patients.

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FR-PO517
Variability of GFR Decline in Alport Syndrome: Insights from a Provincial Database
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Background: Alport syndrome (AS) is one of the inherited causes of CKD due to mutations in the collagen genes making up the glomerular basement membrane collagen. Design of clinical trials for intervention in AS proves challenging without a clear understanding of renal progression over time as observational data is lacking due to small sample size. We present here the utilization of population based data in a simulation to mimic clinical trial recruitment and endpoints to provide insights in trial designs for AS.

Methods: AS patients were identified within a provincial CKD clinical database (PROMIS) in British Columbia, Canada for this observational simulation study. Patients were excluded if they had fewer than 4 GFR-MDRD measurements or 2 as a study entry point to generate 100 random samples. Primary outcome was annual rate of GFR change over 2 years categorized into: > -5 mL/min/yr (progressor), -5 to 2 mL/min/yr (stable), < -2 mL/min/yr (regressor).

Results: 37 pts met inclusion criteria; median follow-up was 48.2 months, and median age of 36. The sample sizes for each random sample at the 3 enrolment gFR levels were: 11, 12 and 10 respectively. Of those that ’enrolled’ at gFR 45-60 mL/min, 72.7% (IQR:63.6%,81.8%) progressed, and 22.7% (IQR:9.1%, 36.4%) remained in stable state. The five-year renal survival rate of patients in CKD3b stage was 85.3%, while it is only 65.3% for patients in CKD4 stage.

Conclusions: Five-year and ten-year renal survival rate of patients with IgAN was 92% and 88%, respectively. Patients in CKD3b or CKD4 stage at biopsy may have a lower renal survival rate and a worse outcome. At the time of renal biopsy, patients with impaired renal function, mass proteinuria, hypertension, anemia and low serum albumin may have a greater risk of progressing to end-stage renal disease.

FR-PO519
Micronas as Predictive Biomarkers of Chronic Kidney Disease (CKD) in Patients (Pts) Undergoing Radical Nephrectomy (RN) for Kidney Cancer
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Background: MicroRNAs (miRs) are small non-coding RNAs involved in cell homeostasis and disease. Our study identified clinical and molecular markers associated with increased risk of developing CKD after RN for renal clear cell carcinoma(RCC).

Methods: 80 pts who underwent RN for RCC at a single institution between 2008-2011 were included. Inclusion criteria: normal renal function at surgery time (gFR > 60 mL/min CKD-EPI formula 2009, serum creatinine <1.1 mg/dL, no proteinuria). No pre-existing glomerulopathy. No evidence of metastatic disease. Minimum follow-up: 12 months post-surgery. FEPE normal adjacent tissue to RCC(-)sm was micro-dissected to isolate cortex(10 glomeruli) and medulla and was subject to RNA extraction. miRs analysis was performed using Nanostring nCounter and validated by Real-time, droplet PCR and in situ hybridization(SH). Cox regression analyses were used to define variables associated with increased risk of CKD.

Results: 47.4% of pts developed CKD(stage 3a-3b-4 KDIGO) 12 months after RN. At multivariable Cox Regression, type II diabetes(pvalue:0.009),basal serum creatinine(pvalue:0.002) and miR-193b over-expression(pvalue:0.017) were independently associated with increased risk of developing CKD after RN for renal clear cell carcinoma(RCC).

Conclusions: Tissue and urinary miRs deregulation may represent an early marker of kidney dysfunction and may anticipate clinical and laboratory evidence of CKD providing an important tool for personalized follow-up and prevention in pts undergoing RN for RCC.

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Societa’ Italiana di Nefrologia

FR-PO520
Urinary Angiotensinogen to Creatinine Ratio Is a Specific Biomarker for Renal Progression in Autosomal Dominant Polycystic Kidney Disease
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Background: Urinary angiotensinogen to creatinine ratio (AGT/Cr) is elevated in autosomal dominant polycystic kidney disease (ADPKD), but whether AGT/Cr is a specific biomarker of ADPKD progression is not known. This study was performed to measure urinary AGT/Cr in subcohorts according to primary renal disease (glomerulonephritis (GN), diabetic nephropathy (DN), hypertensive nephropathy (HTN), ADPKD) and to demonstrate urinary AGT/Cr in subcohorts according to primary renal disease. First-voided morning urine was collected from all patients upon enrollment and stored at -80°C until measurement. Urinary AGT was measured by commercial sandwich enzyme-linked immunosorbent assay (ELISA). Urinary AGT/Cr levels and associated factors were compared among CKD subgroups.

Methods: Nine nephrology centers recruited adult subjects with chronic kidney disease (CKD) stage 3a-4 and classified them into subgroups according to primary renal disease as shown in Table 1. First-voided morning urine was collected from all patients upon enrollment and stored at -80°C until measurement. Urinary AGT was measured by commercial sandwich enzyme-linked immunosorbent assay (ELISA). Urinary AGT/Cr levels and associated factors were compared among CKD subgroups.

Results: A total of 1528 patients were enrolled in KNOW-CKD cohort study (NCT 01630486) from Apr 2011 to Dec 2013. Among them, 153 patients were excluded (71 unclassified subgroups, 71 without urinary AGT measurement, 9 without available eGFR) and a total of 1375 (519 GN, 310 DN, 292 HTN, 254 ADPKD) patients were included in the final analysis. The mean age was 51 years and baseline serum creatinine was 1.9 ± 1.2 mg/dL. The GN and ADPKD subgroups showed younger age and earlier elevation.

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CKD: Risk Factors for Incidence and Progression - II
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of urinary AGT/Cr levels according to CKD stages. When we performed the risk factor analysis separately in GN and ADPKD subgroups, the highest quartile of urinary AGT/Cr was associated with GN subcohort, female gender, hypertension, decreased eGFR, decreased plasma Hb, and higher degree of albuminuria. However, in multivariate logistic regression analysis, ADPKD subcohort demonstrated higher urinary AGT/Cr compared to GN subcohort after adjusting other co-factors.

**Conclusions:** Urinary AGT/Cr is greatly increased in ADPKD independent of albuminuria and renal function.

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### FR-PO521

**Using Biomarkers to Predict Progression to End-Stage Renal Disease within 6 Months of Liver Transplant**

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**Background:** Liver transplant (LT) recipients are at increased risk for CKD and progression to ESRD. Creatinine, the standard for assessing renal function, provides limited prognostic information for recovery from AKI. Our aim is to create a predictive model for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers.

**Methods:** We enrolled 202 patients, of whom 138 have 6mos follow up. 13 patients progressed to ESRD, defined as GFR<20 ml/min; dialysis, or transplant evaluation. Logistic regression models evaluated neutrophil gelatinase-associated lipocalin, IL-18, Cystatin-C, Kidney Injury Molecule-1, & liver fatty acid binding protein for inclusion. Receiver operating characteristic curves and concordance statistics were used to assess the models.

**Results:** In one model, MELD score at LT, pre-LT AKI, pre-LT renal replacement therapy, and highest creatinine 6mos pre-LT were associated with ESRD at follow-up (p<0.05). In another model with biomarkers, only urinary IL-18 was included for its association with progression to ESRD. Creatinine, the standard for assessing renal function, provides limited prognostic information for recovery from AKI. Our aim is to create a predictive model for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers.

**Conclusion:** Our predictive model for progression to ESRD within 6mos of LT incorporating clinical data and biomarkers is associated with higher MELD score at LT, pre-LT AKI, pre-LT renal replacement therapy, and highest creatinine 6mos pre-LT.

*Funding:** Medical and Research Foundation - Cincinnati Children's Hospital

### FR-PO522

**Detection of Inflammatory BioMarkers in Urine Using a Dried, Shelf Stable Transport Device, ViveST**

**Daniel R. Mcclernon,1 Timothy W. Murray,2 Anita M. Mcclellon,1 bioMONTR Labs, Research Triangle Park, NC, 2Vivebio LLC, Alpharetta, GA.

**Background:** Current medical practice assesses health of implanted kidneys by monitoring non-specific signals (serum creatinine) after rejection has started and gold standard diagnostic method is invasive kidney biopsy. Studies of non-invasive biomarkers (CXCL9) have shown utility (CTOT-01) in identifying subsets of patients at risk for acute rejection. A urine based test for post surgical evaluations to pinpoint rejection and expedite therapeutic intervention is needed. Here we describe detection of CXCL9/MIG and CXCL10/IP-10 in urine in combination with a novel collection device ViveST, eliminating need for cold chain transport and storage.

**Methods:** Urine collected and centrifuged (4°C)at 2,000xg (30 min). Supernatant decanted into clean tubes and diluted 1:1 with proprietary diluent buffer. Reconstituted Human, A.99/MIG and CXCL10/IP-10 (R&D Systems) was reconstituted using molecular grade water to concentrations of 10,000pg/ul and serially diluted. Urine was spiked with diluted reconstituted human MIG or IP-10. 1ml aliquots were loaded onto ViveST and dried. ViveST samples were reconstituted with 1ml of molecular grade water and analyzed concurrently with frozen aliquots using quantitative sandwich enzyme immunoassay techniques for MIG or IP-10. Linear regression analysis from seven levels of calibration standard used to calculate MIG and IP-10 concentration.

**Results:** ViveST samples yielded MIG or IP-10 concentrations similar to corresponding frozen aliquots (see table). Replicate aliquots gave similar results.

<table>
<thead>
<tr>
<th>Level</th>
<th>MIG (pg/ul)</th>
<th>IP-10 (pg/ul)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117</td>
<td>198</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
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<td>0</td>
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<td>7</td>
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</table>

**Conclusions:** MIG and IP-10 can be detected in urine as inflammatory biomarker to assess risk of transplant rejection. ViveST can be used as ambient storage and transport device eliminating need for cold chain storage. Additional studies warranted assessing detection of biomarkers at therapeutically relevant concentrations.

*Funding:** Pharmaceutical Company Support - Vivebio LLC

### FR-PO523

**Albuminuria-Induced Apoptosis in Children with Nephrotic Syndrome Is A Result of the Dysbalance in Apoptosis Controlling System**

**Yejevnia Burlaka, Dept of Pediatrics No.4, National O.O. Bogomolets Medical Uni, Kyiv, Ukraine.

**Background:** Albuminuria promotes cell death, and is associated with faster progression of chronic kidney disease (CKD). However, the molecular mechanisms regulating cell death in response to albuminuria are not fully understood.

**Methods:** 53 patients aged 10-15 years with active stage of nephrotic syndrome were included in the study. Immunohistochemical staining of anti-apoptotic factor Bax, anti-apoptotic factor Bcl-xl, number of apoptotic cells in kidney biopsy specimens were done. Comparison of the level of these parameters between the different segments of nephrone at different stages of glomerulosclerosis has been performed.

**Results:** Measurement of the pro-apoptotic factor Bax in kidney slices obtained from children with morphological form of nephrotic syndrome focal segmental glomerulosclerosis (FSGS) showed presence of high level of Bax in both glomerular and tubule-interstitial segments. Higher immunosignals of Bax was evaluated in glomeruli with FSGS I-II st. as compared to tubular segment. When FSGS III-IV st. observed higher expression of Bax was detected in surrounding tubule-interstitial segment. Expression of the anti-apoptotic factor Bcl-xl was studied. Higher expression of Bcl-xl was recorded in tubule-interstitial segment as compared to glomeruli when FSGS I-II st. occurs. When FSGS III-IV st. occurred higher immunosignals of Bcl-xl is localized in surrounding tubule-interstitial segment with almost complete absence in glomeruli. The number of apoptotic cells was analysed. Quantitative analysis of apoptosis in kidney sections of patients with FSGS I-II st. revealed higher apoptotic index (AI) in glomeruli as compared to tubule-interstitial component. In kidney sections with FSGS III-IV st. higher AI was found in tubule-interstitial compartment.

**Conclusions:** Thus, progression of kidney injuries in nephrotic syndrome is associated with increased activity of pro-apoptotic factor Bax and simultaneous reduction of anti-apoptotic factor Bcl-xl. The level of the expression of Bax and Bcl-xl depends on the stage of FSGS and indicates the step-dependent manner of glomerular and interstitial injuries development upon the chronic influence of albuminuria.

*Funding:** Government Support - Non-U.S.

### FR-PO524

**eGFR, Renal, and Cardiovascular Risk and Nucleosome/Nucleotide Backbones of Human Immunodeficiency Virus Patients in the USA**

**Jonathan A. Winston,1 Grace McConney,2 1Icahn School of Medicine at Mount Sinai; 2Case School of Medicine.

**Background:** HIV treatment involves choices in complex environments, and must balance disease management and potential safety issues (kidney and Cardiovascular diseases (CVD)) in an aging population. This study examined renal, CVD and comorbid conditions, and treatment of HIV patients.

**Methods:** Patients diagnosed with HIV using ICD-9 codes were selected from the Quintiles database (33M patients). Patients enrolled for ≥ 1 year during 2012-14, maintaining a single antiretroviral therapy, and for whom baseline eGFR could be computed were stratified based on backbone: regimens including tenofovir disoproxil fumarate (TDF), abacavir (ABC), or other (OTH). eGFR and rate of CV comorbidities at baseline were assessed.

**Results:** 14,942 HIV patients (mean age: 43; 76% male) were included; 85% TDF, 7% ABC, 8% OTH. Mean baseline eGFR was 99 ml/min/1.73 m², with differences observed among regimens (102 TDF, 82 ABC, 87 OTH). Classified by degree of kidney impairment at baseline, regimen was highly correlated with level of impairment, with normal or mild impairment (eGFR<60) more likely to be treated with TDF, and patients with moderate to
severe impairment (eGFR<60) more likely to be on ABC. Several CVD risk factors were more prevalent in ABC patients compared to TDF, hypertension (25% v 13%), dyslipidemia (30% v 16%), and diabetes (12% v 5%) (p<0.001 in all) being the most common.

Conclusions: HIV patients often present with prevalent CVD risk and reduction in kidney function. Physicians make treatment choices that reflect concern for kidney function, consistent with labeling. This choice may come with cost, with more CVD risk factors correlated with alternative choices of NRTIs. As some antiviral regimens may be associated with CVD while others with kidney disease, understanding CVD risk profile versus kidney function protection may help optimize care of patients.

Liveview tool provides the best compromise between accuracy and time required.

Acknowledgments. This study was funded in part by the European Community (FP7-PEOPLE-MCA-ITN-317246, TranCYST project).

Funding: Private Foundation Support

FR-PO526
Renal Reserve: Development of a Kidney Stress Test Kyle Rodenbach,1 Dana F. Fuhrman,1 Paula S. Maier,1 Katherine D. Shaw,1 George J. Schwartz.1 1Peds, Univ of Rochester, Rochester, NY; 2Peds, Univ of Pittsburgh, Pittsburgh, PA.

Background: Renal reserve (RR) is the difference in stimulated versus baseline glomerular filtration rate (GFR); it might predict future kidney health. The purpose of this study was to compare a meat versus liquid protein load in a cystatin-C-based (Cys-C) RR test using cystatin-C-mediated creatinine clearance (CrCl) and iohexol infusion clearance (IoCl) for validation.

Methods: Participants (N=18) were screened for health status, blood pressure, and proteinuria. They followed a low protein diet and took cysteine (20 mg/kg) for two days prior to the study. Water loading was used to maintain urine flow, and two hours were allowed for a stable steady state to be established. Participants 1-10 received a burger (1 g/kg protein); 11-15 received a ProCel® shake (1 g/kg protein); and 16-18 received a high dose ProCel® shake (1.5 g/kg protein). Data were analyzed for significance of RR. Cystatin-C estimated GFR (Cys-C eGFR) was calculated using the CKD-EPI Cys-C formula (Inker NEJM 2012) following IVC catheter calibration (ERM-DA471).

Results: Participants (N=18) had a mean (SD) age of 22 (2) years and were 39% male and 72% white. Baseline GFR (SD) in mL/min/1.73m² averaged 103.4 (14.7) for CrCl; 108.9 (9.0) for IoCl (N=8); and 117.4 (6.1) for Cys-C eGFR. For the burger group (N=10), mean RR (SD) in mL/min/1.73m² was 17.1 (11.6) for CrCl (P=0.001); 8.4 (4.3) for IoCl (P<0.001); and 4.7 (2.4) for Cys-C eGFR (P<0.001). For 1-0.1 g/kg shakes (N=8), mean RR (SD) in mL/min/1.73m² was 15.8 (5.8) for CrCl (P<0.001), 11.7 (9.0) for IoCl (P=0.008), and 2.4 (2.9) for Cys-C eGFR (P=0.05). The burger and shake groups did not differ significantly in RR determined by CrCl, IoCl, or Cys-C but Cys-C-based RR was significantly less than Io-o-based RR for both groups. There were no differences in post-load versus pre-load CrCl clearance ratios.

Conclusions: Cys-C-based RR following a burger provides a simple stress test of kidney function which was validated by classical renal clearances and can be applied to those who recover from acute kidney injury. Why Cys-C-based RR was smaller than Io Cl, the reference standard, is a topic for future investigation.

Funding: Other NIH Support - CTSI, University of Rochester, Private Foundation Support

FR-PO527

Background: Despite the clinical recovery of an acute kidney injury (AKI) episode, progression to chronic kidney disease (CKD) could be observed on long time follow-up. The mechanisms are poorly understood. To analyzed if angiotensin II receptor blockade (ARB) before the ischemic insult is effective in abrogating the severity of the AKI episode and/or the progression to CKD.

Methods: Male Wistar rats were divided into 4-groups of rats: sham; sham plus losartan 3-d before surgery; bilateral renal ischemia for 45-min (UTxI); and losartan administration (3-d) before ischemia (Los+Pre). Animals were studied after 1, 3, 5, 15 days of 9-months. At the end of each experimental period, physiological, histopathological, immunohistochemistry, biochemical and molecular studies were performed.

Results: UTxI group developed CKD characterized by renal dysfunction, proteinuria, renal hypertrophy, glomerulosclerosis, tubular atrophy and tubulointerstitial fibrosis. At the ultra-structural glomerular level, foot process effacement was observed, which was associated a reduction in immune-gold staining for nephrin. Renal injury was mediated by increased oxidative stress, inflammation and up-regulation of TGFÎ¬, aSMA, and Collagen I protein levels. TGFÎ¬ overexpression was mainly observed in epithelial cells. Interestingly, in spite of ARB did not prevent or reduced AKI severity, it was enough effective to prevent CKD. The renoprotection conferred by ARB was associated with the early recovery of renal blood flow, lesser inflammation and greater nuclear hypoxic inducible factor 1Î± (HIF1Î±) staining.

Conclusions: Our data shows that in spite of, losartan pre-treatment did not protect the rats against AKI, it was effective to prevent the transition to CKD. The mechanisms by which losartan prevented CKD were in part due to the early renal blood flow recovery, lesser inflammation and greater HIF1Î± nuclear translocation within the 15 days post-ischemia.

Funding: Government Support - Non-U.S.
FR-PO528
Specific Endothelial Heparin-Binding EGF-Like Growth Factor Deletion Ameliorates Renal Injury Induced by Chronic Angiotensin II Infusion
Fenfua Zeng, Lance A. Kloepfer, Raymond C. Harris. Medicine, Vanderbilt Univ, Nashville, TN.

Background: Transactivation of EGFR by angiotensin II (Ang II) plays important roles in the initiation and progression of chronic kidney diseases (CKD). In vitro studies suggested that HB-EGF may be a critical mediator in this process, whereas its role in vivo has not been reported.

Methods: Age-matched male littermates of HB-EGF−/− mice with endothelial-SCL-Cre-ER (T) (+) or (-) were used. Tamoxifen injections produced control (HB−/−) and mice with specific deletion of HB-EGF from endothelium (HB−/−/−), which underwent untreated hyperlipidemia and systolic minipump-mediated infusion with saline or Ang II for 8 weeks. Systolic blood pressures (SBP) were measured by tail-cuff. Renal injury was evaluated by albuminuria using urinary albumin/creatinine ratios and by morphology with periodic acid-Schiff (PAS) staining. Renal EGFR activation was determined by immunoblotting and immunostaining. Endothelium/podocyte injury, inflammation and renal fibrosis were evaluated by immunostaining.

Results: Compared to control, kidneys from HB−/− mice with Ang II-infusion had significantly reduced EGFR activation. Endothelial HB-EGF deletion did not significantly prevent the hypertension induced by Ang II infusion, albeit lower SBP was detected in HB−/− mice compared to HB−/−/− mice. However, it decreased Ang II-infusion related renal injury, as demonstrated by 1) less albuminuria; 2) less glomerulosclerosis with glomerular score of 0.793 versus 1.652 in the control; 3) preserved endothelial integrity and decreased podocyte injury shown by more glomerular tufts area and WT1 positive cells; and less apoptotic cells measured by cleaved caspase 3 and TUNEL staining; 4) reduced inflammation in perivascular area and interstitium measured by F4/80 and CD3 immunostaining; and 3), reduced renal fibrosis, as shown by α-SMA immunostaining.

Conclusions: Shedding of HB-EGF from endothelium plays an important role in Ang II induced renal injury by linking Ang II-ATIR with EGFR transactivation. Inhibition of HB-EGF shedding could be a potential therapeutic strategy for CKD.

Funding: NIDDK Support, Veterans Administration Support

FR-PO529
Effects of Acute Kidney Injury (AKI) Severity and Co-Morbidities on Chronic Kidney Disease (CKD) Progression
Gregory John Wilson,1,2 Andrew Lawrence Kark,1,2 Andrew John Mallett,1,2,3,4 Alan Salisbury,1,2,3,4 Zaimin Wang,1,2 Helen G. Healy,1 Wendy E. Hoy,1,2,4 Kidney Health Service, Royal Brisbane and Women’s Hospital Queensland, Australia; 1Inst for Molecular Biology and School of Medicine, UQ, Australia; 2Centre for Chronic Disease, UQ, Australia.

Background: AKI is a common and important cause of CKD. It remains unknown how AKI severity influences CKD progression. Which co-morbidities influence the progression of CKD also remains undefined.

Methods: We aimed to explore whether AKI severity and patient co-morbidities influence CKD progression. Patients with AKI associated with a clinical diagnosis of AKI were identified in the Royal Brisbane & Women’s Hospital cohort (n=1150) of the Queensland registry. AKI events were confirmed through historical creatinine values (2005 month plasma samples frozen from a phenotypically characterized cohort of patients with AKI Stage 3 and below from a prior Probiotic Renalys1 study. NMR spectral data of baseline and 6 month plasma samples were analyzed after identical treatment of all samples. A total of 24 baseline samples were differentiated by a change in their BUN. Principal components analysis and orthogonal partial least squares discriminant analysis was used to analyze the data and determine the metabolites that best differentiated the phenotypic groups.

Results: Characteristics of the cohort population were age 57.7 ± 14 yrs, mean BMI 31.3 ± 6.1 Kg/m2, 10 males and 14 females, 20 with HTN, 8 with DM, 11 Caucasian and 9 AA, 3 other, 1 unknown. 16 patients who had a decrease in BUN after 4 months of probiotics treatment could be differentiated based on baseline samples from those whose BUN increased or did not change. The majority of the metabolites that differentiated the groups were microbial related metabolites.

Conclusions: Metabolomics analysis revealed a signature of metabolites that were associated with a decrease in BUN, and holds promise for use in predicting individuals with CKD that would most benefit from use of probiotics. The majority of the metabolites important to the differentiation of groups map to pathways involved in microbial metabolism.

Funding: Other NHI Support - NIH Common Fund for Metabolomics at RTI North Carolina: 1U24DK097193

FR-PO530
Association Between Gut Microbiome and Cardiovascular Risk in Chronic Kidney Disease Patients with Type 2 Diabetes Mellitus
Ruchi Singh, Tetyana L. Vasylyeva. Pediatrics, Texas Tech Health Sciences Center, Amarillo, TX.

Background: Diabetes is one of the leading causes of CKD. It is well established that patients with T2DM often experience persistent low-grade inflammation leading to microvascular deterioration and progression of vascular complications along with impaired gut motility, which impacts their microbomes. The aim of this study was to study the assessment of gut microbiota, plasma zonulin, and inflammatory cytokines (TNF-α, IL-6, IL-10) in conjunction with FGF-23, ET and levels of LPs in CKD (stage 4 and 5) patients with Diabetic Nephropathy (DN).

Methods: Healthy controls were matched by age and gender. Their dietary habits have not been observed. Total of 40 subjects participated in this study. IL-6, FGF-23, LPS. ET-1 and zonulin, levels were measured by ELISA and quantitative analysis of gut microbiota composition (454 pyro sequencing).

Results: Higher circulation serum zonulin, TNF-α, and IL-6, FGF 23, LPS, ET-1 levels were noted in the CKD (stage 4 and 5) patients with DN compared with HCs. Patients with advanced CKD was substantially different from healthy population with increased percentage of LPs producing bacteria. Significant diversity was observed in gut microbiota in study subjects compared to control group. CKD patients had high serum concentration of ET-1 and TNF-α. Zonulin concentration was found positively correlated with LPs, inflammatory markers and FGF-23.

Conclusions: Gut microbiota is a modifiable factor and zonulin could be a future potential target to control chronic inflammatory responses. Gut microbiota and increased gut permeability in patients with advanced CKD secondary to DN results in high level of LPs that mediates chronic inflammation which was implicated in deterioration of cardiovascular health.

FR-PO531
Metabolomics of Chronic Kidney Disease in Cohort of Patients Given Probiotics
Subodh J. Saggi,1 Eli A. Friedman,1 Natarajan Ranganathan,2 Kelly Mercier,2 Susan Meritech,2 Susan Summer,2 1Nephrology/Medicine, SUNY Downstate Medical Center, New York, NY; 2Metabolomics, Research Triangle Inst, Research Triangle Park, NC; 3Kibow Biotechnol Inc., Kibow Biotechnol Inc., Newtown Square, PA.

Background: Persistent reduction in Glomerular Filtration Rate (GFR) below 60 ml/min/1.73 m² 3 years over 3 months are hall marks of Chronic Kidney Disease (CKD). Urea is strongly linked to major uremic toxicity, clinically despite the description of middle molecules as being toxic. Persistent elevation of BUN may accompany reductions in GFR in some patients. We were specifically interested in obtaining pilot data identifying metabolites that differentiated patients with CKD whose BUN decreased after 4 months of probiotics treatment from those whose BUN remained stable.

Methods: Broad spectrum 1H-NMR metabolomics was used to analyze baseline and 6 month plasma samples frozen from a phenotypically characterized cohort of patients with CKD Stage 3 and below from a prior Probiotic Renalys study. zonulin, TNF-α, IL-6, FGF 23, LPS, ET-1 levels were noted in the CKD patients.

Results: Thirty-three metabolites and 31 proteins were identified. Among them, 17 proteins. The data was analyzed with statistic and bioinformatic methods.

Conclusions: Metabolomics analysis revealed a signature of metabolites that were associated with a decrease in BUN, and holds promise for use in predicting individuals with CKD that would most benefit from use of probiotics. The majority of the metabolites important to the differentiation of groups map to pathways involved in microbial metabolism.
FR-PO533

AST-120 Affects the Level of Circulating TNF-Alpha Receptors That Predict Both Renal and Cardiovascular Outcomes in Patients with Advanced Renal Dysfunction

Ran-hui Cha,1 Dong Ki Kim,2 Yon Su Kim.1 1Internal Medicine, National Medical Center; Seoul, Republic of Korea; 2Internal Medicine, Seoul National Univ College of Medicine, Seoul, Republic of Korea.

Background: Tumor necrosis factor alpha and its two receptors have a critical role in kidney diseases. We aimed to establish the role of circulating TNF-alpha receptors (cTNFRs) as a new biomarker of renal disease and to identify the impact of AST-120 on the level.

Methods: 579 patients from 11 medical centers in Korea were prospectively recruited and followed up for 36 months after randomization into AST-120 and control arms. A total of 6 gram of AST-120 was given to participants in AST-120 arm as well as conventional therapy. Major adverse cardiovascular events (MACE) occurred more frequently in patients with higher baseline cTNFRs change of cTNFRs was also independently associated to the more occurrence of composite renal outcomes by the intermediate tertile of cTNFRs after the adjustment for traditional risk factors. More MACEs occurred in patients with higher baseline cTNFRs than those with lower cTNFRs. AST-120 was effective to lessen the increase of cTNFRs.

Conclusions: Baseline and change of cTNFRs did not improve the predictability of composite renal outcomes in comparison with classic biomarkers. But cTNFRs predicted renal outcomes. AST-120 affects the level of circulating TNF-Alpha Receptors that predict both renal and cardiovascular outcomes in patients with advanced renal dysfunction. And AST-120 was effective to lessen the increase of cTNFRs.

FR-PO534

Swimming Exercise Training (EXE) Normalize Blood Urea Nitrogen (BUN), Decrease Glomerulosclerosis, and Attenuates the Loss of Myokine IL6 in Rats with Chronic Kidney Disease (CKD) by 5/6 Nephrectomy (5/6Nx)

Rafael Luiz, Rodolfo Rosso Rampeto, Kleiton Augusto Santos Silva, Luciana Jorde, Edson Andrade Pessoa, Maria A. Gloria, Mario Luis Ribeiro Cesaretti, Nestor Sehor. Nephrology, Federal Univ of SÃ£o Paulo, SÃ£o Paulo, Brazil.

Background: The aim of this study was to evaluate the EXE effects on renal function, glomerulosclerosis and myokine IL6 has been associated with stimulation of hypertrophic muscle growth and myogenesis through regulation of the proliferative capacity of muscle stem cells in rats with 5/6Nx.

Methods: Adult Wistar rats were divided in groups (n=8): Control (CS), Control+EXE (CE), Sedentary 5/6Nx (NS) and 5/6Nx+EXE (NE). The protocol was employed in 5/6Nx rats after 7 days from the surgical procedures. EXE periods were 60min/day 5 days/week during 8 weeks. It was evaluated arterial pressure (AP), maximal exercise test (MExtest), creatinine clearance (CrCl), BUN, proteinuria (uProt), glomerulosclerosis, myokine IL6 (by Lumixen) as well mortality rate.

Results: EXE did not modify the increment in MAP but prevent, at least in part, a lower decline in the MExtest caused by 5/6Nx (29.1 ± 16.2 m/min, p<0.05). A higher CrCl in NE was observed compared with NS (2.27±0.33 vs 0.96±0.20 m/min, respectively (p<0.05). BUN was normalized in NE (43.6±2.73 mg/dL). Proteinuria was not significantly different in NE vs NS group (36.87±3.53 vs 40.13±2.35 mg/24h). Glomerulosclerosis was 48% higher in NS vs NE. Myokine IL6 (pg/m) was decreased in NS (286±40.14) and attenuated the loss in NE (384.00±20.82). A higher mortality rate was observed in NS (70%) vs NE group (39%, p<0.05).

Conclusions: Results suggested that the EXE minimize the impact of 5/6Nx, by decreasing glomerulosclerosis and reducing the impact on CrCl(42%). Finally, attenuating myokine IL6 in NE, the decreasing mortality rate in NE vs NS and by minimizing the impact of 5/6Nx on CrCl indicate that EXE in this protocol, induced protection on renal function. Thus, it is reasonable to suggest that EXE could be an additional strategy to be employed in CKD.

FR-PO535

Does Autophagosome-Proteolysis Contribute to CKD-Induced Muscle Atrophy? Zhen Su,1 Haidong Wang,2 Janet D. Klein,3 William E. Mitch,2 Xiaonan H. Wang.1 1Dept of Nephrology, The First Affiliated Hospital of Wenzhou Medical Univ, Wenzhou, Zhejiang, China; 2Nephrology, Baylor College of Medicine, Houston, TX; 3Renal Medicine, Emory Univ, Atlanta, GA.

Background: CKD-induced muscle wasting results from activation of the ubiquitin proteasome system (UPS). Since FoxO3a modulates the UPS but also activates autophagosomes, we hypothesized that autophagosome-induced proteolysis may contribute to CKD-induced muscle wasting.

Methods: CKD model in mice: subtotal nephrectomy for one month. Muscle overloading model: removal of gastrocnemius and soleus to overload the plantaris muscle (overloading exercise) in normal and CKD mice. Acupuncture with low frequency electric stimulation (Acu/LFES) was applied 15 minutes daily for 2 weeks (Hu, JASN, 26:626 2015). Electrical stimulation used a consistent pulse, electric frequency 20Hz, current 1mA.

Results: Both exercise and Acu/LFES reduced CKD muscle mass. In muscles of CKD mice, mRNAs related to autophagy-lysosomal function, Binp3, Atg12, Atg8, LC3II and Beclin-1, were upregulated and Binp3, Beclin-1 and LC3II proteins were increased. Acu/LFES treatment reversed these changes. Exercise in control mice also increased autophagy-lysosomal related protein LC3-II, Beclin-1, P62 and Yop34. The levels of these mediators were not additive to changes observed in mice with CKD. We cultured C2C12 myotubes in uremic serum and found increased autophagy markers, indicating activation of autophagosomes. Acidification alone did not stimulate autophagy markers. Based on these results, the UPS, but not autophagosomes, is responsible for degradation of structural proteins (myosin and actin).

Conclusions: 1) autophagosome-mediated proteolysis occurs in CKD-induced muscle atrophy. In mice with CKD, the UPS was principally involved in muscle proteolysis; the role of autophagosomes was convoluted. 2) Prevention of muscle atrophy by exercise is not due to inhibition of the autophagy-lysosomal proteolysis pathway in CKD. 3) Muscle atrophy cannot be equated with increased autophagy markers. 4) Acu/LFES and exercise promote different autophagy consequences.

Funding: NIDDK Support, Other NIH Support - R01 AR060268, R01 DK037571

FR-PO536

Indoxyl Sulfate, a Uremic Toxin, Accelerates Skeletal Muscle Atrophy in CKD Condition Yuki Emori,1 Hiroshi Watanabe,2 Masafumi Fukagawa,3 Toru Maruyama.1 1Dept of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto Univ, Kumamoto-shi, Japan; 2Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara-shi, Japan.

Background: Skeletal muscle atrophy is often observed in chronic kidney disease (CKD) patients, especially in patients undergoing hemodialysis. Uremic toxins has been known to link to CKD complications. However there has been no report on the relationship between uremic toxins and skeletal muscle atrophy. The purpose of this study is to investigate the involvement of uremic toxins on skeletal muscle atrophy observed in CKD condition.

Methods: In vitro cytotoxicity of uremic toxins on cell proliferation and differentiation was evaluated by using a mouse myoblast cell line (C2C12). The effect of uremic toxin on proteolysis and protein synthesis system in C2C12 was also evaluated. In the animal study, we examined the contribution of uremic toxin on muscle atrophy using uremic toxin overloaded half- or 5/6-nephrectomized mice.

Results: We focused on six protein bound solutes including indoxyl sulfate (IS), indole acetic acid, p-cresyl sulfate, hippuric acid, kynurenic acid and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid. Among these uremic toxins, IS significantly inhibited proliferation and differentiation of C2C12 myoblast cell, and decreased phosphorylation of Akt. Moreover, IS significantly increased atrophy-related genes expression but it did not affect differentiation-related genes expression. In the animal experiments, IS-overload reduced body weights and skeletal muscle weights of half- or 5/6-nephrectomized mice, and consequently weakened its muscular endurance. IS-overload mice showed increased skeletal muscle atrophy-related genes expression. In the same experimental condition, IS also induced the expression of inflammatory cytokine and transforming growth factor-b in skeletal muscle cells.

Conclusions: IS is the potent uremic toxin inducing skeletal muscle atrophy associated with CKD by increasing muscle atrophy-related genes.

FR-PO537

Myostatin Stimulates Progenitor Cells to Differentiate into Fibrocytes Leading to Muscle Fibrosis in Chronic Kidney Disease Liping Zhang,1 Jingling Dong,2,4 William E. Mitch.1 1Medicine/Nephrology, Baylor College of Medicine, Houston, TX; 2Life Science & Engineering College, Northwest Univ for Nationalities, Lanzhou, Gansu, China.

Background: In chronic kidney disease (CKD), fibrosis develops in damaged kidneys leading to loss of functions. Fibrosis in muscle also complicates CKD but the identity of cells developing into fibrocytes and mechanisms causing fibrosis are not defined. The potential precursors of muscle fibrosis are mesenchymal progenitor cells (fibrotic and adipogenic progenitors (FAPs)) while mechanisms causing fibrosis include myostatin as

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
CKD raises its expression and muscle injury can stimulate injured muscles to develop fibrocytes. Our hypothesis is that CKD stimulates myostatin expression causing FAPs to differentiate into fibrocytes.

**Methods:** 1) we isolated and cultured FAPs, adding recombinant myostatin to determine if it causes FAPs to proliferate and differentiate into fibrocytes. 2) We isolated GFP-labelled FAPs from transgenic, GFP-expressing mice and transplanted them into tibialis anterior (TA) muscles of CKD mice. We assessed conversion of FAPs into GFP-fibrocytes using α-SMA expression. 3) CKD mice were injected with an anti-myostatin peptibody to determine if myostatin stimulates muscle fibrosis. 4) Interactions between myostatin signaling and FAP conversion to fibrocytes were tested by knockdown Smad3 with a lentivirus expressing Smad3 SiRNA.

**Results:** 1) In cultured FAPs, myostatin stimulated their proliferation and conversion into fibrocytes and there is proliferation of FAPs in injured muscles of CKD mice. GFP-labelled FAPs differentiated into TA muscles of CKD mice differentiate into fibrocytes identified as expressing the fibrosis maker, α-SMA. FAP proliferation and muscle fibrosis were prevented in CKD mice injected with the anti-myostatin peptibody. Finally, Smad3 knock-down blocked FAP differentiation into fibrocytes indicating that a myostatin to Smad3 pathway is essential for the conversion of FAPs to fibrocytes.

**Conclusions:** 1) Myostatin stimulates myostatin production to activate FAPs which differentiate into fibrocytes. The process is blocked by an anti-myostatin peptibody, providing a new target for preventing muscle fibrosis as a complication of CKD.

**Funding:** NIHDK Support, Other U.S. Government Support, Private Foundation Support

**FR-PO538**

**Effect of Methoxy Polyethylene Glycol – Epoetin Beta on Plasma Levels of IL-1β, TNF-RI, TNF-RII, sFAS, sFASL, TGFβ, MMP-9 in Patients with CKD**

**Patients with CKD** Piotr Bartnicki, Ewa Majewski, Zbigniew Baj, Jacek Rysz.

**Background:** In patients with CKD are observed disturbances of immune cells function and endothelium dysfunction with high tissue fibrosis. ESAs using in these patients, beyond anemia correction seem to have renoprotective effect and slow progression of CKD. In this study we aimed to determine effect of methoxy polyethylene glycol – epoetin beta (Mircera) on plasma levels of selected parameters in predialysis patients with CKD.

**Methods:** 28 patients with CKD and anemia, treated with Mircera, were enrolled to the study. The healthy control group included 15 volunteers. Plasma levels of evaluated parameters were measured with available enzyme- linked immune-sorbent assay (ELISA) kit.

**Results:** The results of our study are shown in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>CKD before treatment</th>
<th>CKD after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb [g/dl]</td>
<td>14.3 (13.9 – 14.9)</td>
<td>11.6 (11.1 – 12.1) *</td>
<td>9.6 (9.1 – 10.1) *</td>
</tr>
<tr>
<td>eGFR [ml/min]</td>
<td>65 (63 – 74)</td>
<td>29.7 (22.4 – 37.9) *</td>
<td>16.4 (13.9 – 21.8) *</td>
</tr>
<tr>
<td>IL-1β [pg/ml]</td>
<td>2.97 (2.24 – 3.7)</td>
<td>5430 (3906 – 6954) *</td>
<td>273 (157 – 389)</td>
</tr>
<tr>
<td>TNF-RI [pg/ml]</td>
<td>87.5 (66.1 – 109.8)</td>
<td>9092 (7912 – 10703) *</td>
<td>12.3 (8.7 – 15.9)</td>
</tr>
<tr>
<td>sFAS [pg/ml]</td>
<td>0.61 (20.4 – 100.4)</td>
<td>3174 (2666 – 3682) *</td>
<td>2360 (1899 – 2821)</td>
</tr>
<tr>
<td>sFASL [pg/ml]</td>
<td>25.2 (12.1 – 38.5) *</td>
<td>25.2 (16.3 – 34.1) *</td>
<td>5268 (3741 – 6795) *</td>
</tr>
<tr>
<td>MMP-9 [ng/ml]</td>
<td>1125 (659 – 1591)</td>
<td>2687 (330 – 1044) *</td>
<td>687 (330 – 1044) *</td>
</tr>
</tbody>
</table>

*p < 0.05 to control group, **p < 0.05 to CKD before treatment

**Conclusions:** Plasma concentrations of evaluated parameters are significantly higher in CKD patients in comparison to control group. After ESA treatment plasma level of TNF-RI was significantly higher and MMP-9 was significantly lower in CKD patients. These data suggest that Mircera used in correction of anemia in CKD might influence on immune cells function, apoptosis and tissue fibrosis.

**FR-PO539**

**Qualitative Changes in Erythrocytes in Chronic Kidney Disease**

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**Product Research Dept, Chugai Pharmaceutical Co., Ltd., Kamakura, Japan.**

**Background:** Therapeutic control of anemia in chronic kidney disease (CKD) is assessed by monitoring hemoglobin (Hb) levels. However, monitoring Hb alone could potentially fail to reveal pathological changes in erythrocytes, because erythrocyte lifespan is shorter in CKD. Shortening of erythrocyte lifespan may attenuate erythropoietin responsiveness, resulting in poor prognosis of CKD. Erythrocyte lifespan are thought to be shortened by qualitative changes such as deterioration of deformability and stability, but it is not clear which of these aspects are changed in CKD.

**Methods:** To assess qualitative changes in erythrocytes we first confirmed in a rat model of iron-deficiency anemia. Deformability was quantified by laser diffraction electactometry and stability was quantified by hemolysis test. We next produced CKD model rats using 1.1 antibody injection plus uninephrectomy. Epoetin beta pegol (C.E.R.A., 25 mg/kg) was intravenously injected the day after surgery. At 11 wks, Hb levels, erythrocyte deformability and stability, plasma urea nitrogen (UN) and creatinine (pCre) were assessed.

**Results:** Iron-deficiency rats showed significant anemia and had impaired erythrocyte deformability and stability. These changes in erythrocytes were almost normalized by administration of iron sucrose. In the CKD model, Hb level was significantly decreased and deformability and stability of erythrocytes were significantly impaired. Stability significantly recovered and deformability tended to recover in the C.E.R.A. group, although there was no significant difference in Hb levels between the disease group and C.E.R.A. group. Kidney function (UN and pCre) correlated significantly with stability, but not with deformability. Morphologic parameters (mean corpuscular volume and red cell distribution width - standard deviation) did not reflect changes in deformability and stability.

**Conclusions:** Deformability and stability of erythrocytes were impaired in CKD rats, and may be linked with kidney dysfunction. Focusing on qualitative aspects of erythrocytes may provide a better understanding of pathological conditions and therapeutic benefit in anemia.

**Funding:** Private Foundation Support

**FR-PO540**

**Eryptosis in Chronic Kidney Disease**

Grazia Maria Virzi, Anna Clementi, Alessandra Brocca, Massimo de Cal, Claudio Ronco.

**Nephrology-IRRIV.**

**Background:** Even though anemia in CKD results mainly from the lack of erythropoietin, accelerated erythrocyte death(eryptosis) seems to be a contributor factor. Eryptosis is characterized by cell shrinkage and cell membrane scrambling with phosphatidyserine(PS)-exposure at the erythrocyte (RBC) surface. Eryptosis may be triggered by some urmic toxins. P-cresol is an urmic toxin which has negative cardiovascular and cytopathic effects. This study explored if eryptosis is triggered by p-cresol and if different stages of CKD may influence erythrocyte death.

**Methods:** RBCs from healthy subjects were incubated in buffer at a hematocrit of 0.4% in RPMI with different concentrations of p-cresol (0-2.5-5-10-20-40ng/mL) and with plasma from CKD patients (3 for each stage) for 24hours. PS exposure was estimated from AnnexinIV binding in flow cytometer.

**Results:** Increasing concentrations of p-cresol modified significantly the percentage of PS exposure on RBC surface, thus suggesting that increasing concentrations of p-cresol may stimulate eryptosis in vitro. Moreover, there was no significant difference in terms of median values of eryptosis between CKD stages, but a positive trend was evident: eryptosis increase with CKD progression.

**Conclusions:** In addition to its known cardiovascular and cellular effects, p-cresol seems to stimulate eryptosis in vitro and increasing concentrations of this urmic toxin may be responsible for higher levels of eryptosis in vivo. Our data show that CKD plasma contains components able to trigger eryptosis and different stages of CKD may be responsible for different levels of RBC death, thus suggesting that progression of CKD may increase eryptosis in vivo. These results suggest a role of urmic toxicity in the genesis of eryptosis and renal anemia. It is necessary to increase the sample size to validate our hypothesis.

**Funding:** Private Foundation Support

**FR-PO541**

**Palmitate Exacerbates Renal Anemia: Suppression of Renal Erythropoietin Production via Endoplasmic Reticulum Stress**

Reiko Inagi, Tirthun Anusornvongchai, Yu Ishimoto, Akira Okada, Norio Suzuki, Masayuki Yamamoto, Masaoi Nangaku.

**DiV of CKD Pathophysiology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan; DiV of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan; Tohoku Univ School of Medicine, Sendai, Japan.**

**Background:** Derangement of erythropoietin (EPO) production in renal EPO-producing (REP) cells causes renal anemia. Palmitate induces endoplasmic reticulum (ER) stress, which contributes to glomerular and tubular cell damages. Thus, we evaluated the effect of palmitate-ER stress axis on EPO production in REP cells.

**Methods:** C57/B6J or the mice, in which the renal EPO gene was replaced with GFP or REP cells were lineage labeled with tdTomato, were daily injected with palmitate

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 482A
hypoxia (HIF activation with CoCl
 in CKD patients, fibrosis marker α-SMA was downregulated. silenced SIRPα in muscle cells treated with a cytokine mixture, containing cytokines present with CKD vs. control mice. In order to determine a cause and effect relationship, SIRPa significantly increased in cardiac muscles of mice with CKD, with reduction in tyrosine with a heart weight to body weight that is significantly larger vs. control mice. SIRPa was and cardiac muscle cell lysates.

2 months hearts were harvested and left ventricle muscle samples were examined for SIRPα, to contradict vitro experiments, the reason of this phenomenon may be that many neonatal with mild lesion group, E-cad staining in moderate lesion group and severe lesion group HK2 cells group were lower than control-shRNA HK2 cells, in contrast, CTGF and α-SMA westernblot; immunofluorescence was used in different degrees of tubulointerstitial lesions.

to the degree of tubulointerstitial lesion, kidney specimens were divided into 3 groups: mild lesion, moderate lesion, and severe lesion. We handle normal kidney portions as controls. The expressions of integrinβ4, E-cad, CTGF and α-SMA were assessed by qRT-PCR and western-blot; immunofluorescence was used in different degrees of tubulointerstitial lesions.

Results: (1) Compared with negative control, integrinβ4 and E-cad were significantly lower, however, CTGF and α-SMA were increased (2) Integrinβ4 and E-cad in β4-shRNA HK2 cells group were lower than control-shRNA HK2 cells, in contrast, CTGF and α-SMA were increased; integrinβ4 and E-cad with TFb1 treatment were significantly lower than without TFb1 groups, CTGF and α-SMA expressions were increased. (3) Compared with mild lesion group, E-cad staining in moderate lesion group and severe lesion group reduced, α-SMA staining and integrinβ4 staining increased. After being further analyzed, the most of integrinβ4 staining located in neocapillary renal tubules.

Conclusions: integrinβ4 is decreased in the process of EMT, and reduced integrinβ4 can exacerbate HK2 cells from epithelial cell transition to mesenchymal cells, therefore loss of integrinβ4 may be the marker of TIF. However, the results of vivo experiment appeared to be different with vitro analysis, the reason of this phenomenon may be that many neonatal renal tubules possess the ability of proliferation.

Conclusions: These results imply that SIRPα increases fibrosis, and suggesting that SIRPα may have important influences on cardiac muscle fibrosis via a new pathway in chronic kidney disease. Ultimately blocking SIRPα in heart muscle may improve cardiac fibrosis associated with chronic kidney disease.

Funding: Veterans Administration Support

FR-PO544 Retinal Microvascular Abnormalities and Incidence and Progression of Chronic Kidney Disease Charumathi Sabanayagam,1,2 Peng Guan Ong,1 Boon Wee Teo,1 Carol Y. Cheung,2 Ching-Yu Chung,2 Ecosse L. Lamoureux,2 Tien yin Wong,1,2 Singapore Eye Research Inst, Singapore; 'Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore; National Univ of Singapore, Singapore.

Background: To examine the longitudinal association of a panel of retinal vascular parameters, markers of microvascular damage, with the incidence and progression of chronic kidney disease (CKD) in middle-aged Asian adults.

Methods: The population consisted of a cohort of Malay adults aged 40-80 years examined from 2004-06 and again from 2010-2012 (n=1464; 1306 free of CKD and 158 with pre-existing CKD). The outcomes were incidence (estimated glomerular filtration rate [eGFR]=60 mL/min/1.73m²+25% decrease in eGFR) and progression of CKD (drop in eGFR category ≥60, 30-59, 15-30, <15=+25% decrease in eGFR or an annualized eGFR rate/3=3 mL/min/1.73m²/year). Retinal vascular parameters (arteriolar and venular caliber, tortuosity, branching angle, and fractal dimension were measured from baseline retinal photographs using a computer-assisted program (Singapore I Vessel Assessment, SIVA). Retinopathy was graded using a standard protocol. Associations were examined using Cox proportional hazards regression models adjusting for age, sex, blood glucose, systolic blood pressure and baseline eGFR.

Results: Over a median follow-up of 6.6 years, 6.4% (70% had diabetes) developed incident CKD and 26.6% (62% had diabetes) developed progressive CKD. In multivariable models, retinal arteriolar narrowing, retinal venular widening, and presence of retinopathy were significantly associated with increased risk of CKD. The HR (95% CI) of incident CKD was 1.31 (1.01-1.72) per SD decrease in arteriolar caliber, 2.20 (1.10-4.41) for tertile 3 vs. tertile 1 of venular caliber; 2.06 (1.24-3.44) for retinopathy. Increased arteriolar tortuosity alone was associated with progressive CKD (1.57 [1.04-2.37] per SD decrease. All associations were consistently present among those with diabetes.

Conclusions: Retinal vascular abnormalities increased the risk of CKD by more than two times in Asian adults. Our findings provide evidence that retinal imaging may be a useful tool to improve risk stratification for CKD.

Funding: Government Support - Non-U.S.

FR-PO545 Relationship Between Serum Bilirubin and Hyalinization of Renal Arterioles Yusushi Miyagi,1 Kentaro Kohagura,2 Yusuke Ohya,3 Kunitoshi Iseki,1 Department of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyu, Nishihara-cho, Okinawa, Japan; 2Dialysis Unit, Univ of the Ryukyu, Nishihara-cho, Okinawa, Japan.

Background: It has been suggested that there is a relationship between serum bilirubin and renal hyalinosis. In the present study, we examined the relationship between serum bilirubin levels and the hyalinization of renal arteries in patients with chronic kidney disease (CKD).

Methods: We reviewed the clinical records of 138 patients with CKD (mean age: 44 years) who underwent renal biopsy at our department during a 3-year period starting in 2010. Patients who were receiving calcineurin inhibitors were excluded. The subjects were divided into three groups based on their total serum bilirubin levels: tertile group 1 (0.2-0.4 mg/dl; 40 patients), tertile group 2 (0.5-0.7 mg/dl; 61 patients), and tertile group 3 (0.8-1.4 mg/dl; 37 patients). Using the pathological specimens obtained from renal biopsies, the hyalinization of renal arterioles was semiquantitatively evaluated, and the mean score of renal arteriolar hyalinization grade was used for analysis.

Results: Tertile group 1 had markedly higher urinary protein levels and markedly lower serum hemoglobin (HB) levels than tertile group 3. We defined total serum bilirubin levels under 0.5 mg/dl (tertile group 1) as low levels and divided them into two groups of values under and above 0.5 mg/dl. These were set as explanatory factors, and a multiple regression analysis was performed, with the degree of hyalinization of renal arterioles as the objective variable. A low serum bilirubin level was a significant risk factor for the hyalinization of renal arterioles (R² = 0.45, β = 0.26, p = 0.003), even when adjustments were made for age, sex, HbA1c levels, mean blood pressure, history of smoking, and LDL cholesterol levels. Furthermore, even when the explanatory factor of serum HB level was added, the results of the analysis remained the same.

Conclusions: Low serum bilirubin levels may be a risk factor for the hyalinization of renal arterioles independent of classical risk factors of cardiovascular disease.
FR-PO546

Autonomic Nervous Dysfunction in Predialytic Chronic Kidney Disease: 3 Years Observational Follow-Up Study

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Background: Generally, sympathetic overactivity and impairment of the parasympathetic system are often seen in patients with dialytic CKD, COPD, RA as well as elderly. Also, arterial stiffness and edema have been related with mortality in patients with cardiovascular disease. However, to date, few data regarding autonomic nervous system, vascular stiffness, edema in pre-dialytic CKD was proposed. This study was designed to explore the interrelationship of those parameter in pre-dialytic CKD (G3, 4) and uncover the risk factor related with renal functional deterioration.

Methods: Thirty-three patients were enrolled. Hydration status (extracellular water [ECW]/total body water [TBW]) was determined by bioimpedance analysis. Brachial-ankle pulse wave velocity (baPWV) and neck ultrasonography for carotid plaque and intima-media thickness were conducted for checking up of vascular status. CAN was scored using Ewing’s method and we also expressed the standard deviation of normal-to-normal interval (SDNN), low frequency/high frequency ratio (LF/HF ratio). Serial creatinine change over a median follow-up of 3 years was used for assessment of renal function.

Results: Of the 33 patients, 14 (42%) have suffered with CAN. Patients with CAN have higher progressive declining rate of renal function, baPWV, systolic BP compared with patients without CAN. The group having declining renal function has higher CAN score, baPWV and lower SDNN compared with preserved renal function group. CAN score correlated positively with ECW/TBW (r=0.405, p<0.019), mean PWV (r=0.623, p<0.001) and SBP (r=0.513, p<0.002). CAN score correlated negatively with declining rate of renal function (r=0.471, p<0.006), HbaA1c (p<0.001) and albumin (r=-0.484, p<0.004).

Conclusions: Autonomic nervous dysfunction including lower SDNN and increased arterial stiffness associated with CAN may be important risk factors for deterioration of renal function in pre-dialytic CKD patients. Also, autonomic nervous dysfunction was related with arterial stiffness and edema.

FR-PO547

Inhibition of EGFR Alleviates the Development and Progression of Hyperuricemic Nephropathy in Rats

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Background: Hyperuricemia is an independent risk factor for chronic kidney disease and contributes to kidney fibrosis. In this study, we investigated the effect of epidermal growth factor receptor (EGFR) inhibition on the development of hyperuricemic nephropathy (HN) and the mechanisms involved.

Methods: In this experiment, we did Cell Culture and Treatments, processed the establishment of Hyperuricemic nephropathy (HN) model, assessment of serum uric acid, renal Function and other biochemistry index, performed Immunoblot Analysis, Immunohistochemical Staining, as well as ELISA analysis.

Results: In a rat model of HN induced by feeding a mixture of adenine and potassium oxonate, increased EGFR phosphorylation and severe glomerular sclerosis and renal interstitial fibrosis were evident, accompanied by renal dysfunctions and decreased urinary microalbumin excretion. Administration of gefitinib, a highly selective EGFR inhibitor, prevented renal dysfunction, reduced urinary microalbumin and inhibited activation of renal interstitial fibroblasts and expression of extracellular proteins. Gefitinib treatment also inhibited hyperuricemia-induced activation of the transforming growth factor-beta-1 (TGF-β1) and nuclear factor-kB (NF-kB) signaling pathways and expression of multiple profibrogenic cytokines/chemokines in the kidney. Furthermore, gefitinib treatment suppressed xanthine oxidase activity, which mediates uric acid production, and preserved expression of organic anion transporters 1 and 3, which promotes uric acid excretion in the kidney of hyperuricemic rats.

Conclusions: Thus, blocking EGFR can attenuate development of HN via suppression of TGF-β1 signaling and inflammation, and promotion of the molecular processes that reduce uric acid accumulation in the body.

FR-PO548

Probiotic and Yogurt Consumption Is Associated with a Lower Prevalence of Albuminuria: A Cross-Sectional Analysis of NHANES

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Background: Animal data suggest that probiotic supplements may retard CKD progression. Yogurt is the most widely available probiotic food in the United States. However, the relationship between frequent yogurt consumption or probiotic use, and kidney parameters has not yet been evaluated. We aimed to study this association in the National Health and Nutrition Examination Survey (NHANES) database.

Methods: We utilized NHANES data with reported one year yogurt consumption frequency and probiotic use (2003-2005). The “consumers group” was defined as either yogurt consumption ≥ thrice weekly or regular use of probiotic, and we analyzed its association with albuminuria and eGFR after adjustment for demographic and clinical parameters.

Results: We had complete data on 6853 participants (mean age 48.3±20.45.2% male), of which,1359 (20.3%) were frequent consumers and 918 participants (12.2%) had detectable albuminuria (Median=67.1, IQR =-41.6-157.1 mcg/mg). Frequent consumers had a trend towards lower mean UACR compared to non-consumers (mean difference [MD]: -12.3, 95% CI -29.8 to 5.2, P=0.17) that was attenuated after complete adjustment. On the other hand, frequent consumers had decreased odds of albuminuria (UACR > 30 mcg/mg) compared to non-consumers (adjusted Odds Ratio 0.79; 95% CI 0.63-0.97; P=0.05).

FR-PO549

Assessment of Serum Levels of Heavy Metals in Patients with Chronic Kidney Disease of Unknown Etiology

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Background: Chronic kidney disease (CKD) encompasses a wide spectrum of different etiological processes associated with abnormal kidney function and gradual progressive decline in glomerular filtration rate. CKD of unknown etiology (CKDs) has emerged as an important entity accounting for approximately 10% of CKD patients worldwide. Of the environmental toxins implicated in causation of CKDs, heavy metals form an important group. In the present study, we estimated the serum levels of lead, cadmium, arsenic and chromium in patients with CKDs and evaluated their role in the etiopathogenesis of CKDs.

Methods: The study was conducted in the Departments of Medicine and Biochemistry at University College of Medical Sciences and GTB Hospital, Delhi from December 2013 - April 2015. It was a case control, cross sectional study. Ninety subjects in the age group 18 – 60 years of either sex were divided into 3 groups: Group I: Healthy controls (n=30), Group II: Individuals satisfying case definition of CKD(n=30) and Group III: Individuals having CKD of known etiology (CKD)(n=30). Detailed history, complete physical examination, routine investigations, urine albumin excretion (UAER) estimation was done. Estimation of serum level of heavy metals was done using Atomic Absorption Spectrophotometry.

Results: The median levels of lead, cadmium and chromium were significantly higher in patients of group II and this difference was statistically significant as compared to subjects of group I and III. The median levels of arsenic in patients of group II and III were similar but significantly higher than patients of group I. The levels of arsenic, cadmium and chromium were also found to be significantly higher in the health controls (group II) compared to healthy population. Consequently, the UAER levels in patients of group II and III were similar but significantly higher than patients of group I.

Conclusions: As compared to healthy controls, the serum levels of lead, cadmium, and arsenic were found to be significantly higher in patients of CKDs. The study indicates a possible role of heavy metals in causation of CKDs.

FR-PO550

High Prevalence of Elevated Molybdenum Levels in CKD Patients

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Background: Molybdenum (Mo), atomic number 42 is an essential trace element present in water and is crucial for human survival because four mammalian enzymes harbor a pterin-based Mo cofactor (Moco) at their active site and are Mo-dependent. Mo can be lethal in high doses, and chronic toxicity in animals leads to stunted growth, skeletal abnormalities, anemia, and histological changes in the kidney and liver. There is no information about Mo levels in patients with CKD.

Methods: After approval by the ethics board, and as part of a larger study on zinc supplementation in CKD, we studied 87 plasma Mo and copper (Cu) levels in 50 children with an eGFR <90 and >15 mL/min/1.73 m² using the Schwartz formula. Where available,
we also recorded the cystatin C eGFR using the Filler formula in 35 children. Mo and Cu levels were measured using High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS).

Results: The mean Schwartz eGFR was 46±23 and the Cystatin C eGFR was 48±20 mL/min/1.73 m². The median Mo level was 2.26 (interquartile range 1.7, 3.3 ug/L, mean 2.78±1.70 ug/L), significantly higher than the upper reference interval of 1.4 ug/L, and with an exponential increase with lower eGFR.

Conclusions: With worsening kidney function, Mo levels accumulate.

Funding: Clinical Revenue Support

FR-PO551

High Prevalence of Elevated Vanadium Levels in CKD Patients

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Background: Vanadium (V, atomic number 23) is an essential trace element present in many industrial products, especially in steel, which can be very toxic if levels are too high. The excretion of vanadium by the kidneys is rapid with a biological half-life of 20-40 hours in the urine. Chronic poisoning is associated with respiratory symptoms, nervous disturbances, vegetative symptoms, tremors, palpitation of the heart, extrastrioles, anemia, leukopenia, and punctate basophilia of the erythrocytes. While adult data suggest that V is accumulating in dialysis patients, there is no information about V levels in patients with CKD.

Methods: After approval by the ethics board, and as part of a larger study on zinc supplementation in CKD, we studied 87 plasma V levels in 50 children with an eGFR <90 mL/min/1.73 m² and > 15 mL/min/1.73 m². The median Mo level was 2.26 (interquartile range 1.7, 3.3 ug/L, mean 2.78±1.70 ug/L), significantly higher than the upper reference interval of 1.4 ug/L, and with an exponential increase with lower eGFR (r=−0.57, p=0.0002).

Conclusions: With worsening kidney function, Mo levels accumulate, while Cu levels remain unaffected.

Funding: Clinical Revenue Support

FR-PO552

Chronic Nicotine (Ch-Nic) Exacerbates Subpressor Angiotensin II (SP-AngII) Induced Renal Dysfunction in Part via the Renal Sympathetic Nervous System

Kiran B. Chandrashekhar, 1 Rodrigo Maranon, 1 Arnaldo F. Lopez-Ruiz, 2 Andrea F. Soljancic, 1 Istvan Arany, 1 Luis A. Juncos, 1 Nephrology, UMMC, Jackson, MS; 2Physiology, UMMC, Jackson, MS.

Background: Ch-Nic exacerbates SP-AngII-induced renal dysfunction and vascular remodeling while having minimal changes on blood pressure. However, the mechanisms are incompletely understood. Because Ch-Nic activates the renal sympathetic nervous system, we hypothesized that this activation contributes to nicotine’s deleterious effects on SP-AngII-induced renal dysfunction and injury.

Methods: Sprague Dawley rats underwent either sham or renal denervation (RD) surgery and then subdivided to get nicotine (12 g/ml) or vehicle (saccharine 2%). These were randomized to get either SP-AngII (SQ, 200ng/kg/min) or vehicle (saline). Hemodynamics were measured in anesthetized animals and tissue collected for biochemical analysis.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP (mmHg)</th>
<th>RVR (m/min/mmHg)</th>
<th>PL Creatinine (mg/dl)</th>
<th>NGAL U/mg creat</th>
<th>TGF (ng/mg creat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ct+Sham</td>
<td>107±6</td>
<td>15±0.7</td>
<td>0.7±0.02</td>
<td>0.26±0.03</td>
<td>10±6.1</td>
</tr>
<tr>
<td>Ct+RD</td>
<td>107±5</td>
<td>14±0.1</td>
<td>0.7±0.02</td>
<td>0.3±0.4</td>
<td>9.5±1</td>
</tr>
<tr>
<td>Ch-Nic+Sham</td>
<td>108±5</td>
<td>14±0.2</td>
<td>0.9±0.03</td>
<td>0.5±0.06</td>
<td>20±0.6</td>
</tr>
<tr>
<td>Ch-Nic+RD</td>
<td>101±3</td>
<td>15±0.7</td>
<td>0.7±0.04</td>
<td>0.4±0.2</td>
<td>16±1.6</td>
</tr>
<tr>
<td>SP-AngII+Sham</td>
<td>162±4*#†</td>
<td>23±1.3*#†</td>
<td>2.4±0.1*#†</td>
<td>4.3±0.4*#†</td>
<td>29±1.3*#†</td>
</tr>
<tr>
<td>SP-AngII+RD</td>
<td>123±3*#†</td>
<td>17±0.8*#†</td>
<td>2.0±0.07*#†</td>
<td>2.7±0.2*#†</td>
<td>25±1.3*#†</td>
</tr>
<tr>
<td>Sp-AngII+Ch-</td>
<td>172±4*#†</td>
<td>3±1.2*#†</td>
<td>3.0±0.17*#†</td>
<td>8.3±0.4*#†</td>
<td>40±1.4*#†</td>
</tr>
<tr>
<td>+N sham</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP-AngII+Ch+</td>
<td>134±2*#†</td>
<td>18±0.3*#†</td>
<td>2.4±0.04*#†</td>
<td>3.7±0.3*#†</td>
<td>27±1.2*#†</td>
</tr>
</tbody>
</table>

Conclusions: Renal denervation ameliorated SP-AngII-induced HTN, renal dysfunction, inflammation and injury. While RD did not appear to provide additional benefit to blood pressure control in Ch-Nic+SP-AngII group, it provided protection against the renal effects of Ch-Nic in the SP-AngII rats. These results support a role for the sympathetic nervous system in SP-AngII-induced renal dysfunction, as well as in the exacerbating effect of Ch-Nic on SP-AngII mediated renal dysfunction.

FR-PO553

Elevated Plasma Chymase Is Associated with Risk of Chronic Kidney Disease

Jing Chen, 1,2 L. Lee Hamm, 1,2 Damodor R. Kumbala, 1 Chung-shian Chen, 1 Kevin K. Wu, 1 Swapna G. Kallu, 1 Ravi Siriki, 1 Shilpa Gadde, 1 Arnold B. Alper, 1 Myra A. Kleinpeter, 1 Vecchi Batuman, 1 Eric E. Simon, 1 Gabriel Navar, 1 Jiang He, 1,3 Medicine, Tulane School of Medicine, New Orleans, LA; Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, LA; Nephrology, Ochsner Health System, New Orleans, LA.

Background: Chymase is the primary enzyme that mediates angiotensin II formation independent of angiotensin-converting enzyme and also play a role in activating transforming growth factor-βeta and matrix metalloproteinase-9. Experimental studies suggest that it may cause renal and cardiac fibrosis. However, the association of circulating chymase with chronic kidney disease (CKD) is not well studied.

Methods: We investigated the association of chymase and the risk of CKD in 163 CKD patients and 186 controls without CKD. CKD was defined as estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m² or presence of albuminuria. Multivariable analyses were used to examine the relationship of plasma chymase and CKD.

Results: The multivariable-adjusted medians (interquartile ranges) were 1.6 (1.1, 2.1) in patients with CKD vs. 1.2 (0.7, 1.9) pg/mL in controls without CKD (p<0.002 for group difference) after adjusting for age, gender, race, physical activity, smoking, drinking, systolic blood pressure, glucose, low-density lipoprotein cholesterol, body mass index, and history of cardiovascular disease. After adjustment for the above risk factors, the odds ratio for CKD comparing the highest to the lowest tertile of chymase was 2.85 (95% confidence interval, 1.41-5.76).

Conclusions: These data indicate that elevated circulating chymase is associated with risk of CKD.

Funding: Other NIH Support - the National Center for Research Resources, National Institutes of Health, Bethesda, MD.
The Superoxide Urokinase-Type Plasminogen Activator Receptor Serum Levels in Adults with Nephrotic Syndrome

Qiuling Fan, Nephrology, The First Hospital of China Medical Univ.

**Background:** The serum levels of soluble urokinase type fibrinolytic enzyme activators receptor (suPAR) in adults with nephrotic syndrome were analyzed.

**Methods:** The serum levels of soluble urokinase type fibrinolytic enzyme activators receptor (suPAR) in 70 nephrotic syndrome patients with membranous nephropathy, diabetic nephropathy group, lupus nephritis, minimal change kidney disease and focal segmental glomerular sclerosis group was detected by enzyme-linked immunosorbent assay. The relationship between the parameters and suPAR levels were analyzed.

**Results:** Serum soluble urokinase receptor levels of nephrotic syndrome patients are significantly higher than the normal control group (P < 0.01). The serum suPAR levels of FSGS and MN patients were significant higher than MCD patients (P < 0.05). Serum suPAR level was positively correlated with serum creatinine, blood urea nitrogen (r = 0.401, p = 0.001; r = 0.186, p = 0.029) and negatively correlated with eGFR (r = -0.265, p = 0.026; r = -0.373, p = 0.018; r = -0.424, p = 0.007; r = -0.400, p = 0.009).

**Conclusions:** Serum suPAR level was positively correlated with age, serum creatinine, blood urea nitrogen, and negatively correlated with eGFR. The serum suPAR levels of FSGS and MN patients were significantly higher than MCD patients and may be a potential marker to distinguish FSGS and MCD.

FR-PO556

**Urinary Sodium: Impact on Blood Pressure and Progression of Chronic Kidney Disease**

Adriano Luiz Ammirati, Maria Eugenia F. Canziani, Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.

**Background:** Chronic kidney disease (CKD) is characterized by chronicity and progression of renal damage. The presence of hypertension is related to the progression of renal damage. Diets high in salt have been associated with an increased risk of hypertension. Sodium analysis in the urine of 24 h is considered the standard method to estimate the daily intake of this mineral. The aim of this study was to evaluate the impact of sodium intake estimated by urinary sodium in the urine of 24 hours (Nau24hs) on renal outcomes and their impact on hypertension.

**Methods:** Data were collected from medical records of 118 patients with CKD in conservative treatment, that had one Nau24hs dosage and a follow-up of at least five years. Information collected initially and after 5 years were: demographics, etiology of CKD; comorbidities, blood pressure, routine laboratory tests and estimated creatinine clearance (eGFR-Cr). The Nau24hs values were classified into two groups by the median and also divided into tertiles and compared with the rate of progression of CKD (fall of the estimated clearance greater than 20% in 5 years) and the change in blood pressure.

**Results:** Patients had a mean of 186 ± 64 Meq/L of Nau24hs which represented a Na intake of 5.4 g/day. Patients with Nau24hs ≥ 200 Meq/L had higher systolic blood pressure and those with Nau24hs> 200 Meq/L had higher systolic and diastolic blood pressure when compared to other patients. In addition, patients with higher Nau24hs present significant decrease in systolic blood pressure over 5 years. The decrease in creatinine clearance over 5 years (29% of patients) were more frequent in diabetics and those who did not use converting enzyme inhibitors and are associated with the presence of proteinuria. There was no association of Nau24hs with the progression of renal dysfunction.

**Conclusions:** In conclusion, Nau24hs > 200 mEq/L had higher systolic and diastolic blood pressure when compared with subjects with Nau24hs ≤ 200 mEq/L and a follow-up of at least five years.

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

Underline represents presenting author.
Methods: Patients with ≥5 years of potential follow-up were identified from the ChronicKidney Disease Stages Implementation Study (CRISIS). 5-year RRT risk was estimated using a logistic regression model incorporating age, gender, eGFR, albuminuria, PO4, Ca2+, HCO3, and albumin.

Results: 728 patients were included in this analysis (median follow-up 4.4 [IQR 2.4-5.6] years), with 118 patients (16%) progressing to RRT. Mean baseline age was 64±14 years and eGFR 34±14 ml/min/1.73m2.

Time to RRT presented as mean (standard deviation). Percentages represent the proportion of patients within that risk group.

Risk group and number of patients

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number starting RRT</th>
<th>Months to RRT</th>
<th>In-patient start</th>
<th>Transplant eligible / listed</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>&lt;20%</td>
<td>n=91 (13%)</td>
<td>23 (4%)</td>
<td>48 (12)</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>n=28,192 (89.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEDIUM</td>
<td>20 - 40%</td>
<td>n=118 (17%)</td>
<td>32 (35%)</td>
<td>37 (15)</td>
<td>9.5%</td>
</tr>
<tr>
<td></td>
<td>n=2,061</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIGH</td>
<td>&gt;40%</td>
<td>n=98 (14%)</td>
<td>64 (64%)</td>
<td>20 (14)</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>n=31,463 (99.6%)</td>
<td></td>
<td></td>
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</tbody>
</table>

FR-PO560

Effect and Safety of Sofosbuvir (SOF) Containing Direct-Acting Antiviral (DAA) Hepatitis C Virus (HCV) Therapy in a Real-World Population with Chronic Kidney Disease (CKD)

Guillermo Ortiz,1 Gregory L. Hundemer,1 Elke Backman,2 Ravi I. Thadhani,3 Raymond T. Chung,3 Meghan E. Sisc,1 Nephrology Div, MGH, Boston, MA; 2Pharmacy, MGH, Boston, MA; 3Gastrointestinal, MGH, Boston, MA.

Background: Early trials of SOF-based regimens excluded patients with CKD, thus little is known about safety, efficacy, and effect on kidney function.

Methods: We retrospectively evaluated 72 patients with CKD starting DAA treatment (tx) between 11/2013-12/2014. CKD was defined by average eGFR <60ml/min or albuminuria >30mg/g 6 months prior to tx. Safety, tolerability and laboratory results were assessed by chart review. Models predicting sustained virological response (SVR) were performed.

Results: Subjects were aged 61±8 years, 60% white, 22% black, 12% Hispanic, and 74% male. 50% were diabetic, 39% cirrhotic, 54% HCV tx naïve, 39% had prior liver or kidney transplant, and 7% were HIV/HCV coinfected. DAA regimens were: SOF/simeprevir 50%, SOF/ledipasvir 13%, SOF/ribavirin 28%, other SOF regimens 10%, 8% had a transient creatinine rise >0.5mg/dL during tx. Average eGFR on tx was similar to baseline (mean [95% CI]: 57 [52-62] vs. 53 [51 - 63] ml/min, respectively P=0.26). SVR was 77% (95% CI 66-88). 76% experienced at least 1 adverse effect (AE); only 5 (7%) discontinued tx due to an AE.

Conclusions: SOF-containing DAA regimens are effective and relatively safe in patients with CKD. Although AEs were common, serious AEs or significant nephropathy were rare. Lower eGFR at baseline predicted an increase likelihood of HCV cure with SOF-based regimens.

FR-PO561

Risk of Liver Injury After Glucosidase Inhibitors Therapy in Advanced Chronic Kidney Disease Patients: A Population-Based Study

Vincent Wu,1 Chih-chin Kao,1 Yu-Ying Chiu,1 Internal Medicine, National Taiwan Univ Hospital, Taipei; Internal Medicine, Taipei Medical Univ Hospital.

Background: α-glucosidase inhibitors (AGIs) are commonly used to control postprandial blood glucose. However, AGIs-related liver injury has been reported, but whether the relationship of AGIs and liver injury applies to advanced chronic kidney disease (CKD) patients remains uncertain.

Methods: In the nationwide case-control study, we recruited advanced diabetic CKD patients, who has taken AGIs from January 1, 2000 through December 31, 2010 as cases and those with relationship of AGIs and liver injury applies to advanced chronic kidney disease (CKD) patients remains uncertain.

Results: Subjects were aged 61±8 years, 60% white, 22% black, 12% Hispanic, and 74% male. 50% were diabetic, 39% cirrhotic, 54% HCV tx naïve, 39% had prior liver or kidney transplant, and 7% were HIV/HCV coinfected. DAA regimens were: SOF/simeprevir 50%, SOF/ledipasvir 13%, SOF/ribavirin 28%, other SOF regimens 10%, 8% had a transient creatinine rise >0.5mg/dL during tx. Average eGFR on tx was similar to baseline (mean [95% CI]: 57 [52-62] vs. 53 [51 - 63] ml/min, respectively P=0.26). SVR was 77% (95% CI 66-88). 76% experienced at least 1 adverse effect (AE); only 5 (7%) discontinued tx due to an AE.

Conclusions: SOF-containing DAA regimens are effective and relatively safe in patients with CKD. Although AEs were common, serious AEs or significant nephropathy were rare. Lower eGFR at baseline predicted an increase likelihood of HCV cure with SOF-based regimens.

Table 1: Logistic regression model predicting SVR (n=61)

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL Predictors</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>1.25 (0.58-2.67)</td>
</tr>
<tr>
<td>Female</td>
<td>3.10 (0.62-15.55)</td>
</tr>
<tr>
<td>Black</td>
<td>0.44 (0.11,1.79)</td>
</tr>
<tr>
<td>HCV Genotype 3</td>
<td>0.08 (0.01,5.84)</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td>0.11 (0.02,0.69)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.85 (0.51,6.77)</td>
</tr>
<tr>
<td>Price HCV tx</td>
<td>0.58 (0.17,1.99)</td>
</tr>
<tr>
<td>Liver or kidney transplant</td>
<td>1.02 (0.29,3.54)</td>
</tr>
<tr>
<td>Baseline eGFR, per 10 ml/min decrease</td>
<td>1.79 (1.27,2.50)</td>
</tr>
</tbody>
</table>

Conclusions: Few patients with CKD had the full set of laboratory results needed to employ a validated ESRD risk prediction model for population health management. Urine ACR and serum phosphorous results were often unavailable. To improve risk stratification, efforts are needed to more frequently obtain these laboratory tests during clinical care or to develop refined models that use more readily available information.
**FR-PO562**

Add-On Renoprotective Effect of Pentoxifylline in Pre-Dialysis Advanced Chronic Kidney Disease Treated with Renin-Angiotensin-Aldosterone System Blockade – A Nation-wide Database Analysis

**Background:** Pentoxifylline decreases proteinuria in patients with glomerular disease due to its anti-inflammatory and anti-fibrotic properties. A combination therapy of pentoxifylline with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) decreased proteinuria and the glomerular filtration rate (GFR) decline in early chronic kidney disease (CKD). Whether adding pentoxifylline to ACEI/ARB provides additional benefits on renal outcome or survival is unclear in CKD stage 5 patients who have not yet received dialysis (CKD 5 ND).

**Methods:** A prospective cohort study was conducted based on the Taiwan National Health Insurance Research Database. From January 1, 2000 to June 30, 2009, we enrolled 14,117 CKD 5 ND patients with serum creatinine levels >6 mg/dL and hematocrit levels <28% and who have been treated with ACEI/ARB. All patients were further divided into two groups with or without pentoxifylline within 90 days after starting erythropoiesis-stimulating agent (index date). Patient follow-up took place until dialysis, death before initiation of dialysis or December 31, 2009.

**Results:** With a mean follow-up of 12 months, 9,867 patients (69.9%) required long-term dialysis and 2,805 (19.9%) died before progression to end-stage renal disease requiring dialysis. After propensity score-matching, add-on use of pentoxifylline was associated with a lower risk for long-term dialysis or death in those treated with ACEI/ARB (HR, 0.94; 95% CI, 0.90-0.97) or ARB (HR, 0.91; 95% CI, 0.86-0.97).

**Conclusions:** Pentoxifylline exhibited an add-on renoprotective effect in reducing the risk for long-term dialysis in CKD 5 ND patients who received renin-angiotensin-aldosterone system blockade. Randomized studies are needed to validate this association.

**FR-PO563**

Novel Therapy Regimens Have Reduced the High Risks of Bladder and Haematological Malignancies in ANCA-Associated Vasculitis

Chinar Rahmattulla,1 Annelies Eva Lin Berden,2 Sophie-Charlotte Wäcker,1 Marlies Reinders,1 Ernst C. Hagen,1 Ron Wolterbeek,1 Jan A. Bruijn,1 Ingeborg M. Bajema,1 1Leiden University Medical Center; 2Leiden University Medical Center

**Background:** The introduction of immunosuppressive therapy has dramatically improved the prognosis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). As a result, attention has shifted to long-term complications in patients. In this study, we investigate the incidence of malignancies in AAV patients. Additionally, we investigate the effect of therapy on malignancy incidence.

**Methods:** We included patients with histopathologically-proven AAV diagnosed at a large university hospital. Malignancy incidence was assessed with the Dutch National Pathology Database, which covers all the histologically confirmed malignancies diagnosed in The Netherlands. We used the Netherlands Cancer Registry incidence rates for comparing the malignancy incidence in our AAV cohort to that of the general Dutch population.

**Results:** Thirty-six of 138 patients with AAV developed a total of 85 malignancies during a mean follow-up of 9.7 years. We observed 61 non-melanoma skin cancers (NMSCs), three colon carcinomas, three breast carcinomas, three prostate carcinomas, two lung carcinomas, two soft tissue sarcomas, two unknown primary malignancies, and a variety of malignancies that occurred only once. The gender-, age-, and calendar year-adjusted malignancy risk was 2.21-fold (95% CI: 1.64–2.92) higher than that of the general population. Only the incidence of NMSCs was significantly increased compared to the general population (standardized incidence ratio: 4.23, 95% CI: 2.76–6.19). Malignancy risk was associated with the duration of cyclophosphamide therapy, and was not increased in patients that received cyclophosphamide for less than 1 year.

**Conclusions:** AAV patients have a higher risk of malignancies than the general population, but this risk is accounted for solely by NMSCs. Throughout the years, the risk of other malignancies—specifically bladder and haematological malignancies—has decreased in patients with AAV. This finding reflects the beneficial results of ongoing efforts to reduce cyclophosphamide exposure by developing new therapy regimens.
FR-PO566

**Lactobacillus plantarum 299v Reduces the Incidence of Clostridium difficile Infection in Patients Treated with Antibiotics in the Nephrological and Transplantation Department**

Marcin Adamczyk, Agata Kutycz, Katarzyna Kwiecień, Sylwia Małgorzata Dudek, Magdalena Gaspka, Andrzej Wieczek. Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.

**Background:** Lactobacillus plantarum 299v (LP299v) has been introduced into the clinical practice in order to reduce gastrointestinal symptoms during antibiotic exposure. However, it remains controversial whether or not probiotics are also effective in the prophylaxis of Clostridium difficile infections in patients receiving antibiotics. The aim of this clinical, retrospective, single-centre study was to analyze the effects of Clostridium difficile infections among patients receiving antibiotics and hospitalized in the period before and after initiation of LP299v routine use, as a prevention of CDI, in the nephrology and transplantation ward.

**Methods:** Among 3533 patients hospitalized in Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia in Katowice during two years (October 2012 – October 2013 and December 2013 – December 2014) 23 patients with CDI were diagnosed and enrolled in this study. Since November 2013 prevention of C. difficile infection with the oral use of LP299v was performed in all patients treated with antibiotics and who were at a high risk of developing CDI (patients after organ transplantation and receiving immunosuppressive drugs for any other reasons). For the further analysis the observation period was divided into two twelve-months intervals before (October 2012 to October 2013) and after initiation of LP299v use as the prophylactic manoeuvre against CDI (December 2013 to December 2014).

**Results:** It was found a significant reduction of the number of cases of C. difficile infection after beginning of LP299v routinely used (n=2, 11% of all hospitalized patients) compared with the previous twelve-months period of observation (n=21, 12% of all hospitalized patients).

**Conclusions:** Routine use of Lactobacillus plantarum 299v during treatment with antibiotics may prevent C. difficile infection, particularly in patients at high risk of CDI in the nephrology and transplantation ward.

**Funding:** Government Support - Non-U.S.

FR-PO567

**In Patients with Chronic Kidney Disease, Comanagement by Nephrologists is Associated with Lower Risk of Medication Errors**


**Background:** Patients with chronic kidney disease (CKD) are commonly prescribed drug doses that are excessive for their kidney function. Many CKD patients are followed by a nephrologist alone or in consultation with a family physician (i.e. comanagement) versus family physician alone is associated with more anti-hypertensive drugs, lower BMI, blood pressure, the number of anti-hypertensive drugs, ACEI/ARB use, Hb, Alb, corrected Ca, iPTH, and FGF23. We also employed 1:1 (k=1-6) propensity-score full matching, where one BB user matched to at most k non-users.

**Results:** BB users showed significantly-lower eGFR, more proteinuria, higher BMI, more anti-hypertensive drugs, lower Alb, higher 1-84 PTH, higher FGF23, and lower 25OHD levels, most of which suggested a poor risk for CDV at baseline. During a median follow-up period of 190 patient-years, 109 patient reached the outcome. Of those, 12 patients died by RRT, 71 reached a doubling of Cr, and 26 started dialysis. A multivariable Cox model with covariates that were significantly-different between BB users and non-users at baseline showed non-significant HR of 1.58 (C.I. 0.86 – 2.90). We also evaluated a fully-adjusted model and a parsimonious model with a stepwise backward-elimination method; however, the results remained non-significant. The 1 (k=1-6) full matching using propensity score did not show significant results, either. (0.93 (0.52 – 1.68)).

**Conclusions:** The BB therapy was not associated with renal outcomes in CKD patients without prior CDV. Confirmation in a larger study is required.

**Funding:** Pharmaceutical Company Support - Kyowa Hakko Kirin

FR-PO568

**Variation in Co-Medication Use According to Kidney Transplant Immunosuppressive Regimen: Application of Integrated Registry and Pharmacy Claims Data**


**Background:** While modern immunosuppressive therapies (ISx) have substantially reduced acute rejection, ISx medications have many side effects, and transplant recipients must take an array of “co-medications” to help mitigate complications. Co-medication utilization patterns are not well described in large, representative samples due to lack of available data.

**Methods:** We designed national U.S. transplant registry data with pharmacy records (2005-2010) from a large pharmaceutical claims clearinghouse to examine treatments for anemia, metabolic disorders and infections according to ISx regimen in mo 6-12 post-transplant (N=22,433). Associations of ISx with co-medication use (adjusted odds ratio, aOR) were examined with multivariable logistic regression including adjustment for recipient, donor and transplant factors.

**Results:** Compared to a reference regimen of tacrolimus (Tac), mycophenolate (MPA) and prednisone, rapamycin-based ISx was associated with significantly (P<0.05) higher use of ESAs (aOR 2.52), iron (aOR 2.26), statins (aOR 1.47), fibrates (aOR 2.35), and phosphorous binders (aOR 2.85) (Figure). Cyclosporine-based ISx was associated with lower use of ESAs compared to those taking triple ISx, recipients of tacrolimus-based dual and mono-therapies had lower use of statins, ACEI/ARBs, and anti-bacterial agents. Recipients of steroid-free ISx were less commonly treated for new onset diabetes.

**Conclusions:** Co-medication use should be considered in the cost-effectiveness and individualization of ISx regimens.

**Funding:** NIDDK Support

FR-PO569

**Association of Urinary Biomarkers of Injury and Repair with Incident Chronic Kidney Disease in Type 2 Diabetes: An Ancillary Study of the ACCORD Trial**

Girish N. Nadkarni,1 Vecna Rao,2 Faramarz Ismail-beigi,3 Vivian A. Fonseca,4 Sudhir V. Shah,5 Michael S. Simonson,6 Prasad Devarajan,7 Chirag R. Parikh,3 Steven G. Coca.1 Mount Sinai; 1 Yale Univ; 2 Case Western Reserve Univ; 3 Tulane Univ; 4 UAMS; 5 Univ of Cincinnati.

**Background:** Urinary kidney injury molecule (KIM-1), monocye chemoattractant protein (MCP)-1, interleukin (IL)-18, & YKL-40 are biomarkers representing renal injury, kidney fibrosis, and inflammation. We evaluated their association with incident CKD3b in the ACCORD trial.

**Methods:** We designed a case-cohort study of 721 participants & measured KIM-1, MCP-1, IL-18, & YKL-40 from baseline to 4.3 years. 194 eligible participants, 64% were inappropriate dosing. Exposure was defined as one or more outpatient visit with a nephrologist in the 1 year prior to antibiotic prescription. A multivariable logistic regression model was used to determine the independent association between comanagement and inappropriate dosing. Results: 21,348 eligible prescriptions studied, 64% were inappropriate dosing. The patients were 82 (IQR 76-87) years of age with comorbidities including: hypertension (89%), diabetes (49%), coronary artery disease (49%), and congestive heart failure (38%). 77% of all prescriptions were prescribed by family physicians and 2% were prescribed by nephrologists. Multivariable analysis revealed that patients with appropriate prescriptions were more likely to have seen a nephrologist in the one year prior with an unadjusted odds ratio of 1.07 (95% CI 1.01-1.14, p=0.02), adjusted odds ratio 1.23 (95%CI 1.15-1.32, p<0.001).

**Conclusions:** In patients with stage 4 or 5 CKD prescribed an antibiotic, those with an appropriate dose were 23% more likely to have been cared for by a nephrologist in the previous year. Although we cannot conclude what caused the improved prescribing practice, this improvement may, in part, explain the improved patient outcomes associated with seeing a nephrologist in observational studies.

**Funding:** ACCORD Trial

FR-489A

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
clinical characteristics, baseline eGFR & UACR, highest tertiles of uMCP1 & uKIM1 had adjusted HRs of 1.82(95% CI 1.18-2.81) & 1.51(95% CI 1.01-2.27) respectively. Area under ROC improved from 0.70(with eGFR & UACR) to 0.72 with addition of uMCP1 & uKIM1(p<0.05). No association was seen for urinary IL-18 & YKL-40.

**Adjusted associations of TDF exposure with urine α1m levels**

<table>
<thead>
<tr>
<th>TDF Exposure</th>
<th>% Estimate1 (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative TDF exposure (per year)</td>
<td>8.6(11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current vs never TDF use</td>
<td>80 (25,80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past vs never TDF use</td>
<td>43 (1,84)</td>
<td>0.006</td>
</tr>
<tr>
<td>Duration off TDF (per year)</td>
<td>-3 (8,4)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

1 Estimated % difference in α1m attributable to each TDF exposure variable, adjusted for demographics, traditional kidney risk factors, and HIV-related factors.

**Conclusions:** In HIV-infected men, TDF exposure was strongly associated with higher urine α1m levels. α1m is a promising biomarker for the detection and monitoring of TDF-associated tubular toxicity.

**Funding:** NIDDK Support

**FR-PO571**

**Impact of Kidney Function and Urinary Protein Excretion on Pulmonary Function**  

**Yusuke Nakade,1,2,3 Tadashi Toyama,3 Shinti Kitajima,2 Yasuyuki Shinozaki,2 Akinori Haru,2 Mito Shimizu,2 Yasunori Iwata,2 Norihiko Sakai,2 Kengo Furuchi,2 Takashi Wada,2,3  
**Clinical Laboratory, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan; 2Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan; 3Dept of Laboratory Medicine, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.**

**Background:** Although the cardiorenal relationship in patients with chronic kidney disease (CKD) has been investigated, information about the lung-kidney relation is limited. Here, we investigated the impacts of kidney function and urinary protein excretion on pulmonary dysfunction.

**Methods:** The data of pulmonary function tests (PFTs) and kidney function tests from 1 April 2005 to 30 June 2010 were selected from our laboratory database. Data were classified into 4 categories according to eGFR and proteinuria. Category 1: eGFR ≥ 60 ml/min/1.73 m² and urinary protein < 0.3 g/gCr; Category 2: eGFR < 60 ml/min/1.73 m² and urinary protein < 0.3 g/gCr; Category 3: eGFR ≥ 60 ml/min/1.73 m² and urinary protein ≥ 0.3 g/gCr; Category 4: eGFR < 60 ml/min/1.73 m² and urinary protein ≥ 0.3 g/gCr. Pulmonary function data were evaluated according to these 4 categories.

**Results:** A total of 133 participants without major respiratory disease, abnormal computed tomography and smoking history were enrolled. Hb-adjusted %DLCO was strongly correlated with eGFR in participants with a lower eGFR. 

**Conclusions:** This study suggests that eGFR and urinary protein excretion were associated with pulmonary function (Hb-adjusted %DLCO).
FR-PO572
Renal Biomarkers in Diabetes, Role Beyond Retinopathy, Relation to Nephropathy

Background: Diabetic nephropathy and retinopathy remain two of the most frequent complications of diabetes and is the leading cause of end-stage renal disease (ESRD) and blindness worldwide. The concordance rate between both complications is often present in diabetic patients.

Methods: We tried to study the relation between renal biomarkers including serum creatinine (SCr), urinary albumin/creatinine ratio (ACR), serum cystatin-C (cysC) and urinary NGAL (uNGAL) with diabetic retinopathy (DR) in 100 diabetic patients. Patients were classified according to severity into 3 stages: no diabetic retinopathy (No DR), Non-Diabetic Retinopathy (NDPR) and proliferative DR (PDR).

Results: Urinary ACR, serum cysC and uNGAL were higher significantly among patients with DR (NDPR & PDR) than patients without, while SCr showed a non significant rise with progression of retinopathy. All markers were higher among PDR than NDPR group.

Conclusions: Renal biomarkers namely urinary ACR, serum cysC and uNGAL may point to a more advanced stage of diabetic retinopathy, which might be an aid to identify the degree of retinopathy beside the traditional fundus examination in diabetic patients.

FR-PO573
Prognostic Importance of Urea and Urea: Creatinine Ratio for Mortality as Compared to Creatinine Concentrations Alone in the General Population
Ronan Casacub,1,2,3 Peanut G. Stack,1,2,3 John P. Ferguson.1 1Nephrology, Univ Hospital Limerick, Ireland; 2Graduate Entry Medical School, Univ of Limerick, Ireland; 3Health Research Inst, Univ of Limerick, Ireland.

Background: High Creatinine (Cr) concentrations reflect poor kidney function and are associated with a higher risk of death. It is unclear whether other measures of kidney function such as blood urea nitrogen (BUN) concentration and BUN/creatinine ratio, are better predictors of mortality in the general population.

Methods: A cohort of 15,773 non-pregnant subjects age >20, representative of the U.S. population, were identified from the Third National Health and Nutrition Examination Survey (1988-1994). Vital status was obtained through linkage with the National Death Index through to 2006. Subjects were classified into categories of Cr, BUN and BUN/Creatinine ratio (B/Cr). Weighted multivariable Cox regression models, compared hazard ratios [HR] and 95% CI for death among the decile groups and the prognostic capacity of Creatinine Ratio (B/Cr). Weighted multivariable Cox regression models, compared hazard ratios [HR] and 95% CI for death among the decile groups and the prognostic capacity of Creatinine Ratio (B/Cr).

Results: In multivariable analysis, BUN was found to be the most important single function such as blood urea nitrogen (BUN) concentration and BUN/creatinine ratio, are better predictors of mortality in the general population.

Conclusions: The term protein-energy wasting (PEW) implies a state of depleted protein and/or energy stores. An International Society of Renal Nutrition and Metabolism (ISRN) panel proposed objective criteria for the definition of PEW syndrome. However, the extent to which these variables used in PEW syndrome definition are indicative of low protein or energy stores is unknown. Muscle is the largest protein store and fat mass is the largest energy store in the body. Therefore, we examined the associations of these variables with low body mass index (BMI) and fat mass (FM) measured by DXA scans in 11,834 participants in the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: Definitions of PEW variables are summarized in the table. The associations of each PEW variable with BMI and FM in the entire cohort and CKD (CKD-EPI eGFR < 60) sub-population were examined in linear regression models using svy suite in STATA 13.

Results: Mean age was 46.0 yrs, 50.3% were male, 9.5% were black. 6.7% had CKD. Unintentional weight loss and low levels of serum albumin, serum cholesterol, BMI and MAMC were associated with lower LBM and FM. On the other hand, low protein and energy intakes were associated with higher LBM and FM.

Conclusions: Both BUN and Creatinine Concentrations Alone in the General Population. Among patients with malnourished states (Low BUN), higher SC were associated with lower mortality. In contrast, among patients with normal-high BUN concentrations, higher Cr was associated with elevated death risk. Risk Prediction models should take BUN levels into consideration when estimating future death risk.

Funding: Government Support - Non-U.S.

FR-PO574
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Background: Growing evidence suggests that high serum uric acid (SUA) levels are causally related to an increased risk of kidney dysfunction. However, the association remains inconclusive in general Asian populations. Additionally, there are limited studies investigating the influence of SUA levels on the development of albuminuria.

Methods: A total of 2,059 community-dwelling Japanese subjects aged ≥40 years without chronic kidney disease (CKD) were followed for 5 years. CKD were defined as eGFR <60 mL/min/1.73m² or urine albumin/creatinine ratio (UACR) ≥30 mg/g. The odds ratios (ORs) for the development of CKD and the rates of decline in eGFR were estimated according to quartile of SUA (≤40, 4.1-4.9, 5.0-5.8, ≥5.9 mg/dL).

Results: During follow-up period, 396 subjects experienced CKD, of whom 125 had eGFR <60 mL/min/1.73m² and 312 had UACR ≥30 mg/g. The age- and sex-adjusted incidence of CKD increased significantly with higher SUA levels (p for trend <0.001). Compared with those with SUA of ≤40 mg/dL, the multivariable-adjusted ORs for the development of CKD were 1.21 (95% confidence intervals, 0.84-1.74), 1.47 (1.01-2.17), and 2.10 (1.37-3.23) in subjects with SUA of 4.1-4.9 mg/dL, 5.0-5.8 mg/dL, and ≥5.9 mg/dL, respectively. Likewise, there were positive associations of SUA levels with the adjusted risk of developing eGFR <60 mL/min/1.73m² (OR 1.00 [reference] in ≤40 mg/dL, 2.30 [1.10-4.82] in 4.1-4.9 mg/dL, 2.81 [1.34-5.88] in 5.0-5.8 mg/dL, and 3.73 [1.65-8.44], in ≥5.9 mg/dL) and UACR ≥30 mg/g (1.00 [reference], 1.12 [0.76-1.65], 1.35 [0.90-2.03], and 1.91 [1.14-2.87], respectively). Additionally, higher SUA was significantly associated with a greater decline in eGFR (p for trend = 0.002).

Conclusions: Higher SUA level is a significant risk factor for the development of both kidney dysfunction and albuminuria in a general Japanese population.

FR-PO575
Do Protein-Energy Wasting Criteria Reflect Protein/Energy Wasting?
Xiaori Chen,1 G. Wei,1 Robert E. Boucher,1 Dominique Ferranti,2 Michel Chonchol,3 Kalani L. Raphael,3 Irini Bedhu,1,3 1U of Utah; 2VA SLC; 3UC Denver.

Background: The term protein-energy wasting (PEW) implies a state of depleted protein and/or energy stores. An International Society of Renal Nutrition and Metabolism (ISRN) panel proposed objective criteria for the definition of PEW syndrome. However, the extent to which these variables used in PEW syndrome definition are indicative of low protein or energy stores is unknown. Muscle is the largest protein store and fat mass is the largest energy store in the body. Therefore, we examined the associations of these variables with low body mass index (BMI) and fat mass (FM) measured by DXA scans in 11,834 participants in the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: Definitions of PEW variables are summarized in the table. The associations of each PEW variable with BMI and FM in the entire cohort and CKD (CKD-EPI eGFR < 60) sub-population were examined in linear regression models using svy suite in STATA 13.

Results: Mean age was 46.0 yrs, 50.3% were male, 9.5% were black. 6.7% had CKD. Unintentional weight loss and low levels of serum albumin, serum cholesterol, BMI and MAMC were associated with lower LBM and FM. On the other hand, low protein and energy intakes were associated with higher LBM and FM.

PEW variables

<table>
<thead>
<tr>
<th>Lean body mass (kg)</th>
<th>Fat mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;95% CI)</td>
<td></td>
</tr>
<tr>
<td>Albumin&lt;3.25 g/d</td>
<td>-3.5 (-7.5, 0.4)</td>
</tr>
<tr>
<td>Cholesterol&lt;200 mg/dl</td>
<td>-2.5 (-6.8, 1.8)</td>
</tr>
<tr>
<td>BMI&lt;20 kg/m²</td>
<td>-1.9 (-10.3, -9.1)</td>
</tr>
<tr>
<td>Unintentional wt loss&gt;10% over 1 yr</td>
<td>-2.2 (-3.3, -1.0)</td>
</tr>
<tr>
<td>Body fat &gt;5%</td>
<td>NA</td>
</tr>
<tr>
<td>Low MAMC*</td>
<td>-8.6 (-9.0, -8.3)</td>
</tr>
<tr>
<td>Protein intake&lt;0.6 g/kg/d</td>
<td>3.6 (3.0, 4.2)</td>
</tr>
<tr>
<td>Energy intake&lt;25 kcal/kg/day</td>
<td>4.5 (3.9, 4.7)</td>
</tr>
</tbody>
</table>

* 10% or more lower than the 50th percentile of reference group

Results were similar in the CKD sub-population.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

491A
Conclusions: Serum chemistry, body weight and muscle mass PEW criteria appear to be dependent upon both protein stores (as indicated by LBM) and energy stores (as indicated by FM). Dietary variables are not reflective of protein or energy wasting. A modified PEW syndrome definition without the dietary variables would be a better indicator of PEW syndrome.

Funding: NIDDK Support

FR-PO576

Low-Proteinuric CKD and Risk of ESRD in Nephrology Clinics: Emerging Role of Serum Phosphorus
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Background: In low-proteinuric (LP) CKD, factors other than proteinuria (Uprot) likely act as predictors of ESRD. However, comprehensive assessment of epidemiologic features of LP versus high-proteinuric (HP) patients is still lacking. This information is critical in renal clinics where LP patients are common.

Methods: We pooled three prospective cohorts that in 2000-2010 enrolled 2,488 CKD patients stage III-V under stable care from ≥6 months in 40 Italian renal clinics. Patients were followed for ESRD (chronic dialysis-transplant) up to 12/2014. Patients were classified in two groups, LP (56%) and HP (44%), by Uprot ≥0.5 vs <0.5 g/24h, respectively.

Results: Besides lower Uprot (median, IQR: 0.15, 0.06-0.28 vs 1.20, 0.78-2.05 g/24h), LP differed from HP because male gender (55 vs 62%), diabetes (28 vs 35%) and use of anti-RAS (73 vs 78%) were less frequent. In LP, moreover, (70 vs 12) (p<0.05) (14 vs 14) (p=0.001), GFR-EPN (35.2 ±13.3 vs 26.6±13.2 mL/min/1.73m²) and Hb (12.7±1.7 vs 12.3±1.8 g/dL) were higher while systolic BP (137±18 vs 140±18 mmHg) was lower. Serum phosphorus (P) was lower in LP group (1.33±0.83 vs 1.68±0.70 mg/dL, P<0.05). GFR-EPN and Hb (10.0, 8.50-0.97 and anti-RAS (0.74, 0.60-0.91) had a prognostic role exclusively in HP. A negative interaction P*Uprot was detected in HP (β=-0.064, P=0.004). Results were consistent across cohorts.

Conclusions: In renal clinics, LP patients are prevalent and characterized by nontrivial renal risk despite higher GFR. Risk factors for ESRD are peculiar; in particular, results in LP and HP suggest that lower Uprot allows full expression of the negative role of P, the effect being evident for P levels mostly normal.

FR-PO577

Trends in CKD Awareness in the U.S. Population, 1999-2012, Overall and by KDIGO Risk Groups
Yunnuo Yu,1 Tanushree Banerjee,1 Delphine S. Tuot,1 Jennifer L. Bragg-Gresham,2 Mark Eberhardt,3 Sharon Saydah,4 Rajiv Saran,5 Neil R. Powe,6 UCFSC,7 UM,8 CDC.

Background: Despite medical knowledge of chronic kidney disease (CKD) as a risk factor of cardiovascular disease, hypertension, and progression to kidney failure, a majority of patients are not aware of their disease. Early identification and management of CKD can decrease its rate of progression.

Methods: We used cross-sectional National Health and Nutrition Examination Survey data (1999-2012) of non-pregnant adults aged ≥20 years with CKD who had complete urinary albumin and creatinine data (N=8,480-10,296). CKD stages 1-4 were classified using KDIGO's prognosis of CKD risk levels based on GFR and albuminuria. The risk categories range from low to very high risk and predict the risk of CKD progression, ESRD, and mortality. eGFR was estimated using the MDRD equation. CKD awareness was defined by answering “yes” to the question “Have you ever been told that you had weak or failing kidney function?”. The incidence rate of patients are not aware of their disease. Early identification and management of CKD may be reaching those at greatest risk and acceleration might help mitigate CKD progression and associated comorbidities.

Funding: Other U.S. Government Support

FR-PO578

Intermittent Abnormal Kidney Function and Mortality in Community Dwelling Individuals
Donal J. Sexton,1 Scott Reule,2 Robert N. Foley,3 1Medicine, HRB Clinical Research Facility, NUIGalway, Galway, Ireland; 2Medicine, Univ of Minnesota, Minneapolis.

Background: The health implications of permanently abnormal kidney function as measured by estimated glomerular filtration rate and spot urinary albumin excretion has been well characterized to date. However little data is available regarding the implications of intermittent abnormalities in these tests as defined by established thresholds.

Methods: We evaluated the frequency of intermittent abnormal kidney function and its association with all-cause mortality in the US general population using the National Health and Nutrition Examination Survey III, 1988-1994. Mortality linkage data were available through December 2006. Estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI equation and urinary albumin-creatinine ratios (ACR) were measured twice, a mean of 17 days apart (N=1161).

Results: Proportions of abnormal tests included: for eGFR <60 ml/min/1.73m² either test 7.32 %, first test 5.94%, second test 6.86%, first test only 1.64%, second test only 1.38%, both tests 4.31%. Compared to participants with eGFR ≥60 ml/min/1.73m² on both testing occasions, adjusted hazard ratios were 1.8 (95%CI 1.3, 2.4) for intermittent and 1.7 (95%CI 1.1, 2.5) for persistent abnormal eGFR. Proportions with ACR ≥30 mg/g were as follows: either test 16.54%, first test 11.63%, second test 13.55%, first test only 3.19%, second test only 4.91%, both tests 8.44%. Compared to those with ACR <30 mg/g on both occasions’ mortality hazard ratios for intermittent abnormal function was 2.1 (95%CI 1.6, 2.7), and persistent abnormal 2.0 (95%CI 1.5, 2.8). Models were adjusted for age, sex, race, diabetes mellitus, cardiovascular disease (congestive heart failure, previous myocardial infarction or stroke), current smoking, self reported hypertension, systolic and diastolic blood pressure, total cholesterol and body mass index.

Conclusions: CKD as defined by established thresholds may be persistent or intermittent in community dwelling individuals. Participants with intermittently abnormal kidney function as defined by current thresholds were at similar mortality risk to those with persistent abnormal function on both occasions.

FR-PO579

Renal Outcome of APRT Deficiency Presenting in Childhood
Hafnhildur L. Runolfsdottir,1 Runolfur Palsson,1,2 Inger Maria Agustsdottir,1 Olafur S. Indridason,1 Vidar O. Edvardsson,1,3 Faculty of Medicine, Univ of Iceland; 2Div of Nephrology, 3Children’s Medical Center; Landspitali – The National Univ Hospital of Iceland, Reykjavik, Iceland.

Background: Adenine phosphoribosyltransferase (APRT) deficiency is an inherited disorder of purine metabolism that leads to nephrolithiasis and chronic kidney disease (CKD). APRT enzyme data are available on APRT deficiency presenting in childhood.

Methods: All patients in the APRT Deficiency Registry of the Rare Kidney Stone Consortium who presented with clinical manifestations of the disorder and/or were diagnosed with the disease before age 18 years were included in the study. Presenting features, time to diagnosis and disease course were examined. Glomerular filtration rate (eGFR) was estimated with the modified Schwartz equation in children and the MDRD equation in adults. CKD was defined as eGFR <60 ml/min/1.73 m² and acute kidney injury (AKI) according to the KDIGO criteria. Data are presented as median (range).

Results: Eighteen children presented at the age of 1.6 (0.2-16.5) years. Presenting features included redness-brown diabetic spot in 11 patients (55%), kidney stones in 8 (42%), lower urinary tract symptoms in 8 (42%) and AKI in 2. The diagnosis was promptly made in 7 patients, while it was delayed in 12 (63%) patients for 15.2 (0.3-39.2) years. One patient, who did not receive drug treatment, developed ESRD at age 11 years. Twelve patients were placed on allopurinol at the age of 2.1 (0.6-16.5) years. During follow-up of 18.9 (1.7-31.5) years, 3 of these patients developed 4 kidney stone events and AKI occurred in 2 patients during episodes of volume depletion; none had developed CKD. Six patients did not begin pharmacotherapy until age 29.8 (20.5-42.4) years. At last follow-up, at 43.9 (32.5-56.9) years of age, 3 had experienced a total of 9 kidney stone events, 2 had suffered AKI, 3 had stage 3 CKD and one had progressed to ESRD at the age of 44 years.

Conclusions: A substantial proportion of patients with APRT deficiency present in childhood. The commonly observed delay in diagnosis and treatment may have grave consequences. APRT deficiency must be excluded in all children with kidney stones, renal dysfuction and redness-brown diabetic spot.

Funding: Other NIH Support - This study was supported by the Rare Kidney Stone Consortium (U54DK088780), a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR). The Rare Kidney Stone Consortium is funded through collaboration between NCATS and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).
Association of Chronic Kidney Disease with Increased Risk of Recurrence of Upper Urinary Tract Urothelial Cancer – A Population-Based Study

Methods: We conducted a population-based cohort study through Taiwan National Health Insurance Research Dataset. Incident UTUC patient was extracted from Taiwan Cancer Registry Database and linked to data status. Status of CKD including non-dialysis CKD, dialysis ESRD, and renal transplant were identified before the index date of UTUC. Recurrence was defined as either new tumor lesion in bladder, or at the other site of urinary tract, or occurrence of distant metastasis within 3 months after first surgery. Differences of characteristics between CKD and non-CKD group was described as mean ± standard deviation or percentage and tested by independent t test and chi-square test. Competing risk approach was used for estimating cause-specific hazard ratio (C SHR) and 95% confidence interval ( CI ).

Results: Totally, 4,002 UTUC patients from 2001 to 2005 were included and tracked until disease recurrence or end of 5 years after the index date of UTUC. Near half patients accompanied with various stages and status of CKD at index date. UTUC patients with CKD were younger, more female, and had more co-morbidities than patients without CKD. After adjusting factors of age, tumor grade, and co-morbidities, CKD significantly increased risk of UTUC recurrence in female (C SHR: 1.72, 95% CI: 1.33-2.21, p = 0.001); but not in male (C SHR: 0.91, 95% CI: 0.44-1.86, p = 0.79).

Conclusions: CKD increases risk of recurrence in female UTUC patient and is an important prognostic indicator. (This study was granted by the Ministry of Science and Technology (NSC 102-2314-B-037-015-MY3) and by the Ministry of Health and Welfare (MOHW103-TD-B-111-05, MOHW104-TDU-B-212-124-003, budget from health and welfare surcharge of tobacco product). Funding: Government Support - Non-U.S.

Fr-POS81

Single Centre Experience of Late Referral and Achievement of Useable Dialysis Access Over a 9-Year Period
Mohamed Salah Eldin Khogali, Renal Dept, Dorset County Hospital; Dorchester, Dorset, United Kingdom; Renal Dept, Dorset County Hospital, Dorchester, Dorset, United Kingdom.

Background: We describe a single centre, retrospective analysis of late (≤ 90 days) referral for dialysis over a 9 year period from April 2003 till March 2012. Factors that contributed to late referral and success in creating permanent dialysis access were determined.

Methods: Data on adult patients referred ≤ 90 days from dialysis were collected including patient demographics, source of referral, mortality, reason for late referral, creation of permanent dialysis access and use of permanent dialysis access at first dialysis.

Results: One hundred and twenty-seven patients were referred in ≤ 90 days over the 9 year period. Ninety-nine (78%) patients were referred within 30 days prior to dialysis and (22%) patients within 30 – 90 days. Their median age was 63 years and 60% (39) patients were male. Twenty-five (20%) patients were diabetic. Forty (33%) patients died within the first year after referral, 25 (21%) patients within the first 6 months and 15 (12%) patients between 6 months and 1 year (figure1). Fifty-six patients (51%) presented late due to acute renal failure (myeloma 24, vasculitis 14, irreversible acute kidney injury 10, renal cell carcinoma 5, glomerulonephritis 3 and others 9). Twenty-nine patients (23%) referred by physicians and surgeons, and 24 patients (19%) referred by GPs were late referrals of patients with known chronic renal failure. Nine patients (7%) presented late due to lack of understanding of their disease, denial, and fear of the unknown. One hundred and ten patients had permanent dialysis access created and 17 patients no permanent access procedures. The average time to create permanent dialysis access was 44 days post-dialysis commencement. Six permanent haemodialysis accesses were created pre-dialysis, 56 post-dialysis; 19 peritoneal dialysis accesses were created pre- dialysis, 29 post-dialysis.

Conclusions: Overall the number of patients presenting late for dialysis has decreased. Late referral has a poor 1 year survival and most patients require haemodialysis long-term. Only a minority of patients referred late have permanent dialysis access created and used at their first dialysis.

Fr-POS82

Abnormal Global Glomerular Sclerosis Rate in Remnant Kidney of Ipsilateral Nephrectomy to Covariate the Risk of End-Stage Renal Disease within Five Years in Patients of Upper Urinary Tract Urothelial Carcinoma
Sheng-Chen Shyu, Shih-Wei Lin, Pei-Ih Liang, Shih-Ming Yeh, Ming-Yen Lin, Shang-Jyh Hwang, Wen-Jeng Wu, Kaohsiung Medical Univ, Taiwan; National Health Research Insts, Miaoli, Taiwan.

Background: Taiwan has significantly high incidence of upper urinary tract urothelial cancer (UTUC) and end-stage renal disease (ESRD). UTUC coexisted with chronic kidney disease (CKD) may deteriorate cancer progression and increase mortality risk. The aim of study was to explore the association of CKD with the risk of UTUC recurrence.

Methods: This cohort study included 132 cases of non-dialysis UTUC patients post ipsilateral nephrecterectomy from 2002 to 2010. We collected clinical and laboratory data before surgery, tumor size, whether into dialysis after surgery, and followed up to dialysis or to December 31, 2014. Renal histopathology was read by 3 specialists: nephrologists or pathologist. We used logistic regression for studying tubuleinterstitial fibrosis score and global glomerular sclerosis (GGS) rates and Cox regression to investigate factors associated with renal survival.

Results: There was no significant factor associated with tubuleinterstitial fibrosis, but advanced CKD was significantly related to GGS rate adjusted with age and gender [OR (95%CI): 4.8(1.4-16.9), p = 0.014]. Kaplan-Meier survival curve showed five-year renal survival rate was 86.3%. Factors affect five-year renal survival were hypertension (HR[95%CI]): 4.0(1.15-2.52), p = 0.043 and GGS rate [HR(95%CI): 17.4(2.4-124.1), p = 0.004].

Conclusions: Our findings demonstrated that UTUC patients with hypertension before surgery or abnormal GGS rate in remnant kidney have higher risk of entering dialysis within five years post ipsilateral nephrectoerectomy. (This study was granted by the Ministry of Science and Technology (NSC 102-2314-B-037-012-MY3) and by the Ministry of Health and Welfare (MOHW103-TD-B-111-05, MOHW104-TDU-B-212-124-003, budget from health and welfare surcharge of tobacco product). (Funding: Government Support - Non-U.S.)
FR-PO584
The Epicdemic of Chronic Kidney Disease in Rural and Remote Canadian First Nations: Results from Manitoba’s FINISHED Screening Program Paul Komenda, Barry Ad Lalavalle, Thomas W. Ferguson, Navdeep Tangri, Allison Dart, Bing Hu, Audrey Gordon, Caroline D.Chartrand, Lorraine M. Mcleod, Claudio Rigatto, Medicine, Univ of Manitoba, Winnipeg, MB, Canada; Diabetes Education Project, Winnipeg, MB, Canada; Convention Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; Seven Oaks General Hospital Research Centre, Winnipeg, MB, Canada.

Background: Chronic Kidney Disease (CKD) is a global epidemic affecting 10-15% of the general population. Canadian First Nations children and young adults are known to suffer from a high rate of proximate risk factors for CKD, in particular elevated rates of diabetes. The rates of CKD are not well defined in this population. We used data from The First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project, a 3-year initiative completed in 2015 that accomplished community wide screening in 11 rural and remote First Nations communities in Manitoba, Canada.

Methods: Detailed methods of the FINISHED study have been previously published (Lalavalle et al. CJRHD, 2015). An interdisciplinary team screened for CKD in adults and children aged 10+ using both urine albumin-to-creatinine ratio (AUCR) and eGFR in 11 communities across 2 tribal councils. We present here the data on demographic variables, risk factors for CKD, and the prevalence and severity of CKD in the adult (age 18+) screening cohort.

Results: 3346 adults were screened. 26.7% of those screened had CKD defined as elevated urine ACR (micro- or macroalbuminuria) or eGFR < 60 ml/min/1.73m². Road access communities had a lower prevalence of CKD (18.6%) than remote air access communities (36.0%). Macroalbuminuria (urine ACR > 300 mg/g) was present in 5% of those screened (2.8% in road access and 7.5% in air access communities).

Conclusions: Rural and remote Canadian First Nations suffer up to a 3-fold higher prevalence of CKD than the general population and a nearly 5-fold higher prevalence of macroalbuminuria. This prevalence is comparable to high-risk populations such as those with diabetes, hypertension, and CHF, respectively. Given these risks and road access, screening and treatment interventions may be cost-effective, as they have been shown to be in other high-risk populations.

Funding: Government Support - Non-U.S.

FR-PO585
Age and Gender Specific Lifetime Risk of Renal Replacement Therapy Jan A.J.G. van den Brand, Maria Pippas, Vianda S. Stel, Jack F. Wetzels, Kitty J. Jager, Dept. of Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; ERA-EDTA Registry, Academic Medical Centre Univ of Amsterdam, Amsterdam, Netherlands.

Background: Kidney transplantation is the preferred treatment of end stage renal disease (ESRD). Graft and patient survival are highest after transplantation with a graft from a living donor. However, persons who donate a kidney are themselves at risk of ESRD. Personalized risk prediction requires age and gender specific risk estimates. Here, we report lifetime risk of renal replacement therapy (RRT) for ESRD by age and gender across Europe. Lifetime risk of RRT is lower in persons with normal eGFR compared to men. These data offer a basis to provide personalized prediction of lifetime ESRD risk when evaluating a potential kidney donor. The estimates presented here are population averages. We expect that lifetime risk is lower in persons with normal eGFR and no albuminuria.

Methods: We investigated a retrospective cohort of all adult type 2 diabetic patients receiving care in an integrated health care system in central Pennsylvania during the period 1/1/2004-12/31/2014. Patients were risk stratified using the 2002 NKF and, separately, the 2012 KDIGO CKD classification systems. We compared the predictive performance of the two classification systems for death and ESRD using Akaikes Information Criterion (AIC) obtained from multivariate, Cox proportional hazards models. Using only the KDIGO 2012 classification system, we then investigated patients categorized as stage G1 or G2 (with ‘high’ or ‘very high’ albuminuria) for the presence of modifiable risk factors.

Results: 17,385 type 2 diabetes comprised the study population (median follow-up 6.8 years). Median age and eGFR were 60 years and 95 ml/min/1.73m², respectively. 53% were male, 44% had a smoking history, and 16% and 5% had a history of coronary disease and CHF, respectively. Although both classification systems discriminated reasonably well, the KDIGO 2012 system—incorporating uACR—had lower AIC scores and was more likely to minimize information loss. Across all risk factors examined, less than half the population was receiving recommended care.

Funding: Government Support - Non-U.S.

FR-PO586
Characterizing Risk Among Type 2 Diabetics with Preserved eGFR and Abnormal Urinary Albumin Excretion Robert M. Perkins, Alex R. Chang, H. Lester Kirchner, 1 Bayer HealthCare, Whippany, NJ; Geisinger Medical Center, Danville, PA.

Background: Updated CKD risk stratification guidelines promote earlier identification of higher-risk patients. Two conditions are required to improve outcomes among such patients: robust risk characterization, and the presence of modifiable factors.

Methods: We investigated a retrospective cohort of all adult type 2 diabetic patients receiving care in an integrated health care system in central Pennsylvania during the period 1/1/2004-12/31/2014. Patients were risk stratified using the 2002 NKF and, separately, the 2012 KDIGO CKD classification systems. We compared the predictive performance of the two classification systems for death and ESRD using Akaikes Information Criterion (AIC) obtained from multivariate, Cox proportional hazards models. Using only the KDIGO 2012 classification system, we then investigated patients categorized as stage G1 or G2 (with ‘high’ or ‘very high’ albuminuria) for the presence of modifiable risk factors.

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Funding: Government Support - Non-U.S.

FR-PO587
Detecting Bowel Cancer in Chronic Kidney Disease (CKD): The Detect Study Germaine Wong, Univ of Sydney, Australia.

Background: CKD confers a 20% higher risk of colorectal cancer (CRC) than the general population, and has a very poor prognosis, with less than 50% of kidney transplant recipients surviving one year after diagnosis. The benefits and harms of screening for advanced colorectal neoplasms in CKD are unknown. We aim to determine the prevalence and spectrum of advanced colorectal neoplasms in CKD, and to evaluate the test performance characteristics of immunochemical faecal occult blood testing (iFOBT) for screening advanced colorectal neoplasms in CKD.

Methods: Participants with CKD stages III-V, on dialysis and with a kidney transplant, aged between 35 and 74 years were recruited from 10 centres in Spain, Canada, Australia and New Zealand. All received two screening iFOBTs, and those with at least one or more positive screens underwent colonoscopy, with test negatives verified by clinical follow up and data linkage.

Results: Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens. Of the 1602 patients recruited to the study, [CKD stages III-V: n= 734 (45.8%); dialysis: n=392 (24.7%) and transplant n=476 (29.7%)], 345 (21.5%) had one or more positive screens.

Conclusions: This investigation confirms the feasibility of early risk characterization among patients with preserved eGFR and abnormal urinary albumin excretion. Care gaps are highly prevalent among these individuals and may serve as targets to improve long term outcomes.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.

494A
**FR-PO588**

Subclinical Pulmonary Congestion Is Pervasive in Nephrotic Syndrome

Francesca Mallamaei, 1,2 Francesco Marino, 2 Carmela Martorano, 2 Rocco Tripeti, 1 Marianna Bellantoni, 1 Giovanni Tripeti, 1 Carmine Zoccali, 1 National Research Council of Italy, Inst of Clinical Physiology, Reggio Cal Cal, Italy; 2Nephrology, Transplantation and Hypertension Unit United Hospitals, Reggio Calabria, Italy.

Background: In patients with Nephrotic Syndrome (NS) the lung is considered as an organ protected from the risk of edema. However information on objectively measured lung water in NS patients is lacking.

Methods: We measured lung water with an ultrasound technique (US) and with standard transthoracic impedance in an incidence of series of 42 asymptomatic patients with active NS. Eleven of these patients were submitted during NS remission. Transthoracic impedance was measured on 3 healthy volunteers that formed the control group. US lung studies were performed after 5 and 60 minutes of supine resting and after 5 minutes of standing. Transthoracic impedance was measured after 30 min of supine resting only.

Results: In patients with active NS the median number of US-B lines (a metric of lung water) after 5 min in supine position was markedly higher [12; Interquartile range: 7-25; p<0.001] than in healthy subjects [4; 2-9]. The difference between patients [16, 11-35] and controls [4; 2-9] amplified (p<0.001) after 60 min of supine resting and attenuated after 5 min of standing [9, 7-25 vs 4, 3-5, p=0.001]. After NS remission, the number of US B lines reduced to 5 (4-18) at 5 min and to 6.5 (2-22) at 60 min (P=0.001) approaching the normal range. Lung congestion in patients with active disease was fully confirmed by transthoracic impedance measurements (p<0.001 vs healthy controls).

Conclusions: Asymptomatic pulmonary congestion is pervasive in patients with NS. A clinical trial is needed to assess the usefulness of the application of this technique for the management of patients with NS.

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**FR-PO589**

The Incidence of Malignancies prior to the Diagnosis of ANCA-Associated Vasculitis (AAV) Is Not Increased in Comparison to the Incidence in the General Population

Emma Elisabeth Van Daalen, 1 Chinuin Rahmatullah, 1 Ron Wolterbeek, 2 Jan A. Bruijn, 1 Ingeborg M. Bajema, 1 Pathology, Leiden Univ Medical Center, Leiden, Netherlands; 2Medical Statistics and Bioinformatics, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Several studies have found an increased malignancy risk before the diagnosis of AAV, especially in granulomatosis with polyangiitis (GPA), whereas data on microscopic polyangiitis (MPA) are scarce. It has been hypothesized that malignancies and AAV have common pathways in their pathogenesis (Ann Rheum Dis 2004, Rheumatology 2014). Several studies have found an increased malignancy risk before the AAV diagnosis. To further elucidate this hypothesis, we retrospectively retrieved data on 138 patients with biopsy-proven AAV diagnosed in the Netherlands. Malignancies prior to AAV diagnosis were identified using the Dutch National Pathology Database. The malignancy incidence was compared to the incidence in the general population, as reported by the Netherlands Cancer Registry. The Standardized Incidence Ratios (SIRs) were calculated, matching for gender, age and calendar time period. Separate analyses were performed for GPA and MPA.

Results: Twelve patients were diagnosed with cancer before the AAV diagnosis (mean follow-up: 11.8 years). Overall malignancy risk was not increased (SIR: 0.92, 95%CI: 0.48-1.61). Malignancy risks were also not increased for malignancies of the skin, bladder, kidney, lung, stomach, rectum and uterus (SIRs ranging from 1.71 to 4.77, not significantly increased). There was no difference in malignancy risk between GPA (SIR: 1.23, 95%CI: 0.49-2.53) and MPA (SIR: 0.98, 95%CI: 0.27-2.50) patients (relative risk: 1.26, 95%CI: 0.32-5.38).

Conclusions: We did not find an increased incidence of malignancies prior to AAV diagnosis compared to the general population. This is in contrast with previous studies, in which GPA was associated with preceding renal cell carcinoma, bladder cancer and non-melanoma skin cancer. Most other studies have not included microscopic polyangiitis patients, for which malignancy risk was not increased in our study. Our findings do not support the hypothesis that malignancies and AAV have a shared pathogenic pathway.

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**FR-PO590**

Gastrointestinal Symptoms and Hypoalbuminemia in Chronic Kidney Disease Patients

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Background: Hypoalbuminemia is an important risk factor for adverse outcomes in patients with CKD. Little is known about the relationship between gastrointestinal (GI) symptoms and serum albumin level in CKD.

Methods: This is a cross-sectional study of participants (N=3599) in the Chronic Renal Insufficiency Cohort (CRIC) study which collected information regarding potential uremic symptoms. For each of the 4 following symptoms: “bad taste in mouth,” “loss of appetite,” “nausea,” “vomiting,” we created a severity score by multiplying the number of symptomatic days in the past month by a severity score of 1 to 3 (mild, moderate and severe). We then summed up the individual severity score for an overall severity score. Dietary protein intake was measured via 24-hour urine. The main outcome was severe). We then summed up the individual severity score for an overall severity score. Dietary protein intake was measured via 24-hour urine. The main outcome was low serum albumin levels. The main outcome was low serum albumin level. Dietary protein intake was measured via 24-hour urine. The main outcome was low serum albumin levels.

Results:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A bad taste in your mouth?</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Loss of appetite?</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Nausea or being sick to your stomach?</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Vomiting?</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

Odds ratios were adjusted for demographic variables, smoking, and smoking status.

Conclusions: Increased prevalence of GI symptoms become apparent among CKD patients at relatively high eGFR levels (45 ml/min/1.73m²). These symptoms correlated with important nutritional parameters.

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**FR-PO591**

Obstructive Lung Function in CKD: NHANES 2007-2012

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Background: Lung diseases are one of the leading causes of death in the general population. We aimed to study the prevalence of obstructive lung function in those with CKD. In addition, factors associated with obstructive lung function were examined.

Methods: Participants aged 20-79 years from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 who underwent spirometry testing using spirometry protocols were included in this analysis. Global Initiative for Chronic Obstructive Lung Disease classification of COPD (FEV1/FVC <0.7) based on post-bronchodilator spirometric results was used to establish the prevalence of obstructive lung function weights adjusted for non-response to spirometry. CKD was defined as presence of eGFR <60 ml/min/1.73 m² and/or UACR >30 mg/g. Factors associated with obstructive lung function were identified using logistic regression model for the entire cohort, CKD and non-CKD groups separately using (based on spirometry).

Results: Out of 11,995 participants (CKD=1563; Non-CKD=10,432) who completed the spirometry testing, 1,098 participants were eligible for both and only 1049 complete bronchodilator spirometry. Prevalence of obstructive lung function using baseline spirometry data were 25% in CKD and 13% in non-CKD and GOLD criteria were 17% in CKD and 8% in non-CKD. Each 5 ml/m lower eGFR and proteinuria were associated with higher odds of having obstructive lung function in the entire cohort.

Table. Factors associated with obstructive lung function in the study cohort

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Underline represents presenting author.
FR-PO592

Association of Serum Osteoprotegerin with Bone Loss in Chronic Kidney Disease

From the KNOW-CKD Study
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Background: Osteoprotegerin (OPG), a potent inhibitor of osteoclast activation, deactivates the osteoclasts protective and trophic mineral density. This study examined the association between serum OPG and bone loss in patients with chronic kidney disease (CKD), a condition associated with increased risk of bone fracture and mineral and bone disorders.

Methods: BMD at the lumbar spine, total hip and femur neck was assessed by dual energy X-ray absorptiometry; and serum OPG was measured at baseline in 1,423 CKD patients in the prospective KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease. Osteoporosis was defined to T score ≤ –2.5 in patients aged over 50. Results: Mean quartiles of serum OPG were significantly associated with lower BMD (lumbar spine, total hip and femur neck) compared with the lowest quartile of serum OPG. Multivariable linear regression model indicated that serum OPG was independently associated with decreased lumbar spine and total hip BMD (B = –0.489; 95% confidence interval [CI], –0.883–0.095; P = 0.015, B = –0.349; 95% CI, –0.672–0.027; P = 0.027, respectively) but femur neck BMD was not associated with serum OPG in women. No independent association was found between serum OPG and BMD in men after adjustments. In multivariable logistic regression analysis, serum OPG was associated with increased risk of osteoporosis in women, but was not in men (odds ratio [OR], 4.01; 95% CI, 1.27–12.67; P = 0.018; OR, 95% CI, 0.16–1.52; P = 0.311, respectively).

Conclusions: Serum OPG was independently associated with lumbar spine and total hip BMD and increased risk of osteoporosis in female CKD patients. However, these associations were not found in male CKD patients.

Funding: Government Support - Non-U.S.

FR-PO593

Growth in Children with Chronic Kidney Disease: A Report from the KNOW-Ped CKD (Korean Cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease)
Fujin Park,1 Yo Han Ahn,2 Kyoung Hee Han,2 Seong heon Kim,1 Joo Hoon Lee,2 Young seo Park,1 Hee Gyung Kang,1 Hae Il Cheong,1 Curie Ahn,1 IL Soo Ha,1 1Dept of Pediatrics, Seoul National Univ Children’s Hospital, Seoul, Korea; 2Dept of Pediatrics, Jeju National Univ School of Medicine, Jeju, Korea; 3Dept of Pediatrics, Pusan National Univ Children’s Hospital, Yangsan, Korea; 4Dept of Pediatrics, Asan Medical Center; Univ of Ulsan College of Medicine, Seoul, Korea; 5Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.

Background: Growth impairment is common in children with chronic kidney disease (CKD) and can negatively impact psychosocial impact. We investigated the characteristics of growth in Korean children with CKD.

Methods: Clinical characteristics along with anthropometric measurements were examined in subjects of KNOW-Ped CKD, Korean cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease. Findings of 322 children (M/F: 218:104), who were enrolled to the study from July 2010 to December 2013 in seven major pediatric nephrology centers of Korea, were analyzed to investigate the characteristics of growth in Korean pediatric CKD.

Results: Mean height- and weight- z scores of Korean pediatric CKD patients were -0.88±1.43 and -0.91±1.65. Mean BMI- z score was -0.36±1.25. Height deficit was observed from early stage of CKD with mean height- z score -0.42 in CKD stage I. Short stature (z score < -1.88, 20% of the subjects) and underweight (z score < -1.65, 28% of the subjects) were associated with female sex, age younger than 2-year-old at enrollment, co-morbidity, and advanced CKD stage. Low BMI was associated with high blood pressure, co-morbidity and younger age. The final height- z score was -0.86±1.19, which is shorter than predicted adult height- z score (-0.33±0.7) calculated from their parental height.

Conclusions: Growth failure is one of the most important complications in pediatric CKD patient. More profound height, weight and BMI impairment were associated with younger age and co-morbidity. Children with these findings need close attention on their growth and may require earlier intervention to avoid severe growth impairment.

Funding: Government Support - Non-U.S.

FR-PO594

Risk of Early Preterm Delivery in Pregnant CKD Patients – A Model for Counseling – The TOCOS Cohort (Torino Cagliari Observational Study)
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Background: Chronic kidney disease (CKD), whose prevalence almost equals preeclampsia in pregnancy, increases the risks of adverse pregnancy outcomes; the degree of decrease of serum OPG was significantly associated with lower BMD (lumbar spine, total hip and femur neck) compared with the lowest quartile of serum OPG in women. A homogeneously followed-up, low-risk preganant population served as controls. So far there are no largest Italian cohort dedicated to the multidisciplinary follow-up of CKD in pregnancy. Patients: Pregnant women with CKD: 503 live-born singletons in CKD: 835 low-risk controls (2000-2013). Measurements: Outcome: early pre-term delivery. The candidate variables were readily measurable, available, inexpensive (hypertension, proteinuria, kidney disease and function). Bootstraping was used for internal validation.

Results: Early preterm delivery was more frequent in CKD (12.5% vs controls (1%) (p<0.0001). The most parsimonious model (Likelihood ratio test p<0.0001; McFadden’s pseudo R²<0.2290) summarized various combinations of CKD stages, hypertension and proteinuria and defined a scale of risk. First step included CKD stage 1, normotension and proteinuria <1g/24h (OR:2.8); second step included CKD stages 2-5 without hypertension and proteinuria, and CKD stage 1 with either hypertension or proteinuria (OR:19.5 and 20.9); third step included CKD stages 2-5 with either hypertension or proteinuria (OR:44.7); the combination of hypertension and proteinuria was associated with the highest risk, but the low number of cases prevented precise quantification. Limitations: the study was performed in two Centers only. The number of cases with severe CKD is small.

Conclusions: The model may support counselling and clinical management by grading the risk for adverse pregnancy outcomes. Further studies are needed to externally validate the model.

Funding: Government Support - Non-U.S.

FR-PO595

Solitary Kidney Is Associated with a Higher Risk of Adverse Outcomes in Pregnancy
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Background: Chronic kidney disease is associated with adverse outcomes in pregnancy. Data regarding the effect of decreased glomerular filtration rate on pregnancy in women with a single kidney primarily has come from studies of kidney transplant recipients and living kidney donors. We set out to determine the risk of adverse outcomes in women with a single kidney from etiologies other than donation.

Methods: Using data from an integrated health care delivery system from 2000 through 2014, we conducted a study of 1,556 pregnant women hospitalized for childbirth. A total of 333 women had a single kidney with normal kidney function and were matched 1:3 by age and race to women with two kidneys. Adverse pregnancy outcomes included preterm delivery, delivery via cesarean section, preeclampsia/ eclampsia, length of stay at hospital and low birth weight (<2,500 g). Multivariable logistic regression analysis was used to examine the association between a single kidney and adverse pregnancy outcomes.

Results: Of the women with a solitary kidney, the mean (SD) age and mean (SD) gestational age at delivery was 28±6 years and 38±2 weeks, respectively. Compared to women with two kidneys, those with a single kidney had an increased risk of preterm delivery (OR 2.33, 95% CI 1.61-3.38), delivery via cesarean section (OR 1.85, 95% CI 1.33-2.56), and preeclampsia/eclampsia (OR 1.87, 95% CI 1.23-2.85). Women with a single kidney also had an increased risk of a length of stay < 3 days in the hospital (OR 1.50, 95% CI 1.01-2.20) and low infant birth weight (OR 2.99, 95% CI 1.95-4.59).

Conclusions: Women with a solitary kidney from causes other than kidney donation have a higher risk of adverse outcomes in pregnancy.

Funding: NIDDK Support

FR-PO596

Thiamine Deficiency in Non-Dialysis CKD Patients
Yukako Ohyama,1 Toshikazu Ozeki, Shun Minatoguchi, Hideaki Shimizu, Yoshiro Fujita,1 1Department of Nephrology and Rheumatology, Chubu Rosai Hospital, Nagoya, Japan.

Background: Thiamine deficiency is associated with malnutrition, alcoholism and chronic diseases such as cancer. Long use of diuretics also induces thiamine deficiency, which is due to an increased urinary loss of thiamine. Some papers report that thiamine tend to accumulate because of decreased urinary flow in chronic kidney disease (CKD) patients. Others report that a protein restricted diet causes thiamine deficiency in CKD patients. This study aimed to examine the prevalence and factors associated with thiamine deficiency in CKD patients.

Methods: This is a single center cross-sectional study in patients with non-dialysis CKD under regular follow-up in nephrology center of Chubu Rosai Hospital from July 1, 2014 to January 31, 2015. Patients who meet the CKD criteria of Japanese Society of Nephrology were selected. We used the data from the national renal, questionnaire, and nutrition surveys.

Results: The study population consisted of 149 patients aged 71.2 ± 10.9 years with estimated glomerular filtration rate <33 ± 2.1 (mean ± standard deviation) (1.73mL/min/1.73m2). They were divided into low thiamine group (serum thiamine level<30ng/ml) and high thiamine group (serum thiamine level³30ng/ml). In univariate comparisons, patients with low thiamine group had significantly lower protein intake which is estimated by the nutrition survey. The use of loop diuretics was not associated with thiamine deficiency. In multivariate analyses, high age, low eGFR and low protein intake, especially less than 0.8g/kg, were independently associated with thiamine deficiency.

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transplant and 25 glomerulonephritis, predominantly lupus). Most women were considered:

Pregnancy outcomes were analysed.

A year, renal biopsy, disease flare or rejection, and conversion back to mycophenolate.

Protein restriction for CKD patients especially with high age and low eGFR have a high risk of thiamine deficiency.

FR-PO597

Controlled Attenuation Parameter Measured by FibroScan Is Closely Associated with Microalbuminuria in CKD Patients.

Background: Hepatic steatosis can be determined by the measurement of liver controlled attenuation parameter (CAP) using FibroScan. Although the practical methods predicting the risk of metabolic syndrome (MS) development are lacking, recent studies report that this parameter is closely correlated with the presence of MS in the general population. Therefore, we investigated whether CAP measured by FibroScan could predict the presence of MS in chronic kidney disease (CKD) patients.

Methods: A total of 468 CKD patients evaluated. MS was defined by using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Multivariate logistic regression analysis was used to identify the independent association between CAP and MS.

Results: The mean age of the patients was 57.5 years and 225 patients (48.1%) were female. The mean value of CAP was 241.7 dB/m. CAP was independently associated with body mass index (β=7.818, P<0.001), triglyceride (β=0.246, P=0.002) and estimated glomerular filtration rate (eGFR) (β=0.581, P=0.005). MS was diagnosed in 142 (30.3%) patients. In patients with MS, diabetes was more prevalent (59.9 vs. 25.8%, P<0.001), hemoglobin (13.1±2.4 vs. 12.6±2.1 g/dL, P=0.026) and CAP (262.0±60.6 vs. 232.9±40.0 dB/m, P=0.001) levels were significantly higher, while eGFR (82.9±27.5 vs. 91.6±26.0 mL/min/1.73m², P=0.001) was lower compared with patients without MS. Multivariate logistic regression analysis revealed that high CAP levels were independently correlated with the increased risk of MS (per 1 dB/m increase, odds ratio=1.010, 95% confidence interval=1.002-1.018, P=0.014) after adjustment for confounding factors.

Conclusions: High CAP levels measured by FibroScan were significantly associated with an increased risk of MS in CKD patients. These data suggest liver FibroScan could be a practical method for evaluating the risk of MS development in CKD patients.

FR-PO598

Outcomes in Women Switched from Mycophenolate to Azathioprine in Advance of Pregnancy.

Background: Mycophenolate is teratogenic and should be replaced in advance of pregnancy. There is concern that this change may have adverse consequences including transplant rejection and disease flare. The aim of this study was to determine the risk of adverse outcome in women switched from mycophenolate to azathioprine.

Methods: Records of women attending regional renal pre-pregnancy counselling clinics 2011-2014 were examined. Women taking mycophenolate were included and the decision to switch to azathioprine was reviewed. Outcomes were a decline in eGFR within a year, renal biopsy, disease flare or rejection, and conversion back to mycophenolate. Pregnancy outcomes were analysed.

Results: Data were available for 60 women (31 kidney transplant, 4 kidney-pancreas transplant and 25 glomerulonephritis, predominantly lupus). Most women were considered eligible for a switch to azathioprine and one woman chose to switch against advice.

Conclusions: Protein intake is an important factor for thiamine levels of CKD patients. Protein restriction for CKD patients especially with high age and low eGFR have a high risk of thiamine deficiency.

FR-PO599

Controlled Attenuation Parameter Measured by FibroScan Is Closely Associated with Microalbuminuria in CKD Patients.

Background: Hepatic steatosis can be determined by the measurement of liver controlled attenuation parameter (CAP) using FibroScan. Although the practical methods predicting the risk of metabolic syndrome (MS) development are lacking, recent studies report that this parameter is closely correlated with the presence of MS in the general population. Therefore, we investigated whether CAP measured by FibroScan could predict the presence of MS in chronic kidney disease (CKD) patients.

Methods: A total of 468 CKD patients evaluated. MS was defined by using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Multivariate logistic regression analysis was used to identify the independent association between CAP and MS.

Results: The mean age of the patients was 57.5 years and 225 patients (48.1%) were female. The mean value of CAP was 241.7 dB/m. CAP was independently associated with body mass index (β=7.818, P<0.001), triglyceride (β=0.246, P=0.002) and estimated glomerular filtration rate (eGFR) (β=0.581, P=0.005). MS was diagnosed in 142 (30.3%) patients. In patients with MS, diabetes was more prevalent (59.9 vs. 25.8%, P<0.001), hemoglobin (13.1±2.4 vs. 12.6±2.1 g/dL, P=0.026) and CAP (262.0±60.6 vs. 232.9±40.0 dB/m, P=0.001) levels were significantly higher, while eGFR (82.9±27.5 vs. 91.6±26.0 mL/min/1.73m², P=0.001) was lower compared with patients without MS. Multivariate logistic regression analysis revealed that high CAP levels were independently correlated with the increased risk of MS (per 1 dB/m increase, odds ratio=1.010, 95% confidence interval=1.002-1.018, P=0.014) after adjustment for confounding factors.

Conclusions: High CAP levels measured by FibroScan were significantly associated with an increased risk of MS in CKD patients. These data suggest liver FibroScan could be a practical method for evaluating the risk of MS development in CKD patients.

FR-PO600

The Assessment of Incidental Risk for Microalbuminuria According to the Level of Depression Scale.

Background: Depression is one of the most common psychiatric disorders. The observed difference for depression goes beyond function and extends to somatic health. A growing body of evidence shows that depression is significantly associated with chronic kidney disease. Nonetheless, the incidental relationship between microalbuminuria and depression was not identified yet. Therefore, we conducted this study to investigate incidental relationship of microalbuminuria with depression scale.

Methods: This study was conducted for 45,293 Korean men and their spouses without microalbuminuria who got medical health check up in Kangbuk Samsung Total healthcare center in 2010. To assess the degree of their depression, Center for Epidemiologi Studi-EndoScale (CES-D) was used (CES-D ≤ 15: normal, CES-D 16-20: moderate risk group, CES-D > 21: high risk group). On the basis of CES-D score in 2010, they were classified into 3 groups (normal, moderate, high risk group) and monitored for the development of microalbuminuria from January, 2011 to April, 2015.

Results: While the general incidence was 1.7%, the incidence of microalbuminuria increased in proportion to the risk score of depression evaluated by CES-D (CES-D ≤ 15: 0.4%, CES-D 16-20: 1.8%, CES-D > 21: 3.6%). When the hazard ratio (HR) of normal group (CES-D ≤ 15) was set to reference value (HR: 1.00), the HRs for microalbuminuria also increased according to the score of CES-D scale. In addition, these associations were preserved even after adjusting for the various metabolic covariates such as age, physical activity, total cholesterol, LDL-cholesterol, triglyceride, body mass index, and obesity (CES-D 16-20: 1.98, CES-D > 21: 3.37).

Conclusions: Our study showed that the risks of microalbuminuria in proportion to the severity of depression. These findings imply the clinical role of the depression for
FR-PO601
Outcomes in CKD Patients with Hospital Acquired Complications
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Background: Patients with CKD are at increased risk of hospital acquired complications (HACs) including those considered preventable. The impact of HACs on patient and health system outcomes has not been well described.

Methods: Subjects hospitalized from April 1, 2003 to March 31, 2008 from a population based cohort (Alberta Kidney Disease Network) were studied. Outpatient eGFR and proteinuria (protein/creatinine ratio or dipstick) in the year prior to index hospitalization were used to define CKD status. Co-morbid conditions were identified using validated algorithms applied to administrative data. ICD 10 CA was used to classify reason for admission. A specific diagnostic indicator (type II) was used to identify hospital acquired complications (HACs) that were sub-classified as “potentially” and “always” preventable.

We studied the following outcomes: re-admission within 90 days of discharge, all cause mortality at 90 days, and index hospitalization costs. Multivariable regression models examined the association of HACs with re-admission, mortality, and incremental health care costs, accounting for confounders.

Results: Of 536,549 subjects, 45,377 (8.5%) with CKD were hospitalized. In patients with HACs, the OR of re-admission and death at 90 days was 1.37 (95% CI: 1.32 – 1.43), and 3.11 (95% CI: 3.06 – 3.58) respectively compared with those without HAC. Hospitalizations with any HAC were associated with incremental health costs of $4028 (95% CI: $3898 – $4158). A graded association was observed for those outcomes with increasing number of HACs and severity of CKD. Similar results were noted when only potentially preventable HACs were considered.

Conclusions: Complications occurring during hospitalization in patients with CKD is independently associated with an increased risk of hospital re-admission, health care costs, and mortality. Targeted strategies to reduce HACs in this patient population may have a significant benefit.

FR-PO602
Plasma Proteins Associated with Declining Renal Function in Patients with Type 1 Diabetes: Results of a Global Proteomic Analysis Using SOMAscan Platform
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Background: Increases in serum creatinine and cystatin C are considered measures of declining renal function in patients with diabetes.

Methods: To search for other proteins correlated with declining renal function, we conducted a follow-up study, following 30 patients with T1D and proteinuria for 1-3 years. Mean eGFR was 67 ml/min at baseline, and was 59 ml/min at the end of follow-up. Plasma samples were stored at -80°C. Proteins were measured on the SOMAscan platform at baseline and at the end of follow-up. The platform measured 954 proteins for each of the 30 patients, with median limit of detection (LOD) of 1.6pg/mL/dynamic range of 8 logs, and median coefficient of variation (CV) of 5% for individual proteins measured repeatedly in replicate runs of plasma samples.

Results: Renal function change during follow-up in each patient was expressed as the difference between eGFRcre at baseline and at follow-up and was referred to as ∆GFR in replicate runs of plasma samples. 30 patients, with median limit of detection (LOD) of 1.6pg/mL,dynamic range of 8 logs, mean eGFR was 67 ml/min at baseline, and was 59 ml/min at the end of follow-up. Mean eGFR was 67 ml/min at baseline, and was 59 ml/min at the end of follow-up. Spearman rank correlation coefficient between ∆GFR and the percent change in the protein’s level (RFU) (mean: -7.7 ml/min, range: -44 ml/min to 11 ml/min). For each protein, the Spearman rank correlation coefficient between ∆GFR and the percent change in the protein’s level (RFU) (mean: -7.7 ml/min, range: -44 ml/min to 11 ml/min).

Conclusions: In conclusion, increasing or decreasing concentrations of plasma proteins with cold grant loss may reflect worsening renal function, as is the case with cystatin C. However, changes in plasma concentration of these proteins may represent the extent and intensity of the disease process underlying progressive renal decline, which is most likely the case with IL-1β and the TNFR-β.

FR-PO603
Mass Spectrometry Imaging Reveals Disease Specific Alterations in Protein Abundance in Human Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) is a major complication in diabetic patients. However, the progression and development of DN are characterized by multiple pathophysiologic changes. We examined MALDI mass spectrometry imaging (MSI) to discover alterations in protein expression in human DN glomeruli and compared to the morphology and clinical features.

Methods: DN biopsies (n=36) and normal kidney (n=9) were assessed. Complete nephrobiology findings were divided into mild, moderate and severe, based on biopsy findings. Follow-up was available in 23 patients, and patients were sub-grouped into stable DN (decreased eGFR 50-70 ml/min/1.73 m², progressive 50-70 ml/min/1.73 m², and fibrotic DN). Matrix-assisted laser desorption/ionization mass spectrometry (MALDI) is a technology that acquires molecular information from thin tissue sections in a spatially-defined manner. We examined MALDI mass spectra to discover alterations in protein expression in human DN glomeruli and compared to the morphology and clinical features.

Results: DN patients had reduced eGFR and increased proteinuria, compared to normal. Mass spectrometry showed 168 peptide peaks, with 8 peaks increased and 21 peaks decreased in DN compared to Normal. Moderate and severe DN showed more nodular glomerulosclerosis than mild DN by study design (moderate 2.13±0.10, severe 2.17±0.22 vs. mild 0.43±0.30, 0.4+ scale, p<0.05) and mesangial expansion (moderate 1.97±0.09, severe 2.28±0.15 vs. mild DN 1.21±0.15, p<0.05). Peptide maps were more similar in moderate vs severe DN groups, compared to mild DN. Thirteen of 168 peptide peaks were significantly different between the three groups. In progressive DN, 10 peptide peaks were decreased and 1 was increased, compared to stable DN. Of note, these peaks differed from those associated with the morphologic phenotype.

Conclusions: We conclude that different peptide maps correlate with DN onset, severity and prognosis, and that clinical and morphological phenotypes have differing proteomic correlates. These peptides will now be further validated and identified by MS/ MS fragmentation and database searching.

Funding: NIDDK Support.

FR-PO604
Urine Metabolomic Profiling Reveals a Unique Signature for Type 2 Diabetes
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Background: Increases in circulating branched chain amino acids (BCAA) are associated with type 2 diabetes (T2D) and insulin resistance. However, it is not clear whether increased plasma BCAA concentrations result from increased synthesis, or impaired degradation or excretion. Here, we employ a targeted metabolomics approach to evaluate diabetic patients without overt kidney disease to identify urine metabolites associated with T2D, presenting potential urine biomarkers for clinical prediction and further insight into disease pathogenesis.

Methods: We measured 105 urine metabolites by GC/MS in a screening T2D cohort (n=27), validation T2D cohort (n=14), and healthy control group (n=23). We also examined kidney cortex of db/db and control db/+ mice to measure gene expression by Illumina microarray and protein expression by western blot.

Results: Following FDR correction, 57 metabolites were found to be different in the screening cohort compared to controls. When these 57 metabolites were carried forward for analysis in a validation T2D cohort, 24 of these urine metabolites were confirmed to be different from controls using Bonferroni adjustment for multiple comparisons. 16 of the 24 confirmed metabolites were amino acids, and 8 of these represented BCAA degradation products. To further investigate BCAA metabolism, we examined kidney tissue from db/db mice and found that the gene expression of key enzymes related to BCAA catabolism was decreased. Western blot studies confirmed that renal expression of branched-chain ketoacid dehydrogenase, a mitochondrial enzyme complex that catalyzes an irreversible step in BCAA catabolism, was reduced in db/db mice compared with controls.

Conclusions: Prior studies have reported impaired mitochondrial BCAA metabolism in adipose, muscle and liver. However, our results show a robust pattern of increased BCAA concentrations, likely reflecting increased BCAA catabolism and/or increased metabolic flux. The reduced renal expression of BCAA enzymes supports a role for dysregulated BCAA metabolism by the kidney. The elevated BCAA metabolism may have an effect on regulating insulin resistance and the development of kidney disease with T2D.

Funding: NIDDK Support.

FR-PO605
Urineary Matrix Metalloproteinase Activities Are Associated with Renal Hyperfiltration in Adolescents With Type 2 Diabetes
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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. Matrix metalloproteinases (MMP) modify extracellular matrix during vascular remodeling and are known to be elevated in diabetes, and associated with DN in type 1 diabetes. We hypothesized that activities of latent MMP and neutrophil gelatinase-associated lipocalin (NGAL) proteins in urine would be associated with microalbuminuria and hyperfiltration in adolescents with type 2 diabetes (T2D).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Methods: 295 adolescents with T2D (14.0±1.8 years, <2 years duration, BMI ≥85%, and HbA1c ≤5%) in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study had urine and blood evaluated at baseline and annually for 5 years. MMP2, MMP9 and NGAL activities were measured by gelatin zymography and normalized to urine creatinine. Microalbuminuria was defined as albumin-to-creatinine ratio (ACR) ≥30mg/g. Estimated GFR was calculated by Schwartz (eGFR=36.5height/creatinine) and hyperfiltration defined as ≥135mL/min/1.73m². Mixed models evaluated the longitudinal relationships between MMP-2, MMP9 and NGAL with eGFR, ACR, hyperfiltration and microalbuminuria respectively. MMP2, MMP9 and NGAL-MMP9 activities were natural log-transformed (ln) due to skewed distribution.

Results: MMP2, MMP9 and NGAL-MMP9 were associated with eGFR, but not ACR over time after adjusting for age, sex, HbA1c, SBP and treatment group. One standard deviation increase in ln MMP2, ln MMP9 and ln NGAL-MMP9 was each associated with 0.03, 0.046 and 0.001 decrease in ln ACR, respectively. MMP2, MMP9 and NGAL-MMP9 activities were each associated with 1.2, 1.0 and 1.2 increase in ln MMP2, ln MMP9 and ln NGAL-MMP9, respectively. MMP2, MMP9 and NGAL-MMP9 activities were each associated with 0.03, 0.046 and 0.001 decrease in ln ACR, respectively. MMP2, MMP9 and NGAL-MMP9 activities were each associated with 1.2, 1.0 and 1.2 increase in ln MMP2, ln MMP9 and ln NGAL-MMP9, respectively.

Conclusions: Inclusion, urinary MMP and NGAL activities were associated with early DN in adolescents with T2D over time. Funding: Other NIH Support - Juvenile Diabetes Research Foundation Grants 1-2007-62 (K. S. Moulton) and 5-2008-291 (K. Nadeau); National Institutes of Health Grants R4C DK090852 (K. S. Moulton) and K23 RR020038 (K. Nadeau).

FR-PO606
A Serum Metabolite Classifier Predicts Response to ARBs in Diabetes
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Background: Individual patients show a large variability in albuminuria response to Angiotensin Receptor Blockers (ARB). Identifying novel biomarkers that predict ARB response may help optimize treatment. We aimed to discover and validate a novel serum metabolite classifier that predicts response in urinary albumin excretion (UAEx) to ARBs in diabetes.

Methods: Flow injection analysis/liquid chromatography-tandem mass spectrometry based targeted metabolomics was performed on serum samples from type 2 diabetes patients (n=49) enrolled in a clinical study assessing the effect of irbesartan 300mg/day. Individual serum metabolites were selected with LASSO regression to predict UAEx response to irbesartan. The classifier was developed with ridge regression. Improvement in risk prediction was tested on top of a control model (age, sex, HbA1c, SBP, GFR, UAE) by assessing differences in explained variation (R2) between the control model and the classifier model. The classifier was externally validated in a clinical study in type 1 diabetes patients (n=50) testing the effect of losartan 100mg/day. Metabolite mapping was performed on a molecular model of diabetic kidney disease to identify underlying molecular processes contributing to ARB response.

Results: The classifier included 21 metabolites. Median reduction in UAEx was -42% [-69.8 to 1.9] in type 2 diabetes. The classifier was significantly associated with UAEx response to irbesartan (p<0.001) and significantly improved prediction of UAEx response on top of the control model (R2 increase from 0.10 to 0.69, p<0.001). In the external validation cohort, median reduction in UAEx was -43% [-62.2, 23]. The classifier significantly improved prediction of UAEx response to losartan (R2 increase from 0.17 to 0.52, p<0.001). Metabolites included in the classifier were assigned to stress/inflammation pathways and downstream consequences of fibrosis and extra cellular matrix remodeling. Moreover, ADMA, impacting eNOS activity, appears to be a specific factor relevant in ARB response.

Conclusions: A classifier of 21 serum metabolites was identified and externally validated to significantly improve prediction of albuminuria response to ARBs in diabetes.

FR-PO607
Is Urinary Proteomics Useful to Predict Retinopathy in Type 2 Diabetic Patients in the DIRECT Study
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Background: Diabetic microvascular complications affect the kidney and the eyes, being a leading cause of renal failure and blindness. Urinary proteomics has shown promise as an early indicator of future development of diabetic nephropathy. Here we investigate if this could also predict progression of diabetic retinopathy.

Methods: In a post-hoc study of the DIRECT 2 study, a randomized, controlled clinical trial of candesartan for prevention of retinopathy, we studied patients with type 2 diabetes and normoalbuminuria (n=792), followed for a mean of 4.7 years. We address the predictive value of urinary exosomal gelatinase and ceruloplasmin expression based on urine and blood assessed at recruitment of 273 urinary peptides (CE-MS). We also assessed the possibility of a new EYEscore based on discriminative features chosen out of 1161 peptides in a training set of 528 patients. Progression were either 2 step (E2) (primary) or 3 step (E3) (change in retinopathy on the concatenated Early Treatment Diabetic Retinopathy Study severity scale).

Results: Progression of retinopathy was seen in 37% of E2 and 19% of E3 patients. None of the peptides were significantly differently expressed in cases vs control. In Cox models five peptides were associated with E3 but not E2 in the training set but were not validated. The CKD classifier was able to predict E3 (HR 1.54 95% CI 1.02 to 2.13, p=0.042) but not E2 (HR 1.14 p=0.34) during follow-up, independent of treatment (candesartan/placebo), age, gender, systolic BP, baseline UAER, baseline eGFR, HbA1c, and diabetes duration.

Conclusions: In this cohort of patients with type 2 diabetes and normoalbuminuria from a large intervention study, the CKD classifier was an independent predictor of severe but not mild progression in retinopathy. It was not possible to develop a retinopathy specific marker panel with clinically relevant accuracy.

FR-PO608
Urinary Exosomal Analysis Reflects Underlying Kidney Pathology Better Than Whole Urine Analysis
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Background: Predicting or diagnosing underlying kidney pathology by analyzing whole urine has remained unrealized. This is because whole urine mostly represents proteins from the plasma and little from the kidney. Urinary exosomes, on the other hand, being kidney-derived, contain proteins of the kidney. We experimentally tested the hypothesis, ‘urine exosomal proteome more truly represents the underlying pathology of kidney disease than a whole urine based analysis.’ Comparison between whole urine and urine gelatinase and ceruloplasmin, two kidney disease markers, was performed on normal and diabetic kidney disease patients.

Methods: Urinary exosomes were separated from urine by ultra-centrifugation. Gelatinase, an enzyme which measures matrix degrading activity collectively from whole urine and exosomes (mainly MMP-2, 9) was measured using fluorosceinated gelatin as the substrate, and ceruloplasmin, an oxido-reductase enzyme involved in iron metabolism, was measured by sandwich ELISA. Biopsies were immunostained for MMP-9 and ceruloplasmin.

Results: We found that changes in both, gelatinase (decreased activity; 20-50%; p<0.05) and ceruloplasmin (increased levels; 300%; p<0.05), in the urinary exosomes of diabetic kidney patients were in agreement with the alterations of these two proteins in the kidney tissue as judged by immune-staining. In contrast, the levels of these two proteins in the whole urine were highly variable (p>NS) and in disagreement with the results of immune-staining.

Conclusions: In conclusion, our findings support our hypothesis that protein markers found in urinary exosomes better reflect the changes in the kidney than protein measurements carried out in whole urine samples.

FR-PO609
Neutrophil Gelatinase Associated Lipocalcin as an Early Biomarkers of Nephropathy in Diabetic Patients and Effect of RAAS Blockade on NGAL as Marker of Tubular Damage in Diabetic Nephropathy
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Background: T2DM is the primary cause leading to kidney disease. Novel, more sensitive biomarkers that may be used to detect diabetic nephropathy at an early stage, and possibly also detect disease progression or regression after drug therapy.

Methods: 150 Diabetic patients were enrolled in the study from nephrology and endocrinology OPD at Sanjay Gandhi Post Graduate Institute Of Medical Sciences, Lucknow India from 2012-14, 50 each of normo-, micro- and macroalbuminuric with 50 normal healthy control. Serum NGAL and cystatin C were measured at enrollment and after 12-15 months. ACEI as intervention was given in all normo hypertensive ,microalbuminuric and macroalbuminuric Diabetics. After follow up period 1 year repeat NGAL levels assessment. Normoalbuminuric ,normotensive individuals with raised NGAL at the baseline and follow up after 1 year were assessed.

Results: As compared to control population the normoalbuminuric Diabetics had higher levels as well as urinary NGAL levels but lesser than microalbuminuria.Mean NGAL levels were not significantly different between Normoalbuminuric and diabetics. At re-evaluation, mean NGAL value and mean eGFR value in patients with diabetes had increased (p=0.078 and p=0.006 respectively). At both baseline and reevaluation, NGAL positively correlated with cystatin C (p<0.001) and creatinine (p<0.010). NGAL correlated negatively with eGFRr (r= -0.26, p=0.049). Among micro,macroalbuminuric diabetes the baseline urine albumin excretion rate was significantly correlated with the rate of eGFR
Mechanism of Increased Urinary Full-Length Megalin Excretion in Type 2 Diabetes Mellitus Patients with Nephropathy

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Background: Megalin, an endocytic receptor of proximal tubule cells (PTCs), is excreted into urine in both of the extracellular domain and the full-length forms. Previously we developed urinary ELISA systems to measure the two forms of megalin and found that the excretion of the full-length form, mainly present in the insoluble urinary fraction, may be a candidate biomarker for the progression of diabetic nephropathy (DN). We thus aimed to investigate the molecular mechanism of urinary excretion of the full-length form of megalin.

Methods: Megalin content of urinary extracellular vesicles (EVs) from normal control and type 2 diabetes mellitus (T2DM) patients with different albuminuria stages were measured by western blotting. By immunoelectron microscopy and Nanoparticle Tracking Analysis using NanoSight®, we characterized the size and number of the EVs. To study increased EVs' excretion in vitro, we cultured immortalized rat proximal tubule cells (IRPTCs) and treated with advanced glycation end products-modified bovine serum albumin (AGEs).

Results: The number of urinary EVs' excretion is increased in T2DM patients in comparison with the normal control subjects in a correlation with the progression of DN. By immunoelectron microscopy we found that megalin is excreted through the smaller vesicles which are likely to be excreted through AQP5 and AQP2, expressed at the plasma membrane, thus allowing their quantitation in urine samples.

Conclusions: Exocytosis-mediated urinary excretion of full-length megalin via exosomes might be a useful biomarker for early detection and progression of DN.

Funding: Government Support - Non-U.S.

FR-PO612

Urinary Neutrophil Gelatinase-Associated Lipocanal as Complementary to Albuminuria Biomarker of Early Stage Diabetic Kidney Disease in Type 2 Diabetes

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Background: Two clinical phenotypes of diabetic kidney disease (DKD) have been reported, i.e. with or without increased albuminuria. The aim of this study was to assess the usefulness of uNGAL for the preclinical diagnosis of DKD in the course of diabetic mellitus type 2 (DM2).

Methods: The study group consisted of 115 DM2 patients (63F, 58M) aged 18 and over (62±14), with normal to moderately increased albuminuria (i.e. urine albumin/creatinine ratio (UACR) <300 mg/g) and eGFR (CKD-EPI) ≥60ml/min/1.73m. Control group included 22 non-diabetic persons with comparable age (57±14; p=0.1) and sex (9F, 13M; p=0.5), and with similar comorbidities. Urine concentrations of uNGAL, albumin and creatinine (uCr) were measured in the first morning urine sample. Urine albumin/creatinine ratio (UACR), and analogically, uNGAL/uCr were calculated.

Results: In control group, maximum UNGAL/uCr was 39.64 μg/g. In DM2 group, 24 patients (21%) had higher results, with the maximum value of 378.6 μg/g. Twenty three (20%) of DM2 patients had UACR >30 mg/g; of those, 11 had uNGAL/uCr >39.64 μg/g. Among patients with uNGAL/uCr >39.64 μg/g, 13 did not have markedly increased albuminuria (UACR in those patients ranged from 2.35 to 16.10 mg/g). Women with DM2 had significantly higher uNGAL/uCr than men (median 28.06; IQR 9.55-65.60 versus 11.40; 3.36-18.02 μg/g; p=0.001), without significant difference in UACR (p=0.09). uNGAL/uCr in DM2 patients correlated significantly with Hba1C (R=0.28; p<0.013), however, it did not correlate with eGFR (R=0.54; p=0.1), age (R=0.14; p=0.1), or time from DM2 diagnosis (R=0.13; p=0.1).

Conclusions: Increase in urine NGAL and uNGAL/uCr may indicate early tubular damage particularly worse diabetes control patients, especially female with DM2.

Funding: Private Foundation Support, Clinical Revenue Support
The Expressions of Vitamin D and Its Receptor in Patients with Diabetes Associated with Proteinuria and Diabetic Nephropathy

FR-PO615

**Methods**: The prospective follow-up study; 114 diabetes patients were followed for 5.0 ± 1.1 years. Patients were divided at baseline into three groups according to their urinary albumin-to-creatinine ratio (UACR): 68 patients with normoalbuminuria (UACR < 30 mg/gCr), 31 patients with microalbuminuria (30 mg/gCr ≤ UACR < 300 mg/gCr), and 17 patients with macroalbuminuria (UACR ≥ 300 mg/gCr). Progression of albuminuria was the main outcome. Omentin was measured by ELISA, and the values were adjusted for age, BMI, and sex before analysis.

**Results**: Progression either to the next albuminuria level in 16 patients or to end-stage renal disease (ESRD) occurred in 5 patients. No difference in adiponectin concentrations was observed between progressors and nonprogressors in patients with normoalbuminuria. In the patients with microalbuminuria and macroalbuminuria, progression of albuminuria was associated with higher omentin. Progression to ESRD was also associated with estimated glomerular filtration rate (eGFR). When these covariates were included in a Cox regression analysis, eGFR and omentin were significantly associated with progression of albuminuria.

**Conclusions**: Increased serum omentin levels predict the progression from microalbuminuria to macroalbuminuria and progression of albuminuria was associated with higher omentin. Progression to ESRD was also associated with estimated glomerular filtration rate (eGFR). When these covariates were included in a Cox regression analysis, eGFR and omentin were significantly associated with progression of albuminuria.

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**Background**: Vitamin D receptor (VDR) is a member of the nuclear receptor superfamily, and there was no report about the expression of Vitamin D and its receptor in patients with diabetes associated with proteinuria and diabetic nephropathy. So, this study aimed to test the expression trends of VDR in blood, urine specimens and renal tissues of diabetic nephropathy patients, and the relationship with urinary protein, to explore the role of VDR in diabetic nephropathy.

**Methods**: 1. 65 patients who had been diagnosed with T2DM (with or without albuminuria) were enrolled in this study and 25 healthy control subjects were enrolled (NC group). The patients were classified according to the ratio of urinary excretion of albumin/creatinine (ACR). Diabetic patients without proteinuria (DM group, ACR: less than 30 mg/g, n = 25), with microalbuminuria (DN group, ACR: 30 to 300 mg/g, n = 24) and clinical proteinuria (DN2 group, ACR: more than 300 mg/g, n = 18). 2. The expressions of VD and VDR levels in the plasma and urine supernatant were measured by ELISA, and the VDR in blood cells was measured by qRT-PCR. The expressions of VD in kidney tissue were measured by immunohistochemical staining.

**Results**: Plasma VD and VDR levels were significantly lower in DN2 and DN3 groups as compared with NC group (plasma VD 0.78±0.24 and 0.88±0.29 vs. 2.32±1.33 mg/ml P<0.05, VDR 157.52±98.36 and 164.20±64.50 vs. 325.33±194.68 mg/ml P<0.05).[cite2] Urinary VD and VDR levels were significantly elevated in DN2 and DN3 groups as compared with NC group (urinary VD 1.34±0.58 and 1.42±0.44 vs. 1.18±0.56 mg/ml P<0.05, VDR 83.60±31.78 and 88.40±28.10 vs. 60.93±12.03 mg/ml P<0.05). The expressions of VD in kidney tissue in DN groups were obviously lower than those in control groups, differences were statistically significant (P<0.05).

**Conclusions**: These results verify that VDR declined with the increase of the amount of urine protein. Based on these results, VDR may play a role of renal protection in diabetic nephropathy.
FR-PO619
Macrophage Accumulation and Phenotype in Human Diabetic Nephropathy

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**Background:** Macrophage, especially its distinct phenotype is involved in the progress of DN. M1 is characterized with pathogenic function, while M2 displays anti-inflammatory. This study tries to examine the macrophage phenotype and its relationship to the renal function and histological changes in human DN.

**Methods:** We studied retrospectively 46 patients with DN who were confirmed by diagnosis of renal biopsy. Biopsies were divided into I Ha Ib III IV classes according to the pathologic classification of DN. Patients with renal trauma or renal tumor were considered as control group. Serum creatinine, proteinuria were calculated. Kidney tissues were used to assess histological changes and the presence of macrophage marker CD68, M1 marker iNOS, M2 marker CD206, Arg-1, TREM1 and TREM2.

**Results:** In biopsy renal tissue of human DN, Expression of CD68, M1 were significantly increased in the glomeruli (2.835±1.045/gcs VS 1.203±0.547/gcs for normals P<0.031; 2.330±1.343/gcs VS 0.896±0.548/gcs for normals P=0.046) and interstitium (0.037±0.142%area VS 0.019±0.02%area P=0.016; 0.018±0.08%area VS 0.009±0.05%area P=0.023). While M2 were mainly observed in the interstitium (0.019±0.008%area VS 0.010±0.004%area P=0.038). Interstitium M2 correlated strongly with interstitium M1 infiltration. Additionally there was a positive correlation between the glomerular CD68, M1 numbers and serum creatinine (r=0.619, p=0.001; r=0.463, p=0.017), proteinuria (r=0.641, P=0.000; r=0.508, P=0.008), mesangial matrix, interstitial collagen deposition. Likewise, the expression of interstitial CD68, M1, M2 also correlated strongly with serum creatinine (r=0.638, P=0.000; r=0.606, P=0.001; r=0.520, P=0.006), proteinuria (r=0.749, P=0.000; r=0.651, P=0.000; r=0.694, P=0.000), mesangial matrix, interstitial collagen deposition. Besides TREM1,2-positive cells were apparent in the interstitium and the expression levels significantly correlated with interstitium M1,M2 expression respectively.

**Conclusions:** Macrophage infiltration and polarization participate in the development of diabetic nephropathy.

**Funding:** Government Support - Non-U.S.

FR-PO620
Risk of Diabetes Increased According to the Level of Urinary Albumin Excretion Even Within Normal Range

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**Background:** Urine albumin creatinine ratio (UACR) as a reliable index of urinary albumin excretion is getting great attention on its predictive role for various diseases related with diabetes. Nevertheless, predictive value of UACR within normal range was not clarified for diabetes yet. Therefore, this study was aimed at examining the clinical association between normal range of UACR and development of diabetes.

**Methods:** We identified 1,274 non-diabetic Korean men within normal range of UACR in 2005, and followed them up until 2010. All subjects were classified into three categories corresponding to normal range of UACR and development of diabetes.

**Results:** During follow-up, diabetes developed in 97 out of 1,274 subjects (7.6%). Incidence rate of diabetes increased in proportion to the levels of UACR (tertile 1: 4.9%, tertile 2: 7.3%, tertile 3: 10.6%, P<0.001).

**Conclusions:** Elevated UACR, even within normal range, was significantly associated with the future development of diabetes.

FR-PO621
Albuminuria Is Positively Associated with Elevated Numbers of Circulating Endothelial Pre- and Mature Cells, but Inversely Associated with Circulating Fibrocytes

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**Background:** Diabetic nephropathy is characterized as a microvascular disease with enhanced vascular leakiness in the kidney and aberrant tissue remodelling. Abnormal number and function of endothelial cells, stem cells and activation of leukocytes is considered as contributing mechanisms to the “kidney-micro”-vascular leaky syndrome. We determined if circulating endothelial pre- and mature cells, fibrocytes or monocyte sub-populations were abnormally regulated in type 2 diabetic patients with albuminuria.

**Methods:** Cross-sectional study of 37 type 2 diabetic patients; 18 with normalalbuminuria (<30mg/24h) and 19 with albuminuria (30mg/24h). 8-color flow cytometry analysis of peripheral blood was performed. ANCOVA compared expression of cell markers and absolute number of specific cell populations in patients with normoalbuminuria vs. albuminuria.

**Results:** Expression of VEGFR2 was significantly enhanced in patients with albuminuria (p=0.009). Also, the total number of circulating mature endothelial cells (CEC) was significantly enhanced in albuminuria (p=0.001). Circulating fibrocyte number and collagen-1 expression was inversely associated with albuminuria (p=0.037) and TGFbeta stabilizing and M2-associated galectin-3 expression on M1-like and M0-like monocytes was positively associated with albuminuria (p=0.029). In contrast, expression of the M1-associated marker CD11c (p=0.042) was inversely associated with albuminuria on all monocytes, particularly on M0-like macrophages (p=0.014).

**Conclusions:** The enhanced number of CEC together with elevated expression of VEGFR2 may indicate an aberrant function of the CEC with reduced capacity to seal the kidney microvascular disease. The imbalanced M2-polarization of monocytes and aberrant fibrocyte count may favour improper repair leading to excessive tissue fibrosis. Hence therapeutic approaches addressing migratory pattern of CEC, providing adjuvant activating signals or restoring the immune balance might provide novel individualized treatment regimes.

**FR-PO622
Prognostic Value of Tubulointerstitial Lesions and Urinary N-Acetyl-b-D-Glucosaminidase in Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Nephropathy

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**Background:** Recently, it has been reported that some biomarkers of renal tubular injury are useful to predict the renal prognosis in the early stage of diabetic nephropathy (DN). However, how closely such biomarkers reflect actual tubulointerstitial damage remains unknown.

**Methods:** Among 210 patients with type 2 diabetes and biopsy-proven DN, 152 patients were enrolled, 89% of whom had overt proteinuria. The endpoint was defined as a 50% or more decrease of the estimated glomerular filtration rate (eGFR) from baseline to the outcome even after adjustment for those covariates (+1 for IFTA score, HR: 2.20 [95% CI: 1.50-3.21]). On the other hand, the IFTA score was significantly related to the outcome even after adjustment for those covariates (+1 for IFTA score, HR: 0.87 [95% CI: 0.66-1.13]). On the other hand, the IFTA score was significantly related to the outcome even after adjustment for those covariates (+1 for IFTA score, HR: 2.20 [95% CI: 1.50-3.21]).

**Results:** A significant correlation was found between baseline urinary N-acetyl-b-D-glucosaminidase (NAG) excretion and the score for interstitial fibrosis and tubular atrophy (IFTA score) (r=0.39, P=0.001). The influence of urinary NAG on the renal prognosis was attenuated after adjustment for known promoters of progression (+1SD for log NAG, HR: 0.87 [95% CI: 0.66-1.13]). On the other hand, the IFTA score was significantly related to the outcome even after adjustment for those covariates (+1 for IFTA score, HR: 2.20 [95% CI: 1.50-3.21]).

**Conclusions:** The assessment of urinary NAG excretion did not improve the prognostic power of known indicators of progression, whereas the IFTA score did. The IFTA score may be more useful for predicting the renal prognosis than current tubulointerstitial markers, especially in patients with advanced DN.

**Funding:** Private Foundation Support
**FR-PO623**

Is There Any Benefit of Performing Renal Biopsies in Patients with Diabetic Nephropathy when No Other Diagnosis Than Diabetic Nephropathy Is Found?

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**Background:** The risk of renal biopsy has long been thought to outweigh the benefit of performing these on patients with diabetes mellitus (DM) leading to small numbers of renal biopsies in this population. Those biopsied have a propensity to more proteinuria or haematuria precipitating biopsy. Glomerular lesions alone have long been the hallmark of diabetic nephropathy (DN) however looking back at the biopsy can there be more to see?  

All native renal biopsies diagnosed with DN from 2009-2014 were retrieved from archive at Guy’s & St Thomas’ NHS foundation trust. Renal biopsies were performed in patients with DM who had heavy proteinuria or haematuria on presentation. Biopsies with a DN diagnosis alone were identified and Tervaert’s new DN classification was applied. Clinical outcome data was collected from electronic patient records. Cox regression models were used to perform statistical analysis.  

**Results:** 3000 native kidney biopsies were performed from 2009-2014. 34 DM patients had DN alone on renal biopsy, 12 T1DM and 22 T2DM. 20 male, 14 females. Ethnicity: 35% white, 35% black, 3% asian, 27% other. Age range: 24-86 years (median 55). UPCR: 13.492 mg protein/mmol creatinine (median 392) eGFR: 7-74.9 (median 23). 8.8% 5 year mortality. Glomerular IV and Interstitial fibrosis III lesions were significant predictors of mortality. Glomerular IV and Interstitial fibrosis III lesions were significant predictors of mortality. Glomerular IV and Interstitial fibrosis III lesions were significant predictors of mortality.  

**Conclusions:** Interstitial fibrotic lesions are as important as glomerular lesions in predicting renal survival. Determining the significance of the compartments in predicting outcome may be more sensitive; however few biopsies are undertaken in this population. The role of an earlier renal biopsy showing less well established features in the DN population that could be reversed may need to review our practice unless sensitive and specific biomarkers are found to correlate with the underlying histopathology.

**FR-PO624**

Understanding the Relationship Between Histopathology and Renal Function in Hypertension and Diabetes

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**Background:** Much of the literature relating clinical and pathologic variables in patients with diabetes mellitus (DM) and hypertension (HTN) has relied on biopsy series. To gain unbiased insight into the degree of interstitial fibrosis (IF) and glomerular sclerosis (GS) associated with decline of renal function in DM and HTN, we have correlated histopathology with renal function, DM and HTN status in patients undergoing tumor nephrectomies.  

**Methods:** Data and renal tissue were collected on nephrectomy patients from 7 centers. We used Spearman correlation coefficients to compare eGFR with pathologic assessment of IF and GS (manual count). Bivariate linear regression was used to test the association between log-transformed percent IF or GS and eGFR, stratifying by presence of DM or HTN.  

**Results:** Of 251 patients, there were 60 without DM or HTN, 89 with HTN alone, and 102 with DM (+/- HTN). Median age was 62, 42% were female, 60% were Caucasian, median systolic blood pressure was 134 mmHg, and median eGFR was 66.5. There was a significant association between decline in eGFR and both IF (rho=-0.50, p<0.01) and GS (rho=-0.53, p<0.01). eGFR of 60 was associated with a geometric mean (95% CI) IF and GS of 7.3% (5.1-10.3) and 8.3% (5.7-12.1) for patients without DM or HTN, 9.2% (7.5-11.2) and 9.9% (8.1-12.1) for patients with DM or HTN, and 10.9% (8.8-13.5) and 9.6% (8.0-11.6) for patients with DM and HTN. Stage 3 CKD was associated with a median IF and GS of 10% (IQR 8.7-10.8) for patients with HTN, and 10.9% (8.8-13.5) and 9.6% (8.0-11.6) for patients with DM. Stage 3 CKD was associated with a median IF and GS of 10% (IQR 5-15) and 11.3% (IQR 5.7-18.8) overall, and with median IF and GS of 10% (IQR 5-20) and 11.9% (IQR 5.7-20.8) in DM.  

**Conclusions:** While IF and GS are similar at a given eGFR, patients with DM have a trend toward a greater degree of IF and GS at the same level of eGFR compared to those with isolated HTN. Stage 3 CKD is associated with median IF of 10% though there is high inter-individual variation. This highly variable histopathology should be considered when patients with DM are included into clinical studies, and kidney biopsies might be useful to include in categorization.  

**Funding:** Pharmaceutical Company Support - Boehringer Ingelheim

**FR-PO625**

Efferent Arterioles Are Special Target for Obesity

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**Background:** The link between obesity and renal disease is unclear. Hyperfiltration is suspected to induce arteriolar hyalination and glomerular hypertrophy in moderate to severe obesity. To assess morphological changes in the outer circle, we investigate human normal renal tissue from 7 mild obese cases (Ob)(BMI 27) and 3 lean cases (Le)(BMI 19) with hypertension and compared with 7 hypertensive case (HT) and 4 control(Con).  

**Methods:** Total 130 of serially cut paraffin sections were double immunostained with CD34 as endothelial marker, and smooth muscle actin as medial marker, followed by PAS stain. Incidence of hyalinosis in afferent and efferent arterioles, intraglomerular cystic dilation connecting to efferent arterioles, segmental sclerosis, sclerotic glomeruli(GS) and average size of glomeruli were assessed using 30-40 glomeruli per case.  

**Results:** The morphological data were as follows; average glomerular diameter 203±26, 181±19, 156±14 um, incidence of arteriolar hyalinosis 43±13%, 47±29%, 20±16% in control, respectively (*P=0.05 vs Con, **P=0.05 vs Con and HT). Higher incidence of cystic dilatation near efferent arterioles was noticed in Ob (21±15%) than HT and Con (2±15%, 0%, respectively(**P=0.05). Obese cases revealed neither significant intimal thickening nor distortion in the interlobular arteries, no segmental sclerosis, low incidence of GS (11%) and minimal interstitial damage(<10%).  

**Conclusions:** Efferent arterioles are targets for obesity, which suggest that specific mechanism of glomerular hyperfiltration involves obese cases, even in mild form.  

**Funding:** Government Support - Non-U.S.

**FR-PO626**

A Pathological Scoring System to Predict Renal Outcome in Diabetic Nephropathy

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**Background:** With association between diabetic nephropathy (DN) and renal outcome increasingly clear, we aimed to create a new DN pathological scoring system that could predict renal outcome.  

**Methods:** We studied 205 patients with DN confirmed by renal biopsy between March 1998 and January 2010 who met inclusion criteria. Renal biopsy included clinical parameters and Tervaert classifications. Hazard ratios (HRs) for end-stage renal disease (ESRD) were estimated by adjusted Cox regression. Overall pathological risk score (D-score) was calculated by summing the products of beta-coefficient and bootstrap-inclusion fractions, its predictive utility evaluated by Kaplan-Meier methods and c-statistics with 10-fold cross-validation for the year of risk of ESRD.  

**Results:** D-scores of glomerular classes 1, 2A, 2B, 3, and 4 were, respectively, 0, 3, 4, 6, and 6. Those of interstitial fibrosis and tubular atrophy classes 0, 1, 2, and 3 were 0, 7, 9, and 11, and those of interstitial inflammation classes 0, 1, and 2, respectively, 0, 3, and 4. D-score of hyaline class 2 was 3 and that of arteriosclerosis class 2 was 1. So a patient’s D-score could be 0-25.

**HRs for ESRD in patients with D-score £14, 15-18, 19-21, and 22-25 were, respectively, 1.00 (ref) (1.61) (1.84-1.90), 19.78 (2.15-182.40), and 45.46 (4.63-446.68) after adjusting for clinical factors. When comparing c-statistics, a model that included D-score in addition to age, eGFR, and proteinuria, showed a slight improvement from 0.901 (0.861-0.942) to 0.932 (0.898-0.965). The net reclassification index also showed better reclassification (0.24 <0.02 to 0.49).”  

**Conclusions:** In addition to clinical parameters, D-score may have improved prediction of 10-year risk of ESRD. Patients with D-score £14 had excellent renal prognosis.  

**Funding:** Private Foundation Support
Methods: A total of 396 patients with T2D and biopsy-proven DN from Nanjing DN registration system who were followed-up for at least 1 year were recruited and median 5-year follow-up. Renal outcomes were defined by progression to end-stage renal disease and doubling of serum creatinine.

Results: Of the participants, the mean baseline eGFR was 73.86 ± 33.52 mL/min per 1.73 m². The levels of the urinary tubularinterstitial injury markers including the NAG, RBP and NAGL were significantly different among quartiles of serum phosphorus (P < 0.01). The participants whose eGFR >90 mL/min per 1.73 m² had a higher rate of tubulointerstitial injury (interstitial fibrosis tubular atrophy scores of 2 and 3, P = 0.005; interstitial inflammation scores of 1 and 2, P = 0.035) in hyperphosphatemia (>1.45 mmol/L) group than in lower phosphorus group (<1.17 mmol/L). Participants with baseline levels of serum phosphorus in higher quintiles had a higher cumulative incidence of ESRD (log-rank, P < 0.01). In the analyses adjusted by age, sex, diabetes status, BP, FBG, BMI, proteinuria, cholesterol, and eGFR, the relationship between higher serum phosphorus and an increased risk of ESRD remained. The association between serum phosphorus and ESRD risk persisted and was stronger when the sample was restricted to those with a baseline eGFR equal to 60-90 mL/min per 1.73 m², but not when it was restricted to patients with a baseline eGFR of 30-60 mL/min per 1.73 m².

Conclusions: These findings indicated the baseline serum phosphorus is associated with tubulointerstitial injury of T2DN patients. And serum phosphorus >1.45mmol/L is an independent risk factor of ESRD in T2DN, especially in the patients with eGFR>60 mL/min per 1.73 m².

Funding: Government Support - Non-U.S.

FR-PO628

Longitudinal Changes in Estimated Glomerular Filtration Rate in Youth with Type 1 Diabetes: Insights From the SEARCH for Diabetes in Youth Study

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Background: Diabetes is the leading cause of kidney disease in the US. The natural history of kidney function early in type I diabetes (T1D) is relatively unknown.

Methods: SEARCH for Diabetes in Youth is a multicenter cohort study of incident diabetes in youth <20 yrs at diagnosis. Cystatin C (CysC) was measured at two study visits; values were calibrated for assay drift and standardized to the reference material. GFR was estimated using the CysC-based Filler equation, the only pediatric equation validated in hyperfiltration. Participants were stratified by change in eGFR: gain of >3.5 mL/min/1.73m², loss of >3.0 mL/min/1.73m², or stable. Nominal multinomial regression was used to predict eGFR gain vs stable, eGFR loss vs gain, and no albuminuria. Multivariate logistic regression analysis was performed to determine risk factors, including DR, associated with DN in the Korean population.

Results: Among the 971 DM patients, the prevalence of microalbuminuria was 93.3% and that of macroalbuminuria was 5.5%. The prevalence of eGFR <60 mL/min/1.73m² was 9.1%, and half of those were nonproteinuric DKD. We observed a prevalence of 20.0% for DR and 3.8% for proliferative DR/PDR. Multiple logistic regression analysis revealed that HbA1c ≥7.5% (OR = 1.24; 95% CI = 1.12–1.39), and PDR (OR = 2.80; 95% CI = 1.32–5.96) were independent risk factors associated with diabetic kidney disease, and the older age [adjusted odds ratio (aOR) = 1.19; 95% confidence interval (CI) = 1.09–1.31] and the presence of hypertension [aOR = 5.90; 95% CI = 1.37–22.71] were significantly associated with nonproteinuric DKD.

Conclusions: Nonproteinuric renal dysfunction in type 2 DM is not rare. PDR is associated with proteinuric DKD, however, DR and PDR are not significantly associated with nonproteinuric DKD.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO629

A Cross-Sectional Study for Evaluating the Diagnostic Accuracy of Cystatin C and N-Acetyl β-D Glucosaminidase in Predicting Diabetic Nephropathy


Background: Diabetic nephropathy (DN) is classified into V stages. Amongst which, stage I and II reclassifies proximal tubule damage, stages III and IV in stage III reclassifies irreversible glomerular damage stages. The inability of creatinine and microalbuminuria to detect early reversible stages urges the necessity of new efficient diagnostic biomarkers. Thus, we have selected proximal tubule originated proteins, cystatin c (cyst c) and N-acetyl β-D Glucosaminidase (NAG) to study their efficacy in detecting early manifestations of DN.

Methods: Uriminary serum cyst c and NAG were estimated in total 491 age-matched patients enrolled for our cross-sectional study. Their efficacy was compared with urinary microalbuminuria, serum creatinine and eGFR in patients with varying type 2 diabetes (T2DM) duration and various stages of DN.

Results: Patients with 5-10 years of T2DM duration showed a significant increase in cyst of proteinuria. However, urinary NAG increased in DN in patients with varying type 2 diabetes duration. The ROC curve signifies diagnostic efficacy of urinary cyst c (AUC 0.820) over urinary NAG (AUC 0.678), in detecting T2DN patients susceptible to develop DN.

Figure 1: Comparison of urinary Cystatin c and NAG in various groups

Conclusions: Urinary cyst c in comparison to urinary NAG plays a significant role in predicting the early renal decline in T2DM patients with varying duration of diabetes. Furthermore, the presence of such low molecular weight protein and renal origin enzyme indicates pathogenesis of proximal tubule in early stages of DN.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO630

The Relationship Between Diabetic Retinopathy and Diabetic Kidney Disease in a Population-Based Study in Korea (KHNANES V2-3)

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Background: Previous studies of the association between diabetic kidney disease (DKD) and diabetic retinopathy (DR) used only albuminuria/proteinuria as chronic kidney disease (CKD) markers and, hence, did not consider eGFR. This study aimed to evaluate the prevalence of DKD and the association between DKD, as evaluated by both proteinuria and eGFR, and DR in the large cohort of patients with type 2 diabetes from the Korean National Health and Nutrition Examination Survey (KNHANES).

Methods: From the fifth (2011, 2012) KHNANES, 971 participants with type 2 diabetes were included. Selected samples were weighted to represent the entire civilian population in Korea. DKD was defined as diabetes with the presence of albuminuria and/or impaired GFR. Nonproteinuric DKD was defined as estimated glomerular filtration rate (eGFR) calculated by Modification of Diet in Renal Disease (MDRD) equation < 60 ml/ min/1.73m² and no albuminuria. Multivariate logistic regression analysis was performed to determine risk factors, including DR, associated with DN in the Korean population.

Results: Among the 971 DM patients, the prevalence of microalbuminuria was 93.3% and that of macroalbuminuria was 5.5%. The prevalence of eGFR <60 mL/min/1.73m² was 9.1%, and half of those were nonproteinuric DKD. We observed a prevalence of 20.0% for DR and 3.8% for proliferative DR/PDR. Multiple logistic regression analysis revealed that HbA1c ≥7.5% (OR = 1.24; 95% CI = 1.12–1.39), and PDR (OR = 2.80; 95% CI = 1.32–5.96) were independent risk factors associated with diabetic kidney disease, and the older age [adjusted odds ratio (aOR) = 1.19; 95% confidence interval (CI) = 1.09–1.31] and the presence of hypertension [aOR = 5.90; 95% CI = 1.37–22.71] were significantly associated with nonproteinuric DKD.

Conclusions: Nonproteinuric renal dysfunction in type 2 DM is not rare. PDR is associated with proteinuric DKD, however, DR and PDR are not significantly associated with nonproteinuric DKD.

Funding: Government Support - Non-U.S.

FR-PO631

A Decrease in Blood Pressure During Follow-Up Is Associated with an Increased Risk of All-Cause Mortality in Patients with Type 2-Diabetes and Renal Impairment – The Swedish National Diabetes Register (NDR)

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Background: A U-shaped relationship between systolic blood pressure (SBP) and risk of all-cause mortality has been found in patients with type 2 diabetes (T2D) and renal impairment (RI). We here assess the association between time-dependent mean SBP, change in SBP during follow up and risk of all-cause mortality.

Methods: 27,322 patients with T2D and RI (eGFR<60 mL/min/1.73m² MDRD) classified into 10 mmHg intervals according to SBP at baseline were followed for 4.7 years. The risk of all-cause mortality was estimated using time-dependent mean SBP and change in SBP from last observation by time-dependent adjusted cox model. A smoothing spline describe the influence of mean SBP and the change in SBP on the hazard function.

Results: During follow-up 8265 deaths occurred. Using SBP 130-139 mmHg as a reference group a time-dependent mean SBP <130 mmHg was associated with increased risk of all-cause mortality in all (HR 1.28, 95% CI 1.20, 1.36) and in patients without
previously congestive heart failure (n=23 799) (HR 1.26, 95% CI 1.18, 1.36). In addition, a 25-50 mg/mL decrease in SHP from the last observation was associated with an increase in risk of all-cause mortality (HR 1.44, 95% CI 1.33, 1.56) compared to a change in the range -10 to 30 mmHg.

Conclusions: A systolic blood pressure < 130 mmHg and a decrease in systolic blood pressure during follow up with or without previous congestive heart failure, is associated with an increase the risk of all-cause mortality in patients with type 2-diabetes and renal impairment. Intensity of hypertensive medication and co-morbidities are important confounders and will be further evaluated.

FR-PO632

Increased Expression of WNT5a in Renal Tubules Is Associated with Diabetic Nephropathy in Humans, Malik Asad Anjum, An Xiao, Dean Troyer, Michael J. Solhaug, Anca Dobrian, Jerry L. Nadler, Liwei Huang, Internal Medicine, Eastern Virginia Medical School, Norfolk, VA; 2Pathology, Sentara Norfolk General Hospital, Norfolk, VA.

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease worldwide. In recent years, convincing data has come forward suggesting that inflammatory pathways play a pivotal role in the pathogenesis and progression of DN. Identification of these inflammatory pathways and associated biomarkers may help in the early diagnosis of DN and development of novel targeted therapeutic strategies to help prevent, treat and even slow the progression of DN. Wnt5A, a secreted glycoprotein, plays an important role in normal kidney development and is also a pro-inflammatory factor which has been associated with renal fibrosis and disruption of matrix metabolism. The objective of our study was to investigate the expression of WNT5A in diabetic kidneys in humans.

Methods: 11 subjects with biopsy confirmed DN were included in our experimental group. Normal kidney tissues from non-diabetic subjects who underwent nephrectomy for renal cell carcinoma were used as controls. Exclusion criteria for the experimental group were HIV positivity, chronic/acute inflammatory diseases (including hepatitis C) and steroids/immunosuppressant medication. WNT5a expression was evaluated in paraffin embedded tissues.

Results: Immunohistochemical analysis of WNT5a expression showed positive staining on the apical side of the plasma membrane of the renal tubular epithelial cells in control kidney tissues. The intensity of the staining is increased in patients with DN compared to normal kidney control tissues. In patients with DN, WNT5a expression is localized both in the cytoplasm and on the apical side of the plasma membrane of the renal tubular cells. WNT5a is also expressed on glomerular cells, but there are no differences in Wnt5a expression between the tissues from diabetic subjects and controls.

Conclusions: Our results suggest that WNT5a expression in renal tubules might have a pathogenic role in the development of human renal tubular fibrosis. These studies are the first to demonstrate an increase in WNT5a expression in renal tubules in DN.

Funding: NIDDK Support

FR-PO633

Accuracy of Serum Creatinine and Glomerular Filtration Rate Estimation for Adjusting Metformin Prescription in European Type 2 Diabetics, Olivier Muranne, Coralie Fafin, Pierre Delanaye, Martin Flament, 1Nephrology, CHU, Nice, France; 2Nephrology, Hospital, Liege, Belgium; 3Physiology, APHP, Paris, France.

Background: There is a debate in the literature about the thresholds of serum creatinine (Scr) above which the drug is contraindicated (1.5 mg/dL in men & 1.4 mg/dL in women). For KDOQI, recommendation is a dose-adjustment between 45 and 30 mL/min and a withdrawal below 30 mL/min. However, in DM2, estimation of renal function based on Scr alone or on eGFR may vary from the true renal function (mGFR). The purpose of our study was to define the performance of the GFR assessment method (Scr or eGFR calculated with Cockcroft-Gault (CG) or CKD-EPI) in terms of metformin dose adjustment in DM2 who underwent a GFR measurement.

Methods: In 243 DM2 patients, GFR was measured by urinary clearance of ¹⁵⁃TcDTPA. Non indexed GFR was used. We analyzed the agreement between classification of patients based on mGFR and, first, Scr alone with a cutoff value of 1.5 mg/dL in men and 1.4 mg/dL in women, second, on eGFR with threshold values of 45 or 30 mL/min. When both methods classified the patient in the same subgroup, the data were considered concordant otherwise overprescription (underprescription) was defined for discordance according to mGFR.

Results: Age was 61 ± 12 y/o, median mGFR was 42 [30-61] mL/min. Based on mGFR, the distribution of the patients according the following GFR class: [90-45] 11045%), [44-30] 74(30%), < 30: 59(24%). In patients with a Scr above the cutoff value, mGFR(mL/min) was < 30 mL/min in respectively 23:40 women and 33:106 men. With a threshold of 45 mL/min then 30 mL/min, concordance was found in 80%85% then 8888% of the patients for the CG and CKD-EPI. With a threshold of 30 mL/min, discordance was an overestimation (or understimation) in 22%(9) and 19%(8) or (14%6) and 11%(5)% of the patients with the CG and CKD-EPI.

Conclusions: In this population creatinine-derived equations outperformed Scr alone in correctly classifying the patients in prescription subgroups. However, even with creatinine-based equations, discordance with mGFR occurs in 1220% of the patients. New strategies such as drug concentration monitoring may be necessary to improve appropriate prescription of metformin in DM2.

FR-PO634


Background: Change in albuminuria may have useful prognostic value. We sought to assess the association between change in urine albumin-to-creatinine ratio(UACR) and the risk of all-cause death, cardiovascular disease(CVD), and end-stage renal disease(ESRD) in the ADVANCE trial.

Methods: We defined UACR change(baseline to 2 years) as >30% decrease, <30% decrease to >30% increase(minor change); reference, and >30% increase. Follow-up for outcome ascertainment commenced at the second UACR measurement. We used Cox regression to estimate the hazard ratio(HR), after adjustment for demographics, ADVANCE randomized treatment assignments, comorbidities, laboratory measurements(including baseline UACR), and drug use.

Results: From baseline to 2 years, 34% of 9195 patients experienced a UACR decrease of >30%, 36% experienced a minor change, and 40% experienced an increase of >30%. Over the next 2.9 years(median), 526 deaths, 524 CVD events, and 12 ESRD events were recorded. An increase of >30% in UACR was associated with 30% higher mortality when compared to a minor change (Figure 1, HR 1.30, 95%CI:1.18-1.49). Increase in UACR was associated with increased CVD or ESRD, although the direction of effect was similar. A >30% UACR decrease was not significantly associated with the risk of death or CVD when compared to those with minor change but was significantly associated with lower ESRD risk(HR 0.10, 95%CI:0.01-0.79).

Conclusions: In type-2 diabetes patients, >30% increase in albuminuria predicted higher mortality while >30% decrease was associated with decreased ESRD risk. Our results suggest change in albuminuria may be a potential prognostic marker for clinical outcomes in type-2 diabetes.
Results: QTc interval was prolonged significantly at the end of HD in all sessions (p<0.001). Change in glucose level (mean±SD -1.8±4.2 vs -1.7±3.0) did not have a significant effect on the change in QTc interval (p=0.396), which was not different in diabetic subjects compared to non-diabetic group (p=0.390). Serum K+, Mg2+ and Ca2+ levels dropped significantly (p<0.001) during all 3 HD sessions. There was no significant difference in heart rate level and the drop in K+, Mg2+ and Ca2+. The change in Mg2+ (p<0.05) and Ca2+ (p<0.05) levels but not K+ (p=0.202) were more pronounced in diabetic subjects. The change in Mg2+ levels in diabetic subjects was associated with QTc prolongation (p<0.05).

Conclusions: Significant QTc prolongation occurs at the end of HD in people with and without diabetes, often reaching abnormal levels and appears to be related more to changes in blood electrolytes than glycaemia. The fall in serum Mg2+ levels during HD had a larger effect on QTc than K+ or Ca2+ and this appears to have a more pronounced effect in diabetic subjects. The changes in QTc may increase the risk of cardiac dysrhythmia and sudden death in HD patients.

FR-PO636
Markers of Inflammation and Endothelial Dysfunction Are Associated with Cardiovascular Morbidity and Mortality in Type 2 Diabetic Patients with Microalbuminuria
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Background: Accumulating evidence suggests that inflammation and endothelial dysfunction link type 2 diabetes (T2D) to cardiovascular disease (CVD). We evaluated the predictive value of markers of inflammation and endothelial dysfunction for combined fatal and non-fatal CVD and for all-cause mortality in patients with T2D and microalbuminuria but without known coronary artery disease (CAD).

Methods: Prospective study including 200 patients. All received intensive multifactorial treatment. Markers of inflammation (TNF-α, ICAM-3, hsCRP, SAA, IL-1α, IL-6, IL-8) and endothelial dysfunction (thrombomodulin, VCAM-1, ICAM-1, E-selectin, P-selectin) were measured at baseline. Adjusted score models included sex, age, total cholesterol, smoking, HbA1c, creatinine, systolic blood pressure and urinary albumin excretion. Fully adjusted models additionally included NT-proBNP and coronary artery calcium score (CAC).

Results: Participants were 76% men, age (± SD) 59 ±9 years, HbA1c was 7.9 ±1.3% and UAER (IQR) was 103 (39–230) mg/d. Occurrence of CVD (n=40) and mortality (n=26) was traced after 6.1 years (median). In adjusted Cox analysis, higher TNF-α predicted the CVD endpoint and mortality (p=0.002). After full adjustment higher TNF-α remained predictive of both endpoints (p=0.007). Higher thrombomodulin and ICAM-3 were associated with risk of CVD and mortality in adjusted analyses (p=0.05) and predicted mortality after fully adjustment (p=0.001). Higher VCAM-1 and ICAM-1 were associated with risk of mortality in adjusted (p=0.002) and fully adjusted models (p=0.005). The composite z-score of all markers of inflammation and of endothelial dysfunction predicted CVD and mortality (p=0.008).

Conclusions: In patients with T2D and microalbuminuria without known CAD, biomarkers of inflammation and endothelial dysfunction were independently associated with risk of CVD and mortality. Especially TNF-α was a robust predictor, even after adjusting for albuminuria, NTproBNP and CAC.

FR-PO637
Predictors of Glycemic Status and Associations with Mortality in Incident Diabetic Hemodialysis Patients
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Background: In the general population, intensive glycemic targets confer higher mortality in diabetics with cardiovascular risk. In diabetic hemodialysis (HD) patients, some but not all studies show that lower glycemic levels defined by HbA1c are associated with higher mortality. We sought to examine predictors of low glycemic status in HD patients, and hypothesized that lower glycemic levels are associated with higher mortality.

Methods: In a 5-year national cohort (1/2007-12/2011) of incident diabetic HD patients with or without known CAD measures during the 1st 91-days of dialysis, we examined predictors of low HbA1c (<6%; ref 6–<8%; ≥8% separately examined) using logistic regression. We then examined the association of HbA1c with all-cause mortality. Baseline and time-dependent HbA1c as a proxy of long-term and short-term exposure—mortality associations, respectively, were examined using case-mix laboratory adjusted Cox models.

Results: Among 63,607 diabetic HD patients, 37% had low HbA1c levels. Female gender and non-Hispanic race/ethnicity; lower BMI and nPCR; and higher serum bicarbonate, creatinine, and albumin were associated with higher risk of low HbA1c. Baseline HbA1c levels <7% were associated with lower mortality. However, time-dependent HbA1c levels <5% were associated with higher mortality.

Conclusions: Baseline HbA1c levels <7% were associated with lower mortality, suggesting that moderately low glycemic status has long-term benefits in diabetic HD patients. Yet time-dependent HbA1c levels <5% were associated with higher mortality, suggesting that very low glycemic status carries short-term risk. Further studies are needed to determine if pharmacotherapies targeting these glycemic ranges reduce mortality in diabetic HD patients.

Funding: NIDDK Support, Private Foundation Support

FR-PO638
Waist-Hip Ratio Is Associated with Renal Hyperfiltration in the Non-Diabetic, Middle-Aged General Population
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Background: Renal hyperfiltration (RHF) is a maladaptive response to increased metabolic stress in the kidneys which may result in chronic kidney disease. Diabetes causes RHF, but whether obesity in non-diabetic persons is a cause of RHF has not been adequately studied in the general population. This study aimed to establish whether RHF assessed by measured glomerular filtration rate (GFR) is associated with obesity independently of metabolic and cardiovascular risk factors.

Methods: We performed a cross-sectional study of a representative sample of 1594 persons recruited from the general population of the municipality of Tromsø, Norway, aged 50-62 without prevalent cardiovascular disease, diabetes or renal disease. GFR was measured by iohexol clearance. Obesity was classified according to body mass index (BMI), waist circumference (WC) and waist-hip ratio (WHO). RHF was defined as >90th percentile of residuals from a linear regression of absolute GFR on age, sex, weight and height.

Results: In multivariable adjusted logistic regression models, the odds ratios (95% confidence intervals) for RHF were 1.56 (1.11-2.18) per 0.10 increase in WHO, 0.82 (0.51-1.32) per 5kg/m2 of BMI and 1.23 (0.92-1.65) per 10 cm of WC. WHR was consistently associated with RHF across different models. Higher BMI and WC were significantly associated with RHF only when an alternative definition of RHF, not adjusted for body weight, was used. Higher BMI, WC and WHO were also independently associated with increasing GFR analyzed as a continuous variable.

Conclusions: Central obesity measured as WHR is associated with RHF and higher GFR independently of age, sex, body weight, metabolic indices (including fasting glucose,
insulin and HbA1C) and cardiovascular risk factors (including ambulatory blood pressure, antihypertensive medication and smoking status). WHR may be a better indicator of the renal effects of obesity than BMI or WC.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Private Foundation Support, Government Foundation - Non-U.S.

FR-PO639

Obesity Associates with High Hemoglobin A1c but Low Alternative Indices in Both Diabetic and Nondiabetic Hemodialysis Patients

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Background: The GIDE (Glycemic Indices in Dialysis Evaluation) study is evaluating several glycomic markers in hemodialysis (HD) cohorts with and without diabetes. We have reported that alternative glycemic indices may be elevated out of proportion to hemoglobin A1c (HgbA1c). Because obesity is known to affect markers of glycemia, we examined its association with these indices.

Methods: A combined cohort of 2,394 active HD patients (1,424 with diabetes, 970 without) from 26 U.S. FMCNA facilities had baseline indices [HgbA1c; albumin-adjusted and unadjusted fructosamine (AlbF; F) and glycated albumin (GA) or percent GA] measured Jan-Mar 2013 and monthly until April, 2015. Mean of body mass index (BMI) was determined for the entire cohort. Obesity—BMI³30kg/m². Cox models adjusted by age, sex, race, ethnicity, vintage, HD catheter, baseline comorbidity and laboratory albumin values were utilized to determine associate between obesity with death outcome.

Results: Average BMI (kg/m², mean±SD) by risk as determined by indices (low=within target range, high=above target range) are shown in (table 1).

<table>
<thead>
<tr>
<th>Indices</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgbA1c &gt; 7%</td>
<td>28.8 ± 11.4</td>
<td>31.6 ± 8.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent Glycated Albumin &gt; 15.7%</td>
<td>29.8 ± 12.4</td>
<td>28.9 ± 9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fructosamine &gt; 285 μmol/L</td>
<td>31.0 ± 14.6</td>
<td>28.7 ± 9.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AlbF ≥ 974 μmol/g</td>
<td>29.5 ± 11.8</td>
<td>28.6 ± 7.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycated Albumin &gt; 300 μmol/L</td>
<td>29.3 ± 11.4</td>
<td>29.2 ± 10.4</td>
<td>0.0008</td>
</tr>
<tr>
<td>HgbA1c &gt; 2.8%</td>
<td>29.1 ± 11.1</td>
<td>31.6 ± 8.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The Hazard Ratio (HR) for death was reduced with obesity [HR=0.76, 95%CI (0.62, 0.94), p=0.01].

Conclusions: Obesity is positively correlated with HgbA1c but negatively correlated with other glycemic indices in hemodialysis patients. Further studies are needed to elucidate underlying mechanisms and assess the relationship of these findings to superior survival outcomes in obese HD patients.

FR-PO640

BMI and Causes of Death in Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) is associated with higher risk for cardiovascular related death. In CKD, a higher body mass index (BMI) is associated with a lower risk for death, but cause specific death details are unknown across the BMI range.

Methods: We included 54,306 patients with CKD (two estimated glomerular filtration rate <60 ml/min/1.73 m² 90 days apart; January 2005 – December 2012) from our institutional electronic medical record-based CKD registry. We examined the associations between various causes of death (cardiovascular, malignancy and non-cardiovascular/ non-malignancy related deaths obtained from the State of Ohio mortality files) across the BMI range using the Cox proportional hazards model.

Results: During a median follow-up of 3.7 years (25th percentile-75th percentile: 1.8-5.8), 14,518 patients died. In the multivariable model, an inverted J-shaped association was noted between BMI and overall, cardiovascular, malignancy-related, and non-cardiovascular/ non-malignancy related deaths.

Similar associations were noted for BMI 25-29.9, 30-34.9, and 35-39.9 kg/m² categories. BMI>40kg/m² was not associated with cardiovascular and non-cardiovascular/ non-malignancy related deaths in CKD. Sensitivity analyses yielded similar results even after including only those with ≥2-year follow-up, adjusting for proteinuria, and excluding diabetes and hypertension from the models. However, the inverse associations between higher BMI and cardiovascular deaths were not observed among smokers.

Conclusions: In those with CKD, compared to BMI of 18.5-24.9 kg/m², those who are overweight, class 1 and 2 obesity are associated with lower risk for cardiovascular, malignancy-related and non-cardiovascular/ non-malignancy related deaths. Future studies are needed to confirm these findings.

Funding: Pharmaceutical Company Support - CCF CKD registry creation was supported by an unrestricted grant from Amgen to the Department of Nephrology and Hypertension at Cleveland Clinic

FR-PO641

Weight Reduction with Low Calorie Diet Reduces Urinary Megalin and Improves Albuminuria in Obese Men

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Background: Megalin, an endocytic receptor in proximal tubules, is involved in the mechanisms of albuminuria in diabetic nephropathy. A urinary full-length megalin (C-megalin) assay is linked to the severity of diabetic nephropathy and IgA nephropathy. Also, albuminuria is a frequent sign of obese individuals and could be reduced by losing body weight. We investigated the relationship between level of urinary C-megalin and albuminuria on a weight reduction program in obesity.

Methods: Thirty-three obese male volunteers (age 36.6 ± 6.9 years, BMI >25 kg/ m²) were enrolled but 30 subjects completed the 12-week weight reduction program. The program consisted of replacement of evening meal by a low caloric formula food (MICRO-S®) for first 4 weeks and followed by bi-weekly dietary counseling session with nutritionist. Of these, 20 subjects with metabolic syndrome were included (based on the Japanese criteria). Urinary albumin/Cr ratio (ACR) and urinary C-megalin were measured at baseline and after the program.

Results: The mean weight loss was 5.2 ± 2.9 kg (5.6% of the original BW). The baseline ACR ranged from 2.8 to 52.9 mg/gCr. After the program, BMI, waist circumference, BP, total cholesterol, and FFA were significantly decreased. HDL-cholesterol and adiponectin were significantly increased. Overall, ACR was not changed (11.9 ± 12.4 vs 8.8 ± 5.3 mg/gCr). However, in the cases with ACR >8 mg/gCr at baseline (n=11), ACR was more effectively reduced (22.9 ± 15.1 vs 12.7 ± 6.4 mg/gCr) without a change in eGFR. The reduction of ACR was correlated with the reduction of urinary C-megaltn. No other parameters like insulin resistance were associated with the reduction of ACR or C-megaltn.

Conclusions: Losing BW with a formula food is effective in reducing urinary ACR in obese men. This improvement of ACR is related to the reduction in urinary C-megaltn. Since albumin is excreted into urine by its increased glomerular leakage and/or decreased proximal tubular reabsorption via megalin and cubulin, our observations suggest that megalin metabolism in proximal tubules may determine albuminuria in obesity.

FR-PO642

Obesity Management in Patients with Chronic Kidney Disease (CKD): A National Survey

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Background: Obesity contributes to the development and progression of CKD and may be a barrier to, or increase risks of, transplantation. Evidence for how the renal multi-disciplinary team (MDT) should proceed is limited and sometimes counterintuitive i.e. association of increased weight and better survival on haemodialysis. The study assessed approaches to obese patients with CKD across the UK and describes the availability of, and extent of co-working with, bariatric services.

Methods: An online survey tool was designed and sent by the British Renal Society to UK renal clinical directors and dieticians. The survey focused on patients with CKD stage ≥ 3, with proteinuria and co-existent Obesity stage II (BMI > 35kg/m²) as these patients are most likely to progress to ESRD.

Results: 58/71 (82%) of UK units responded with respondents split between dieticians (53%) and nephrologists (47%). Most respondents (78%) thought the prevalence of obesity has increased over the last decade. There was no consensus on the BMI cut off for kidney transplantation: 30%, 16%; 35%, 71%; ≤40, 12%; none, 2%. The 3 most common actions for initial obesity management were: to provide education/motivation (81%); dietary referral (69%) and test fasting glucose and lipids (43%). Thereafter only 33% would refer to bariatric services. The main perceived barriers to weight loss were: lack of patient motivation (79%); no funding (60%); lack of services (53%). 54% of renal units co-locate with bariatric services. Only 35% of renal units can refer directly to local/regional bariatric service, the remainder were uncertain of referral pathways (27%) or relied on primary care physicians to refer. Only 5 units (9%) have a joint care pathway for obese patients with CKD undergoing bariatric surgery.

Conclusions: The response to obesity in CKD falls short of National (NICE) guidelines. The increasing prevalence of obesity is a challenge to the renal MDT. Strategies to tackle this include wider recognition of the problem; identifying and sharing best practice and alleviation of hyperfiltration. However, there are also concerns about deleterious effects associated with cardiovascular complications. To prevent progression of systemic cardiovascular complications in DM patients, glycemic control is important. However using of anti-diabetic agents was restricted in patients with renal impairment. In this study, we examined the efficacy and safety of the glucagon-like peptide analogue, liraglutide to treat type 2 DM patients with renal impairment.

Methods: Twenty type 2 diabetes patients with renal insufficiency (Age; 65.4y; DM duration;11.9y, eGFR,21.6ml/min/1.73m²) were enrolled. Anti-diabetic agents were switched to liraglutide from others. Prior to liraglutide therapy, 9 patients used insulin, 8 used oral antidiabetic agents, and 3 were only diet therapy. During 24 months liraglutide use, we examined the change of blood pressure and renal function. Echocardiography was examined at baseline and 24 months after liraglutide initiation.

Results: Hemoglobin A1c, and systolic/diastolic blood pressure levels were gradually decreased with liraglutide use. Renal function indicated by eGFR was not changed (table1), and the slope of the reciprocal of serum creatinine was improved after use of liraglutide (p<0.001). Moreover Liraglutide induced ameliorating left ventricular function(LVMI and EF).

FR-PO643

Effects of Renin-Angiotensin Blockade (RASB) on the Components of Early Interstitial Expansion in Patients (pts) with Type 1 Diabetes (T1D)

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Background: Interstitial expansion is important for GFR loss in the later stages of a variety of disease processes, including diabetic nephropathy (DN). The Renin-Angiotensin System Study (RASS; NEJM 2009;361:40) considered whether RASB with enalapril or losartan compared to placebo could slow progression of early DN lesions over 5 years (yrs) in 285 normoalbuminuric (NA), normotensive (NT), normal GFR T1D pts. RASS found no difference between the treatment groups in albuminuria or eGFR at 5 yrs. However, this early DN study was limited by a single research center, 7 from each treatment group, with a wide range of change in Vv(Int). The response to obesity in CKD falls short of National (NICE) guidelines.

Methods:

- At baseline, 49% of the Int was made up by Col, 12% by C, 26% by PTC, 7% by S, and 2% by artifact. Overall there was no change in Int composition during RASS. Compared across treatment groups, there were no statistically significant effects of treatment group on the Vv of any of the Int components. Rv (171.5 cm³) remained stable in all groups.

Conclusions: RASS found that NA, NT, normal GFR T1D pts had surprisingly rapid increases in Vv(Int/Cortex). The response to obesity in CKD falls short of National (NICE) guidelines.

No adverse events were seen.

Conclusions: These findings suggest that liraglutide therapy for type 2 diabetes patients with renal impairment was safe and effective for decreasing glucose levels and blood pressure. Moreover it preserved renal function and improving left ventricular function.

FR-PO645

Do SGLT2 Inhibitors Affect GFR and Albuminuria in Diabetic Patients? A Systematic Review and Meta-Analysis

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Background: SGLT2 inhibitors are a new class of antihyperglycemic drugs that lower blood glucose levels by inhibiting renal glucose reabsorption. SGLT2 inhibitors can have potential renoprotective capacities through modulation of tubuloglomerular feedback and alleviation of hyperfiltration. However, there are also concerns about deleterious effects on renal function caused by volume depletion.

Methods: We performed this systematic review and meta-analysis to assess the effects of SGLT2 inhibitors on estimated GFR (eGFR) and urinary albumin/creatinine ratio (ACR) in diabetic patients. We conducted a systemic search of Pubmed, Embase, Cochrane Central Register of Controlled Trials and Sinomed through April 2015 to identify published randomized double-blind controlled trials of SGLT2 inhibitors reporting renal outcomes. Two reviewers worked independently to extract data and assess the quality of included studies. Random effects model were used in data synthesis.

Results: We retrieved 2279 studies, 53 of which met the predefined criteria. Among included studies, 33 studies examined short-term effect with follow up less than 26 weeks, and 20 studies examined long-term effects with follow-up longer than 48 weeks. 4 studies included subjects with CKD 2-4. SGLT2 inhibitors did not cause statistically significant changes in eGFR (mean change,-0.19 ml/min/1.73m², 95% CI, -0.86 to 0.47) or in ACR (mean change, -23.76 mg/g, 95% CI, -66.75 to 19.23).

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only, Underline represents presenting author.

508A
Effects of Statins on Diabetic Kidney Disease in Patients with Type 2 Diabetes

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

**Background:** Renoprotective properties of statins have received much attention; however, a recent large cohort study found no beneficial effect of statins on diabetic kidney disease (DKD). Furthermore, whether there are differences among statins in their effects on the kidney remains unclear.

**Methods:** This was a single-center historical cohort study of Japanese adult ambulatory patients with type 2 diabetes. We studied 412 patients who were newly prescribed one of the following 4 statins: pravastatin, rosuvastatin, atorvastatin and pitavastatin, and who had estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m². As the control group, 946 patients without a prescription history of statins were enrolled. Two outcomes were defined: 1) annual decline in eGFR and 2) progression to a more advanced stage of albuminuria. To adjust for the effects of confounding factors, we used the propensity score (PS) as the covariate. PS was estimated using a multinomial logistic regression model that included 18 clinical parameters. Furthermore, to take into account the varying number and spacing of eGFR measurements, and the variable follow-up period for each individual, we conducted the linear mixed-effects model regression analysis. The intercept and slope were treated as random effects.

**Results:** During the median follow-up period of 5.3 years (range, 2.0–8.6 years), the adjusted eGFR decline (±standard error) in the control group (1.6 ± 0.1 mL/min/1.73 m²/year) was significantly slower than that in rosuvastatin (2.4 ± 0.2, p=0.001), atorvastatin (2.6 ± 0.3, p=0.003) and pitavastatin group (2.3 ± 0.3, p=0.036), but not in pravastatin group (1.7 ± 0.2, p=0.780). Next, during the median follow-up period of 4.2 years (range, 0.1–8.5 years), 138 patients showed progression of albuminuria stage. The adjusted hazard ratio (vs. control group) for the albuminuria progression was 0.85 (p=0.690), 0.86 (p=0.670), 1.01 (p=0.980), and 0.69 (p=0.462) in pravastatin, rosuvastatin, atorvastatin and pitavastatin group, respectively.

**Conclusions:** Statins may have no beneficial effect on the progression of DKD. Instead, some statins are likely to be associated with faster renal function decline.

Glucose Targets for Preventing Diabetic Kidney Disease and Its Progression: A Meta-Analysis

**Methods:** Using standard Cochrane methods, we did a systematic review and meta-analysis of randomized controlled trials that evaluated intensive versus standard glycemic control admistered to adults and children with type 1 or type 2 diabetes with or without kidney disease. Intensive glycemic control was defined by a treatment targeting an HbA1c level <7.0% or fasting glucose levels <120 mg/dL. Effect sizes were calculated using a random-effects model. Studies were critically appraised using Cochrane methods.

**Results:** 10 studies involving 28,885 participants were eligible for inclusion. In studies at low risks of bias, intensive glycemic control had uncertain effects on doubling of serum creatinine (0.91; CI 0.34-1.47) and end-stage kidney disease (1.21, CI 0.12-11.98). Tight glycemic control reduced the onset (0.82, CI 0.71-0.93) and progression (0.56, CI 0.36-0.87) of microalbuminuria. In absolute terms, treating 1000 patients with tight glycemic control for 1 year might prevent 7 experiencing new-onset albuminuria and 22 with worsening albuminuria.

**Conclusions:** Intensive glycemic control among adults with diabetes had very uncertain effects on doubling of ESKD and progression of kidney failure, while providing small clinical benefits on the onset and progression of microalbuminuria.

Patient Benefits and Cost Savings Predicted for Mineralocorticoid-Receptor Antagonist Treatment of Early and Advanced Diabetic Kidney Disease

**Background:** Exploratory studies suggest that mineralocorticoid-receptor antagonists (MRA) may improve outcomes in patients with diabetic kidney disease (DKD). Finerenone (BAY 94-8862) is a selective, potent and non-steroidal MRA for the treatment of patients with DKD and is currently being studied in two clinical phase III trials, “FIDELIO” and “FIGARO”.

**Methods:** A Markov cohort model was used to emulate disease history, treatment effects, and outcomes for DKD patients with various disease severities (by albuminuria, measured by urinary-albumin-creatinine ratio [UACR], and chronic kidney disease [CKD] stage, measured by estimated glomerular filtration rate [eGFR]). Efficacy of finerenone is accomplished by reducing albuminuria evidenced by phase 2 trial data. The model has US...
blood and 24-hour urine samples were collected at baseline (pre, days -2 to 0) and the last 3 diet days (on, +19 to +21). Each subject’s tests were averaged by period, and the group averages analyzed by one-way ANOVA and between groups by t-test. Urinary N excretion was adjusted per 70 kg. Body composition [total (T), fat free mass (FFM), kg] was measured by bioimpedance (BIS).

**Results:** mean±SD. ADA or Paleo pre-on; a, p<0.05; Δ Paleo vs Δ ADA: b, p<0.1; c, p<0.05; d, p<0.01.

Both groups had equally modest nonsignificant declines in weight.

**Conclusions:** The higher acid diet had significantly greater loss of fat free mass associated with a greater loss of urinary urea and ammonium. A plant based low acid weight loss diet may be better in maintaining lean body mass compared to a usual acid diet.

**Funding:** Clinical Revenue Support

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### FR-PO650

**Independent Association of Systolic Blood Pressure and Hemoglobin A1c Levels on Clinical Outcomes in Diabetic Patients with Normal Kidney Function**

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**Background:** Systolic blood pressure (SBP) goal of <140mmHg is recommended for majority of patients with diabetes mellitus (DM). It is however unknown if glycemic control modifies the association of uncontrolled hypertension (HTN) with mortality and morbidity in DM patients.

**Methods:** We examined 894,661 US veterans with DM and baseline eGFR >60 ml/min/1.73m² (mean age 66.6±10.9 years, 97% males, 17% African-Americans). The association of mutually exclusive combined categories of hemoglobin A1c (AIC: <6.5, 6.5-6.9, 7.0-7.9, 8.0-8.9, 9.0-9.9, and 10%) and SBP (<120, 120-139, 140-159, 160-179, and >180mmHg) with the risk of all-cause mortality, incident CKD, coronary heart disease (CHD), and stroke was examined in Cox models adjusted for baseline characteristics, statin use, and co-morbidities, using patients with A1c 6.5-6.9% and SBP of 120-139 mmHg as referent.

**Results:** A total of 221,983 (25%) patients died, and 178,628 (20%), 43,374 (5%) and 29,536 (3.5%) developed incident CKD, CHD and stroke, respectively, during a median follow up of 7.4 years. SBP displayed a U-shaped association with mortality in each A1c category. Conversely, SBP >120-139 mmHg was associated with a monotonous increase in the risk of CKD, CHD and stroke in all A1c categories. A1c levels were linearly associated with worse outcomes for all end points and in all SBP categories.

**Conclusions:** SBP above 120-139 mmHg and higher A1c levels were associated with higher mortality and morbidity in diabetic patients, independent of each other. Tight glycemic control may reduce mortality and morbidity across all SBP categories in patients with normal kidney function.

**Funding:** NIDDK Support, Veterans Administration Support

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### FR-PO651

**High Acid Diets Increase Urinary Nitrogen Excretion and May Decrease Muscle Mass in Obese Diabetics**

Lynda A. Frassetto, Umesh Masharani, Anthony Sebastian. UCSF, San Francisco, CA.

**Background:** We have previously shown that decreasing dietary acid loads with bicarbonate supplements lowers urinary nitrogen (N) excretion in postmenopausal women. Here we examined whether we could lower urinary N excretion in obese diabetics by increasing plant food intake (“Paleo diet”) compared with a “usual” acid diet (America Diabetes Association diet).

**Methods:** 12 obese well controlled type 2 diabetes (7 Paleo, 5 ADA) were enrolled in a 21 day no-weight loss controlled metabolic diet study. Daily protein intake per 2500 kcal averaged 116 g on the Paleo and 127 g on the ADA diets (p=0.7). Fasting arterialized

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### FR-PO652

**Clinical Benefit of Pre-Dilution On-Line Hemodiafiltration for Removal of Low-Molecular-Weight Proteins and Fibrobast Growth Factor-23 in Patient with Diabetic Nephropathy**

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**Background:** Increased concentration of fibroblast growth factor 23 (FGF-23) is reportedly associated with increased risk of cardiovascular complication and mortality in dialysis patients. Therefore, there is a possibility that reduction of FGF-23 levels may improve prognosis of diabetes patients with elevated its levels. We compared the removal performance of low-molecular-weight proteins (LMWP) and FGF-23 between pre-dilution on-line hemodiafiltration (HDF) and hemodialysis (HD) with super high-flux dialyzer.

**Methods:** The study involved 31 patients (15:HDF, 16:HD, 4 hrs, Qd:600 mL/min). Blood flow rates were 284±20 for HDF, 281±14 mL/min for HD. Replacement fluid volume in HDF was 49.2±9 L/session. Removal rates (RR,%) and removal amounts (RA,mg) of urea nitrogen (UN), creatinine, β2-microglobulin (β2-M, MW:11.8Kda), α1-microglobulin (α1-M, 33KDa) and FGF-23 (32KDa) were examined. We followed the changes in FGF-23 levels of patients for 4 month period.

**Results:** Ks/V, RR's of UN and creatinine were significantly higher in HD than in HDF, whereas RR's and RAs of β2-M, α1-M, and FGF-23 were significantly higher in HDF. RRs of β2-M and α1-M were 80.3±3.7 and 42.0±6.1 for HDF, 73.5±4.1 and 25.0±6.8 for HD, respectively. RR and RA of FGF-23 were 66.0±6.5 for HD, 51.1±8.3 for HD and 0.11±0.01 for HD, respectively.

**Conclusions:** The results confirmed that HDF was superior to HD in removing LMWP and FGF-23, which are removed mainly by convection. The convection volume can be much easily controlled in HDF than HD because HDF utilizes internal filtration. The RRs of FGF-23 were 24 points higher than those of α1-M in both modes despite the small difference in MW, suggesting that distribution volume of FGF-23 was smaller than that of α1-M. No clear tendency was detected in changes of FGF-23 during 4-month observation period.

**Funding:** Clinical Revenue Support

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### FR-PO653

**Comparison of Removal Performance of Small- to Large-Molecular-Weight Substances Between Pre-Dilution On-Line Hemodiafiltration and Hemodialysis with Super-High-Flux Dialyzer**

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**Background:** In pre-dilution on-line hemodiafiltration (HDF), net dialysate flow rate is reduced, because replacement fluid accounts for 30 to 50% of total dialysate flow (Qdtotal). Therefore, removal efficiency of small-molecular-weight substances by diffusion is reduced, whereas that of low-molecular-weight proteins (LMWP) by convection is...
improved. In hemodialysis (HD) using super high flux dialyzer, the increased blood flow rate (QB) increases amount of fluid filtration, thereby improving the removal efficiency of LMWPs. In this study, we compared the removal efficiency of small- to large-molecular-weight substances between HDF and HD to verify the superiority of HDF.

**Methods:** The study involved 62 patients (31: HD, 31: HDF). Super high flux dialyzers for HD and high-performance hemofilters for HDF were used. Qd was 500 for HD and Qdtotal was 600 mL/min for HDF. Replacement fluid volume for HDF was 44.4 ± 10.0 L per session. QB was 256 ± 23, 257 ± 25 mL/min and Treatment time was 4.1 ± 0.2, 4.0 ± 0.1 hours in HD and HDF, respectively. Removal rates (RR) of β2-microglobulin (β2-M:1.18kDa), protein (PRL:23kDa), α1-microglobulin (α1-M:33kDa) and α1-acid glycoprotein (AGP:44kDa) were investigated. Kt/V for urea and plasma clearances (CL) of β2-M, PRL and α1-M were measured.

**Results:** RR (%) of each substance was significantly higher in HDF than in HD (P < 0.005). BM:79.8 ± 3.2 vs. 70.8 ± 4.7, PRL: 75.3 ± 5.5 vs. 69.2 ± 6.6, α1-M: 40.0 ± 4.1 vs. 31.5 ± 6.4, α1-AGP: 11.9 ± 4.3 vs. 7.4 ± 4.8. Kt/V was 1.56 ± 0.22 (HDF) and 1.51 ± 0.19 (HD). Plasma CLs (mL/min) of β2-M were 95.7 ± 3.6 and 73.6 ± 3.7, those of PRL were 57.3 ± 4.3 and 28.1 ± 5.5 in HDF and HD, respectively.

**Conclusions:** The performance of HDF in removing LMWPs was superior to that of HD and there was no significant difference in Kt/V in both modes. An increased conversion by HDF greatly contributed to improved removal of LMWPs and appropriate control of dialysate flow rate improved the removal efficiency for small molecular substances to the level achieved by HD.

**Funding:** Private Foundation Support

**FR-PO654**

The Effect of Increasing Kt/V<sub>ema</sub> in the HEMO Study on Levels of Non-Urea Solute Toxins

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**Background:** In the HEMO study, outcomes were no better in patients randomized to “high dose” thrice weekly hemodialysis providing spKt/V<sub>ema</sub> 1.73 than in those randomized to “standard” hemodialysis providing spKt/V<sub>ema</sub> 1.32.

**Methods:** This study assessed whether “high-dose” treatment lowered levels of non-urea solutes. Solutes were measured by LC/MS/MS in plasma samples obtained at least 3 months after randomization in 1281 HEMO subjects.

**Results:**

<table>
<thead>
<tr>
<th>Solute</th>
<th>standard</th>
<th>high-dose</th>
<th>% change (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethylamine oxide µM</td>
<td>107±63</td>
<td>97±65</td>
<td>9 (-15,-2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Phenylacetylglutamine mg/dl</td>
<td>4.6±5.1</td>
<td>4.3±2.6</td>
<td>7 (-13,-9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symmetric dimethylarginine µM</td>
<td>4.3±1.4</td>
<td>4.2±1.3</td>
<td>-4 (-7,-1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Asymmetric dimethylarginine µM</td>
<td>0.92±0.24</td>
<td>0.93±0.23</td>
<td>-1 (-2, -3)</td>
<td>0.74</td>
</tr>
<tr>
<td>p-Cresol Sulfate mg/dl</td>
<td>3.3±1.7</td>
<td>3.4±1.7</td>
<td>2 (-4, 8)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Increasing Kt/V<sub>ema</sub> caused statistically significant but only modest reductions in the levels of trimethylamine oxide, phenylacetylglutamine, and symmetric dimethylarginine. Mathematical modeling showed that limited reduction in the levels of these solutes was a predictable consequence of the intermittency of treatment. Their reduction ratios with standard treatment were high and the increased intensity of treatment reflected by a 30% increase in Kt/V<sub>ema</sub> in HEMO’s high dose arm could not remove much more solute. Remarkably, increasing Kt/V<sub>ema</sub> in HEMO caused no reduction in the levels of asymmetric dimethylarginine or p-cresol sulfate, two solutes which have been associated with cardiovascular disease in dialysis patients. Modeling showed that stability of their plasma levels could be accounted for by increased solute production accompanying the increase in Kt/V<sub>ema</sub> and/or the presence of non-dialytic clearance.

**Conclusions:** Levels of non-urea solutes may fall only slightly or not at all when Kt/V<sub>ema</sub> is increased above standard levels for thrice weekly treatment. Treatments that are more effective in reducing solute levels may be required to improve outcomes.

**Funding:** NIDDK Support, Veterans Administration Support

**FR-PO655**

Improved Protein-Bound Uremic Toxins Dialytic Removal with Use of Albumin Binding Competitors: An In Vitro Human Whole Blood Study

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**Background:** Protein-bound uremic toxins (PBUT) are intensively studied retained solutes that accumulate in chronic kidney disease patients. Efficient removal of PBUTs is critical to improving the dialytic removal of PBUTs by increasing their free fractions with use of protein binding competitors.

**Methods:** The binding properties of indoxyl sulfate (IS), indole-3-acetic acid (IAA) and hippuric acid (HIAA), and their binding competitors, iopropen (IBU), furoxicidone (FUR) and tryptophan (TRP) were studied by rapid equilibrium dialysis (RED) to select suitable model compounds for the HD study. The method was then tested in an in vitro HD experimental model with human whole blood spiked with PBUTs. After 10 min baseline test, the binding competitors were introduced upstream of dialyzer blood inlet. The removal of urmicotoxins was estimated as the amount leaving dialysate outlet relative to the amount entering blood inlet.

**Results:** The infusion of IBU and FUR mixture (647±100µmol/l and 126±100µmol/l in blood, respectively) in the HD model increased removal of IS from 6.3 ± 0.1 to 15.2 ± 0.3 % (mean ± standard deviation) (2.4-fold) and IAA removal increased from 15.9 ± 0.2 to 29.8 ± 0.6 % (1.9-fold). TRP (1mmol/l in plasma) infusion increased the removal of IS and IAA to 9.4 ± 0.1% and 26.0 ± 0.3% (1.4- and 1.3-fold, respectively). Only moderate effects were observed in the change of HIPA removal.

**Funding:** Pharmaceutical Company Support - Renal Research Institute

**FR-PO656**

Variable Recovery Time After Hemodialysis Treatment

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**Background:** Prolonged recovery time after hemodialysis (HD) may predict adverse clinical outcomes. In the Frequent Hemodialysis Network a patient’s response to the Recovery Question was consistent over time. To determine if this consistency is also present among patients undergoing thrice weekly HD we compared responses to the Recovery Question after each treatment in a given week.

**Methods:** We asked 256 patients in 3 DCI HD facilities “How long did it take you to recover after your last treatment?” The number of patients who answered the question on the 1st, 2nd, and 3rd treatment was 221, 207, and 200, respectively; 148 patients (57.8%) answered the question on all 3 occasions. Recovery time was categorized as <0.5 hours (h), 0.5 to 6 hours and ≥ 6h.

**Results:** Among the 148 patients who answered the Recovery Question 3 times, recovery times were 6.9, 4.5 and 9.3 hours after the 1st, 2nd, and 3rd treatment was 221, 207, and 200, respectively; 148 patients (57.8%) answered the question on all 3 occasions. Recovery time was categorized as <0.5 hours (h), 0.5 to 6 hours and ≥ 6h.

**Conclusions:** This method increases the removal of PBUTs and has no effect on non-protein-bound solutes. Achieving higher dialytic removal of PBUTs by infusion of binding competitors is feasible and efficient to apply in current HD settings.

**Funding:** Pharmaceutical Company Support - Renal Research Institute

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

Underline represents presenting author.

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Among the patients with consistent short vs. long recovery, there were no differences in age, race, and vintage. There was a trend for women (59%) to be more likely to have recovery ≥ 6 h (p=0.09). After the 1st dialysis of the week, recovery was more likely (40%) to be ≥ 6 h among patients dialedy with a dialysate sodium concentration (DNa) <140 mEq/L vs. with a (DNa) ≥ 140 mEq/L (22%). However, similar differences were not observed for the 2nd and 3rd treatments.

Conclusions: There is significant variability among individual patients answers during the week when the recovery question is asked after each treatment.

FR-PO657
Quality Control and Improvement Union of Hemodialysis Centers: A New Management Model
Lijieying Han, Mei Wang. Dept. of Nephrology, Peking Univ People’s Hospital, Beijing, China.

Background: With the increasing incidence of end stage renal disease (ESRD) in China, more dialysis facilities are being opened. There are huge variations of patient care staffing levels and quality of care. How to maximize the utilization of existing health resources, optimize the management of hemodialysis patients and improve quality control are important issues. The aim of this study was to investigate the feasibility and effects of quality control and improvement union comprised of best hospitals and basic hospitals on patients’ medical quality control and improvement.

Methods: The HD union was constructed and specific measures were determined including, 1) Quarterly continuous quality improvement (CQI) meetings, 2) education based on typical cases including extensive discussions, guidelines and latest research results introductions, 3) lectures focusing on key questions, 4) opening green channel and construction of two-way referral system. Paired t-test was used to compare the differences of medical parameters of each hemodialysis center before and two-years after construction of HD union.

Results: The leading center of HD union was the HD center from Peking University People’s Hospital. Cooperating centers were other eight centers from class three and class two hospitals. After quarterly CQI meetings, all union members learned how to do medical quality control and improvement, constructed standards and procedures for diagnosis, cure and nursing of their HD center, established the institutions of lab exam and regular round frequency, added necessary examinations and implemented all-around management of HD patients. Green channel for intractable cases transfer were applied successfully. Thereafter, MMT appears to be a feasible and acceptable intervention for CKD patients and home practice. There were no significant between-group differences in affective response, anxiety, depression, self-reported health or coping skills at baseline or in change over time. Retention rate was 91.7% overall and 83.3% for the MMT group.

Conclusions: MMT appears to be a feasible and acceptable intervention for CKD patients during HD, although effectiveness remains to be demonstrated. Small sample size and low baseline distress levels in the study population limited the power to establish effects of MMT. Further research is needed to determine if abbreviated MBRS is sufficient to benefit tolerability of HD in this population. Focus on patients with higher baseline distress levels in future research would increase the likelihood of observing clinical benefit.

FR-PO659
Fluid Management Parameters Are Associated with Dialysis Recovery Time in Conventional Dialysis Patients
Wael F. Hussein,1,2 Rohini Arramredddy,1,2 Marc Reiterman,1 Sumi J. Sun,1 Brigitte Schiller,1,2 1Dept of Medicine, Division of Nephrology, Stanford Univ, Palo Alto, CA; 2Satellite Healthcare, San Jose, CA.

Background: Longer dialysis recovery time (DRT) is associated with increased mortality and shorter time to hospitalization. We studied the association of fluid management and hemodynamics with recovery time in conventional hemodialysis (HD) patients.

Methods: Self-reported DRT, obtained by asking “How long does it take you to recover from a dialysis session?”, was recorded for 2,689 patients undergoing thrice weekly adequate HD in 46 centers in 3 states. Ordinal logistic regression was used to study the association between patient and dialysis characteristics with DRT. Statistical adjustments were made for age, gender, race, vintage and baseline distress levels in the study population likely limited the power to establish effects of MMT. Further research is needed to determine if abbreviated MBRS is sufficient to benefit tolerability of HD in this population. Focus on patients with higher baseline distress levels in future research would increase the likelihood of observing clinical benefit.

FR-PO660
Different Adsorptive Properties of Hemodialysis Membranes May Cause Selective Depletion of Plasma Proteins
Jan Mares, Lukas Kielberger. Nephrology, Charles Univ, Plzen, Czech Republic.

Background: During hemodialysis (HD) session, plasma proteins are adsorbed to the surface of HD membrane. The resulting biofilm affects both dialyzer permeability and biocompatibility. The aim of this study was to analyze its composition in different HD membranes.

Methods: Twelve long-term HD patients were assigned to 4 HD with three different dialyzers in a cross-over design: ethylene-vinyl-alcohol/EVAL (KF-201-1.8C, Asahi Kasei), polysulfone (F8 HPS, Fresenius), and vitamin E-substituted polysulfone (ViE-18, Asahi Kasei). After HD session, the biofilm was eluted with acetic acid. Obtained proteins (200 µg) were separated by 2-dimensional electrophoresis and fractions showing distinct abundance across groups were identified by tandem mass spectrometry. Blood was sampled along the session to enable subsequent confirmatory studies (ELISA).

Conclusions: Long DRT affects a large proportion of HD patients. Optimizing UFR and controlling IDH are critical measures to improve quality of life for these patients.

FR-PO668
Feasibility of Mindfulness Meditation Training During Dialysis for Patients with Chronic Kidney Disease and Effect on Tolerability of Sessions
James C. Wasserman,1 Daniel Schupack,2 Andrew E. Williams,3 Paul K. Han,4 George K. Dreher,5 Mary Bitterauf.1 1Div of Nephrology, Maine Medical Center, Portland, ME; 2Center for Outcomes Research and Evaluation, Portland, ME; 3Maine Medical Center, Portland, ME; 4Maine Medical Center Research Inst, Portland, ME; 5MaineHealth, Falmouth, ME.

Background: Hemodialysis (HD) for CKD entails >/= 12 h of weekly treatment, creating significant distress for patients. Mindfulness-Based Stress Reduction (MBSR) has effectively helped patients with other chronic diseases cope with distressing symptoms and treatments. An abbreviated form of MBSR (Mindfulness Meditation Training, MMT) was incorporated into HD sessions to explore its feasibility, acceptability and potential effects on distress.

Methods: 12 patients were randomly assigned to MMT during HD or usual care. The MMT group underwent weekly 1-h individual sessions during HD for 4 wk. Within-session change in affective response was assessed with the Self-Assessment Manikin (SAM), validated measure of affective valence, arousal and dominance. Anxiety, depression, self-rated health and coping skills were also assessed with validated measures. Patient perceptions were assessed with qualitative interviews at study’s end.

Results: In qualitative interviews, patients reported improved tolerability of HD session length, positive intention to continue meditation and no significant issues with MMT sessions or home practice. There were no significant between-group differences in affective response, anxiety, depression, self-reported health or coping skills at baseline or in change over time. Retention rate was 91.7% overall and 83.3% for the MMT group.

Conclusions: MMT appears to be a feasible and acceptable intervention for CKD patients during HD, although effectiveness remains to be demonstrated. Small sample size and low baseline distress levels in the study population limited the power to establish effects of MMT. Further research is needed to determine if abbreviated MBRS is sufficient to benefit tolerability of HD in this population. Focus on patients with higher baseline distress levels in future research would increase the likelihood of observing clinical benefit.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mathematical Model of Protein Transport and Plasma Refilling in Hemodialysis
Bengt Lindholm,1 Mauro Pietriibiasi,2 Małgorzata Debowska,2 Alicja Wojcik-Zaluska,2 Wojciech T. Zaluska,2 Jacek Waniewski,2 ‘Baxter Novum & Renal Medicine, Karolinska Inst, Stockholm, Sweden; 2Inst Biocybernetics & Biomedical Engineering, Warsaw, Poland, Rehabilitation and Physiotherapy, Med Univ Lublin, Lublin, Poland; ’Nephrology, Medical Univ Lublin, Lublin, Poland.

Background: Mathematical modeling offers a way to estimate quantities we cannot access directly during hemodialysis (HD). Here we propose a whole-body model of vascular refilling describing water and protein shifts across the capillary membrane during HD. The model was applied to reproduce profiles of plasma volume and serum total protein concentration in patients (pts) undergoing HD. Methods: The double-compartment model (vascular and interstitial space) was based on balance equations of protein mass and water volume in each compartment. The net transport across the capillary wall is the sum of the flow through the membrane’s pores and lymphatic flow. The capillary membrane is described according to the three-pore theory. Two transport parameters of the model, the relative number of large pores (Lp) and the total permeability surface area product (LpS) of the capillary membrane, were estimated from volumetric data and blood samples collected in 20 stable, non-diabetic pts during 60 HD sessions. Results: Lp and LpS were estimated to 10.0 ± 8.4 mL/min/mmHg and 0.062 ± 0.041. The model predicted profiles of plasma volume and serum total protein concentration with an average root-mean-square error < 2%, with larger errors only in pts with very high initial drop in blood volume. When increasing the assumed value of interstitial/serum protein ratio from 0.3 to 0.6, while the total refilling rate remained similar, the value of individual pore flow changed so that filtration through large pores at its peak was 40% smaller and absorption through small and ultrasmall pores was 80 and 60 % higher, respectively. Conclusions: The model proposes a mechanistic interpretation of fluid transport processes induced by ultrafiltration during HD. The estimated values of individual flows through each kind of pore and lymphatic absorptive represent the relative impact of these not-measurable quantities on total vascular refilling. Funding: Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

Effect of Computationally-Optimized Vibration on Clearance of Solutes During In Vitro Hemodialysis
Katherine N. Ghabrian,1 Susan J. Lewis,1 Joseph L. Bull,2 John J. Pirte,1 Bridgett A. Scoville,1 Thomas Veloseni,1 Brad Urrerant,3 Selim Perkins,4 Bonnie A. Malley,5 ‘Coagulation Laboratory, Univ of Michigan, Ann Arbor, MI; 2Dept of Biomedical Engineering, Univ of Michigan, Ann Arbor, MI; 3St Alexius Medical Center, Hoffman Estates, IL; 4Dept of Physiology and Pharmacology, Western Univ, London, ON; 5Dept of Mechanical Engineering, Univ of Michigan, Ann Arbor, MI.

Background: Our previous in vitro studies demonstrated that the addition of vibration enhances dialytic clearance of solutes by a median of 18% during CVVHD. In this study, we applied computational fluid dynamics to determine vibration’s effects during hemodialysis and correlated them using an in vitro hemodialysis model. Methods: Based on predictions of a computational fluid dynamic models, two vibration settings (120 Hz/0.176 mm [360 Hz/0.075 mm] were selected and applied to a F8 dialyzer (1.8 m² Fresenius) during in vitro hemodialysis using blood-dialysate flow rates of 300/600 mL/min, respectively. Mean transmembrane clearances were analyzed for six solutes: urea, creatinine, gentamicin, vancomycin, indoxyl sulfate, and hippuric acid. Albumin, free hemoglobin, and LDL concentrations were measured after 4 hours of dialysis with applied vibration to assess blood and dialyzer integrity. Results: A one-way ANOVA revealed no significant difference between the control group and non-control vibration groups in solute clearance: urea, F(2,27)=1.801, p=0.184; creatinine, F(2,27)=2.525, p=0.099; gentamicin, F(2,27)=0.273, p=0.763; vancomycin, F(2,27)=0.003, p=0.997; indoxyl sulfate, F(2,27)=0.390, p=0.680; hippuric acid, F(2,27)=0.398, p=0.675. Four hours of vibration had no significant effect on blood and dialyzer integrity as measured by concentrations of albumin (F(1,22)=0.185, p=0.675), hemoglobin (F(1,22)=1.038, p=0.319), and LDL (F(1,22)=0.185, p=0.672). Conclusions: Although vibration has been shown to enhance solute clearance in patients, in this study we were unable to reproduce these results using our in vitro hemodialysis model using flow rates typically seen with intermittent hemodialysis. Funding: Other NIH Support - National Center for Advancing Translational Science [2ULTR00403].

Sevelamer Hydrochloride Improves Oxidative Stress in Maintenance Hemodialysis Patients
Siren Sezeg, Bahar Gurlekdemirci, Cihat Burak Sayin, Emre Tutal, Zeynep Bal, Fatma Nurhan ozdemir Acar. ‘Dept of Nephrology, Baskent Univ Faculty of Medicine, Ankara, Turkey.

Background: Oxidative stress plays a key role in the pathogenesis of cardiovascular diseases. Superoxide dismutase (SOD) and malondialdehyde (MDA) are well-known antioxidant enzymes that detoxify advanced glycation end products (AGEs). We thought that avoiding calcium intake and through pleiotropic effects, sevelamer hydrochloride might be a differential influence in terms of oxidative stress. The aim of this study is to examine the effects of phosphate binders (PBs) on the components of the oxidative stress and clinical and biochemical parameters including pulse wave velocity in our maintenance hemodialysis (MDH) patients. Methods: A total of 111 patients (mean age: 52.2 ± 14.3 years; mean duration of dialysis: 9.7 ± 4.8 years) undergoing maintenance hemodialysis and using the same PBs at least one year were enrolled into the study. Patients were divided into two groups according to usage of PBs as sevelamer based PB (group 1; n = 84 and calcium based PB (group 2; n=27). Biochemical parameters were assessed from monthly clinical visits. Serum AGE, MDA and SOD levels were determined by ELISA method. Pulse wave velocity (PWV) was determined by using the SphygmCor system. Results: Groups were similar in means of demographic characteristics and URR levels. Patients in group 1 had significantly lower AGE (p: 0.018), higher MDA (p: 0.027) and SOD (p: 0.012) levels. Although both baseline and first year PWV values were similar in two groups, PWV values significantly decreased in group 1 (p<0.001) where increased in group 2 (p: 0.021) in the second year analysis. In linear regression analysis, serum AGE levels were detected as the unique predictor of DPWV (p: 0.005). For each 1 mL/min of increased level of AGE resulted in 0.53 cm/sec of increased level of PWV (p: 0.005, CI: 0.016-0.089).

FR-PO666

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Conclusions: Despite similar phosphorus levels and dialysis adequacy, sevelamer decreases serum AGE and increases serum MDA and SOD levels as well as improves PWV. Thus, sevelamer improves the oxidative stress and cardiovascular risk by pleiotropic effects when compared to calcium based phosphate binders.

FR-PO666
Preliminary Study About Optimal Dosage of Heparin Locking Solution to Maintain the Patency of Hemodialysis Catheter Jung-woo Noh, Eunjung Kim, Ja-Ryong Koo. Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym Kidney Research Inst, Seoul, Korea.

Background: Hemodialysis catheters (HC) are routinely heparin locked to maintain patient patency. This practice may cause bleeding episodes. The amount of heparin for heparin locking solution at many dialysis centers has been decreased recently to reduce the risk of bleeding. However, the effect of this change on patency of HC is unknown. We compared the patency of HC between four types of heparin amount of 4000, 5000, 7500, and 15000 units (U).

Methods: This observational study included 126 chronic hemodialysis patients using HC in Hallym University Medical Center from March 2011 to July 2014. 29 patients received a 4000 U, 41 patients received a 5000 U, 44 patients received a 7500 U and 41 patients received a 15000 U of heparin. The primary outcome was composite outcome: frequency of thrombolytic instillation, change of hemodialysis line due to dysfunction of HC and HC obstruction due to thrombosis. We also compared activated partial thromboplastin time (aPTT) levels between groups just before and 10 minutes after the end of each hemodialysis.

Results: The composite outcome were 2.44±5.42, 1.06±3.46, 0.40±1.18 and 0.52±1.16 episodes/100 catheter-days, respectively (p=0.03). 4000U group showed especially high rate of occurrence of events compared to other groups receiving more than 5000 U of heparin. However, event rate of HC obstruction due to thrombosis was not significantly different: zero episodes/100 catheter-days for 4000U and 15000U groups, 0.01±0.05 episodes/100 catheter-days for 5000IU group and 0.14±0.61 episodes/100 catheter-days for 7500 IU group. At 10 minutes after heparin lock, prolonged aPTT was observed in all groups. When 10 minutes aPTT levels between 4000 U group and other groups are compared, those of 7500 U (p=0.007) and 15000 U (p=0.004) groups were significantly prolonged. But there were no bleeding complications in those groups.

Conclusions: Low concentration heparin lock solution with total amount of 4000 U do not increase HC obstruction due to thrombosis, but increase in thrombolytic instillation and set change. Higher concentration heparin lock solution with total amount over 7500 U prolonged the aPTT without bleeding complication.

 Funding: Clinical Revenue Support

FR-PO667
Association Between Depressive Symptoms and Dependency with Mortality in Hemodialysis Patients After 5 Years of Follow-Up Joaquín Manrique, María del cielo Mena, Eva Cerdán, Laura Catalan. Servicio de Nefrología, Complejo Hospital de Navarra, Pamplona, Spain; Nursing Staff. Servicio de Nefrología, Complejo Hospital de Navarra, Pamplona, Spain.

Background: The prevalence of depression and its role in mediating survival of patients with end-stage renal disease (ESRD) has been highly controversial. Moreover, according to the population ages, their limitations in performing daily activities affect their wellbeing.

Methods: We have evaluated depressive symptoms and dependency associated with mortality in a longitudinal study of 148 hemodialysis (HD) outpatients followed for 5 years. Depressive symptoms were assessed using the Beck Depression score (BDs), and dependence by Barthel scale (BS) performed by nursing HD staff.

Results: Depressive symptoms are common among patients on hemodialysis. Both of them may as well as increase the burden on caregivers and the use of health services.

Conclusions: Our study shows that the disability in self-care and the presence of depressive symptoms are associated with increased mortality and decreased survival of patients on hemodialysis.

 Funding: None

FR-PO668
Limitations of Access Recirculation due to a Low Access Flow Rate on Middle Molecule Clearance During Post-Dilution Hemodiafiltration J. Ken Leypoldt, Markus Storr. Renal Therapeutic Area, Baxter Healthcare Corporation, Deerfield, IL; Research & Development, Gambro Dialyssatoren GmbH, Hechnigen, Germany.

Background: Post-dilution hemodiafiltration (HDF) with a high convective volume (CV) is associated with lower overall patient mortality, potentially due to high middle molecule (MM) clearance from the patient (Kp). A higher CV can most readily be achieved by extending the treatment time or increasing the blood flow rate (BFR); however, the effect of access recirculation due to a low access flow rate (AFR) when increasing the BFR on MM Kp during HDF has not been previously quantified.

Methods: A theoretical mass balance model for assessing the effect of a low AFR on MM Kp was formulated. Access recirculation was assumed to occur when the BFR exceed the AFR. The model demonstrates that higher MM Kp is dependent on HDF membrane properties, AFR, BFR, CV and the fluid removal rate from the patient (FRR).

Results: Sample results are tabulated for a patient with a hematocrit of 33% at different AFRs and BFRs maintaining a fixed filtration fraction of 25% during a 4-hour HDF treatment with a FRR of 0.5 L/hour. MM filter clearance was assumed to depend on CV with a diffusive clearance of 75 mL/min and a sieving coefficient of 0.7.

When the AFR is higher than the BFR, MM Kp increases with increasing CV. At low AFR, increasing the BFR above the AFR results in a lower MM Kp than expected. Indeed, increasing the BFR above the AFR can even lead to a reduction in MM Kp.

Conclusions: High convective volumes during post-dilution HDF achieved by using high blood flow rates may not result in higher middle molecule clearance if the access flow rate is low. Routine assessment of access recirculation or access flow rate may be necessary during post-dilution HDF with high blood flow rates to improve patient outcomes.

 Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

FR-PO669
Protein Biofilm and Its Relation to Dialyzer Permeability for Middle Molecular Weight Markers in Three Polysulfon Membranes Lukas Kielberger, Jan Mares. 1st Dept of Internal Medicine, Charles Univ Teaching Hospital, Plzen, Czech Republic.

Background: Membrane permeability, particularly in terms of middle molecular clearances, is largely dependent in vivo on the formation of a protein biofilm. Our aim was to assess its dynamics during HD session together with molecular composition of the biofilm.

Methods: 12 HD patients were assigned in a cross-sectional design to Xevonta® HD2® (B-Braun, 2.3 m²), CorDiax FX100® ( Fresenius, 2.2 m²) and Polyflux® 210H (Gambro, 2.1 m²) dialyzers. Blood pre- and post-dialysis was sampled at 0, 15, 60, and 240 min; spent dialysate was collected from the dialyzer and produced for analysis.

Results: At the beginning, Xevonta and FX dialyzers showed significantly higher in vivo sieving coefficients for all MWs up to 26 kDa (ml/min) then Polyflux dialyzer (p<0.01). After 15 min, Xevonta and FX permeability decreased significantly (p<0.01) in all MW classes while in Polyflux, only MW<21 kDa (BFRP) were affected (p<0.01). The total protein content of membrane biofilm was similar in all three dialyzers: 118±85, 41±10, and 40±17 mg protein per dialyzer for Xevonta, FX, and Polyflux, resp. Significant differences in protein composition were captured in 48 out of 231 protein fractions. Among them, complement factor H-related protein 3 (FHR3), insulin-like growth factor binding protein 4 (IBP4), or multiple fibrin fragments (FDP) were identified. While FDP and IBP4 were prevalent in eluates from FX and Xevonta dialyzers (p=0.005 and 0.001, resp.), FHR3 was abundant in Xevonta only (p=0.01).

Conclusions: Even with modern biocompatible dialyzers, in vivo permeability decreases along HD session, probably due to biofilm formation. The decrease occurred irrespective of total protein adsorbed, compromising rather membranes primarily more permeable and higher MWs. Differences in biofilm composition are complex and may impact both dialyzer permeability and biocompatibility.

 Funding: Government Support - Non-U.S.
FR-PO670
Protective Effects of Intravenous L-Carnitine (LC) Administration on Development of Cardiomyopathy in Hemodialysis (HD) Patients Takahisa Uchino, 1 Jyunichiro Hashiguchi, 1 Satoshi Funakoshi, 1 Hiroshi Ichinose, 2 Osamu Sasaki, 1 Kenji Sawae, 1 Miki Yano, 1 Yutaka Morita, 1 Kazunori Utsunomiya, 1 Yoko Obata, 2 Tomoya Nishino, 7 Miwa Shirahama, 1 Takashi Harada, 2 Nagasaki Kidney Center, Nagasaki, Japan; 2Nagasaki Univ School of Medicine, Nagasaki, Japan.

Background: Due to loss via dialyzer patients on maintenance HD often suffer from dialysis-related cardiac deficiency, causing various clinical symptoms. Cardiomyopathy Consensus Conference in 2003 convened by The National Kidney Foundation had reported that the level of evidence was “moderate” for cardiomyopathy. Recent studies have shown that L-carnitine can improve left ventricular (LV) function in HD patients. In this study, we aimed to investigate whether intravenous administration of LC can prevent the development of cardiomyopathy in HD patients as assessed by M-mode ultrasound cardiography (UCG).

Methods: Thirty-eight HD patients without reduced left ventricular function were treated with intravenous administration of 1000mg/kg body of LC at the end of every HD session for 12 months. M-mode UCG assessments were undergone in all subjects at the three points: 1 year prior to the treatment, the start of LC administration and year after the treatment.

Results: As shown in Figure 1, average %FS (fractional shortening) significantly declined during 1 year before the start of LC, then stabilized after the treatment, suggesting LC administration might protect the progression of LV contraction impairment. Average early diastolic filling velocity (E) / atrial filling velocity (A) ratio showed similar pattern, suggesting LC treatment could be protective in LV diastolic disorder. LC treatment also might delay LV hypertrophy progression.

Conclusions: Intravenous LC administration can be a candidate therapy for protection of the development of cardiomyopathy in HD patients.

Funding: Private Foundation Support

FR-PO671
Symptoms and Quality of Life Among Patients Receiving HD Mark L. Unruh, 1 Kim J. Cox, 1 Stephen H. A. Hernandez, 2 Sanah Parvez, 2 Mark Parshall. 2 "Div of Nephrology, Univ of New Mexico; 2College of Nursing, Univ of New Mexico.

Background: Health-related quality of life (HRQOL) assessment is a required condition of coverage for HD providers, but standard measures may not adequately reflect the impact of symptoms and treatment on QOL for patients receiving HD or the concerns that matter most to them. The purpose of this qualitative study is to more fully characterize patients’ perspectives on the symptoms and treatment experiences affecting their QOL.

Methods: We conducted semi-structured interviews with a diverse sample of 50 HD patients (48% Female; 42% Hispanic; 30% American Indian; 14% Black; 12% Non-Hispanic White) to elicit their experiences with diagnosis and treatment of ESRD and the symptoms and aspects of treatment that have the greatest impact on their QOL. Interviews were audio-recorded, transcribed, and analyzed for themes using an interpretive-approach.

Results: Participants recalled that the initial diagnosis of ESRD was received with shock and denial. Over time, patients reported that QOL was associated with “taking control” of some features of their treatment. Common symptoms associated with HD, such as cramping and fatigue, were described as potentially manageable when patients were able to participate in decisions about fluid removal and scheduling of HD treatments. Patients who formed a partnership with their providers to negotiate fluid removal reported fewer episodes of severe cramping and improved QOL. Similarly, being able to choose among a variety of days and shifts for HD treatment enabled patients to manage fatigue, work hours, travel, and attendance at social events. These factors were critically important to the QOL in our relatively young sample (median age = 53; median duration of HD treatment = 4 years).

Conclusions: This is one of the largest and most diverse qualitative studies of symptoms among patients undergoing HD. There were few differences in symptoms or the impact of treatment on QOL among racial and ethnic groups. Findings highlighted the importance of fluid management and fatigue to patient experience.

Funding: Pharmaceutical Company Support - Dialysis Clinic Inc.
FR-PO675
Association of Time-Averaged Concentration of Hemoglobin with Mortality: Results from a Large U.S. Hemodialysis Cohort

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In hemodialysis (HD) patients the time averaged concentration of hemoglobin (Hb_tac) can be estimated from pre- and post-HD hemoglobin (Hb) levels. It has been suggest that Hb_tac may be an appropriate indicator for anemia management (Siga, Int Urol Nephrol 2014). However, the association between Hb_tac and mortality has not yet been evaluated.

Methods: We analyzed hemoglobin data obtained by Crit-Line™ monitor (CLM) in chronic HD patients. A 6-month baseline period with at least 10 CLM measurements preceded a 12-month follow-up during which outcomes were noted. We used Hb values from HD sessions following a short interdialytic interval. Hb_tac was computed as follows (Krisper, NDF 2000): Hb_tac = 0.5 × Hb_post + 0.38 × 1.28. We defined Hb_post as the average Hb between minutes 5 to 20 from the start of the CLM recording, and Hb_post as the average of Hb between minutes 5 to 20 from the end of the CLM recording. The relation between Hb_tac during baseline and mortality was explored by spline analysis of hazard ratio (HR).

Results: We studied 982 patients (136) with a total of 19,142 CLM measurements. Average Hb_tac was 10.72 g/dL (SD 0.81, range 7.27 – 14.62 g/dL). The mortality rate during follow-up was 11.6 per 100 patient-years. The minimal HR (figure 1B) was 0.82 at Hb_tac of 10.87 g/dL. The solid line represents mean HR, the dotted line 95% confidence intervals.

Conclusions: Hb_tac is associated with mortality, levels around 10.9 g/dL are associated with the lowest mortality risk. Studies are required to further explore methods to estimate Hb_tac based on Hb measurements by the CLM and the usefulness of Hb_tac for mortality prediction.

Funding: Pharmaceutical Company Support - Fresenius Medical Care Company Support - Sanofi Aventis

FR-PO676
Prediction of Changes in Serum Albumin Levels Among Hemodialysis Patients by Serum Neutrophil Gelatinase-Associated Lipocalin Levels

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Circulating concentration of neutrophil gelatinase-associated lipocalin (NGAL) or LCN2 is elevated in acute and chronic kidney diseases. Recently, we reported that, in a cross-sectional study, serum NGAL concentrations in maintenance hemodialysis (HD) patients were determined independently by % creatinine generation rate, white blood cell count and anion gap, indicating that NGAL is a marker of good nutritional conditions. Clinical impact of NGAL was further evaluated in a prospective analysis.

Methods: Correlations of baseline nutritional indices with baseline and follow-up serum albumin levels and with changes in albumin levels after a year were investigated among 87 HD patients using linear regression analysis.

Results: Follow-up albumin levels were positively correlated to baseline NGAL, serum albumin levels and rank of variables in the risk model.

Conclusions: Serum NGAL level in HD patients appears to be a unique biomarker allowing prediction of alteration in serum albumin levels in a year.


FR-PO677
Race, Health-Related Quality of Life and Mortality in a Large Cohort of Brazilian Multiracial Hemodialysis Population

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Background: Studies developed in patients undergoing maintenance hemodialysis (MHD) in the United States (US) indicate that the survival and the health-related quality of life (HRQOL) are better in African Americans and other racial minorities than in Whites. Similar to the US, Brazil is a country with a diverse racial population. There is a lack of studies to investigate if there are differences in HRQOL and mortality by race in Brazilian MHD patients. The present study developed in a multiracial Brazilian MHD population investigated associations of race (Whites as reference) with HRQOL and survival.

Methods: A prospective cohort of 1084 MHD patients (11.8% White, 61.3% mixed race, 26.1% Black) enrolled in the Prospective Study of the Prognosis of Chronic Hemodialysis Patients (PROHEMO) developed in nephrology clinics of Salvador, Brazil. The predictor variable was race (White as reference). Outcomes were mortality and HRQOL scores, using the KDQOL-SF. Multivariable linear regression was used for differences in scores and Cox regression for mortality. Associations were adjusted for age, sex, diabetes, heart failure, blood hemoglobin and vintage.

Results: Mean age was significantly lower (P<0.001) in Blacks (49.2±14.0 yrs) and mixed races (47.6±14.5 yrs) than in Whites (55.0±13.7 yrs). In the multivariable linear regression differences were not observed by race for PCS, MCS, disease burden and effects of kidney disease. For symptoms/problems, a significantly (P=0.043) higher adjusted score (difference=3.6) was observed in Whites (than in Blacks). In the Cox model with complete adjustment for covariates, the hazard ratio (HR) was 0.95 (95% confidence interval (CI) 0.66-1.35) for the comparison between mixed race and White and 1.10 (95% CI=0.75-1.61) for the comparison between Blacks and Whites.

Conclusions: In disagreement with studies developed in the United States, this study developed in a multiracial Brazilian hemodialysis did not show worse HRQOL and higher mortality in whites as compared to patients of mixed race and Blacks.

Funding: Government Support - Non-U.S.
FR-PO678
Low Lymphocyte Counts Are an Independent Predictor of Mortality in Chronic Hemodialysis Patients: A Retrospective Cohort Study

Background: Mortality in chronic hemodialysis populations remains high. Lymphopenia has been associated with increased cardiovascular risk in the general population but few data are available on the effect of low lymphocyte counts on long-term survival of hemodialysis patients.

Methods: Retrospective study of a single-center cohort of 689 hemodialysis patients using monthly laboratory results and dialysis parameters extracted from a center database and a national registry. The effect of baseline and time-changing lymphocyte counts on overall mortality was studied using the Kaplan Meier and Cox proportional hazard methods.

Results: Lymphopenia (<1200 µL) was present in approximately one third of incident hemodialysis patients and correlated with older age, lower creatinine, lower phosphorous, higher Kt/V and a positive history of ischemic heart disease. Lymphopenia was not associated with classical markers of malnutrition-inflammation complex such as albumin, normalized protein catabolic rate, BMI and CRP. Baseline lymphopenia was associated with classical markers of malnutrition-inflammation complex such as albumin, hemoglobin, BMI, CRP and Kt/V and history of ischemic heart disease.

Conclusions: Lymphopenia is highly prevalent in hemodialysis patients and is a strong predictor for patient death. The association was stronger when lymphocyte counts were considered as a time-changing variable and independent of other risk factors for patient death. Lymphopenia was not associated with markers of the malnutrition-inflammation complex such as albumin, CRP and Kt/V and history of ischemic heart disease.

FR-PO679
Current Status of Hemodialysis in China
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Background: In May 2010, the first nationwide, web-based prospective renal data registration platform, the Chinese Renal Data System (CNRDS) was launched in China. The purpose of this study was to determine the current status of hemodialysis in China by analyzing the data from CNRDS.

Results: (1) There were 4047 domestic hemodialysis centers and 339748 survival patients were registered by the end of 2014. (2) In the 339748 patients, 58.85% were male. The average age was 54.9 years and average dialysis duration was 42.2 months. The three leading causes of ESRD were glomerulonephritis, diabetic nephropathy and hypertensive renal diseases. (3) 4322 patients died in 2014, with an average of 61.9 years and average dialysis duration of 39.7 months. The main causes of death were cardiovascular events and stroke, followed by infection and gastrointestinal bleeding. (4) In the patients, 44.1% had predialysis blood pressure less than 140/90mmHg; 55.4% had hemoglobin concentration ≥100g/L and 80.3% had albumin levels ≥35g/L. 39.6% had serum calcium between 2.10 and 2.50mmol/L; 34.7% had serum phosphorus between 1.13-1.78mmol/L; 53.9% had PTH between 130 and 600pg/ml.

Conclusions: As Chinese National Health and Family Planning Commission have enhanced the basic medical security system on hemodialysis, both the population and the quality of hemodialysis have increased in recent years.

Funding: Government Support - Non-U.S.

FR-PO680
Outcomes and Quality of Care in Rural versus Urban Managed Dialysis Patients
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Background: A proportion of patients are managed in remote satellite units in Manitoba, Canada. Urban nephrologists oversee all dialysis care; however family physicians (FP) co-manage patients. This study examines outcomes and quality of care indicators in rural vs urban managed patients.

Methods: Prospectively collected clinical data from the Manitoba Renal Program and administrative health data housed at the Manitoba Centre for Health Policy were analyzed retrospectively. All adult (~1990 to 2010) and pediatric patients (~90 days to 2010) were included. Individuals dialyzing in rural satellite units (n=510) more than 50% of the time were compared to their urban (n=2629) counterparts. Differences in cohort characteristics were analyzed at baseline as well as differences in primary care and quality indicators. Regression analyses examined differences in hospitalizations and days in hospital. Cox proportional hazard models were performed to examine differences in survival.

Results: Patients in rural satellite units vs urban were younger, 58 ± 6 yrs (p=0.002), but were more likely to have DM 69.4 vs 55.3% (p<0.0001), PVD 9.4 vs 4.0% (p<0.001) and HDL (1mM, Angiogram or PTCA) 42.8 vs 34.2% (p=0.002). More rural patients accessed a FP at least once per year 85.7% vs 67.3% (p<0.0001) and 85.3% vs 68% (p<0.001), after controlling for sex, income, Charlson, era, age and region at the start of dialysis.

Conclusions: Survival in a cohort of patients dialyzing in remote satellite units was found to be superior to their urban counterparts, after controlling for co-morbidities. A potential reason might be increased primary care involvement, although differences were not seen in traditional quality of care indicators.

Funding: Private Foundation Support

FR-PO681
Applying Hemodialysis Clinical Quality Indicators to Individual Patients: A Useful Mortality Prognostic Tool in Clinical Practice?

Background: Hemodialysis (HD) care is routinely assessed by a set of clinical and laboratorial parameters, known as Clinical Quality Indicators (CQI). CQI registry and monitoring constitutes an instrument to evaluate the quality of care provided at each HD unit. The purpose of this study was to determine whether CQI, applied on an individual patient basis, is a predictor of mortality.

Methods: Retrospective study that included 334 patients of a HD Unit from 2011 to 2014. Demographic, clinical and laboratory data were collected. The CQI considered were eleven, which included target variables: spgKtV ≥ 1.4; weekly dialysis time ≥ 720 minutes; Albumin ≥ 3.5 g/dL; Hemoglobin between 10 and 12 g/dL; phosphatemia between 2.5 and 5.5 mg/dL; Ca×P product < 55 mg²/dL; PTH levels between 150 and 600 pg/ml; Ferritin between 200 and 800 mg/dL; Mean arterial pressure < 105 mmHg; Intelectal weight gain (IWG) ≥ 4% and fistula as vascular access. Single CQI were rated in a binary form (0 = not reached target/1 = reached target) at each monthly evaluation and the average were determined. Ultimately, the eleven parameters were added in a single variable for each patient (CQIP).

Results: During follow-up, 33% of patients died. In the Cox regression model, age (HR 1.09; CI 1.07-1.11; p<0.001), diabetes (HR 2.88; CI 1.92-4.32; p<0.001), peripheral arterial disease (HR 1.65; CI 1.09-2.44; p= 0.016) and CQIP (HR 0.73; CI 0.62-0.87; p<0.001) were shown to be independent predictors of mortality, after adjustment for other clinical and demographical factors. When CQIP was replaced by its constituent variables, albumin (HR 0.06; CI 0.08 -0.32; p<0.001), PTH (HR 2.8; CI 1.10-3.93; p = 0.023), IWG (HR 0.34; CI 0.14-0.83; p = 0.018) and fistulae presence (HR 0.61, CI 0.4-0.93, p = 0.021) presented statistical significance.

Conclusions: A set of parameters, generally applied as a quality care indicators, proved to be an independent predictor of death when applied to individual patients. This should be regarded as an easy and practical prognostic tool to be applied in current practice.

FR-PO682
Association of Estimated Glomerular Filtration Rate at Commencement of Maintenance Dialysis with Mortality Among Patients with Advanced Chronic Kidney Disease in Singapore
Tazeen H. Jafar,1 Jin Ai Zhen,1 John C. Allen,1 Saeideh Tavajoh,1 Khuan yew Chow.1 'Duke-NUS Graduate Medical School Singapore; 2National Disease Registry Office, Health Promotion Board, Singapore.

Background: Recent evidence suggest that higher estimated glomerular filtration rate (eGFR) at commencement of dialysis may be associated with increased mortality. However, there is scarcity of data on patients of Southeast Asian origin. We analyzed and compared mortality risk in patients with early and late start dialysis as measured by kidney function at dialysis initiation among Southeast Asian population of Singapore.

FR-PO683
Enhanced the basic medical security system on hemodialysis, both the population and the quality of hemodialysis have increased in recent years.

Funding: Government Support - Non-U.S.
Methods: We performed a retrospective analysis of patients enrolled in the Singapore Renal Data System database from 2008 to 2011. Patients were classified into groups by eGFR at dialysis initiation.

Results: In this total incident population (n=3708), a total of 1510 individuals died during a median follow-up period of 2.8 years. The hazard ratio (HR) and 95% CI associated with different levels of eGFR at commencement of RRF are shown in table below. The main multivariable model (n=3189 without missing information on covariates) associated with the eGFR at dialysis initiation within the groups: age, gender, level of education, smoking, presence of diabetes, ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, malignancy, hepatitis B, hepatitis C, kidney transplant, and modality of dialysis. Additional models accounted for serum albumin (n=2657), and serum ferritin (n=2462), and serum calcium (n=1628).

The results were consistent after accounting for serum albumin, serum ferritin, and serum calcium in the multivariable models.

Conclusions: Late initiation of dialysis is associated with a lower risk of mortality in comparison with early dialysis initiation in Southeast Asians in Singapore.

FR-PO683
Predicting Mortality for Patients Who Are on Hemodialysis–A National Cohort Study in Taiwan
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Background: Comorbid conditions and medical history provide prognostic information for dialysis patients. The objective of this study was to develop a prognostic model to predict short-term (6-months) and 1-year) and long-term (2.5-years) survival for incident hemodialysis (HD) patients.

Methods: Incident Taiwanese hemodialysis patients from 2006 to 2010 were extracted from National Health Insurance claim records. Prognostic model was developed by using combined conditions (summarized as Taiwan index), monthly income and medical history during one year before initiation of dialysis. Somner’s D statistic was used to assess the discrimination ability of our model.

Results: A total of 36,875 incidence HD patients were included in this study and the last follow-up day was December 31, 2011. More comorbid burden, male gender, history of acute kidney injury, dementia, admitting to intensive care unit, staying at nursing home and ever using ventilator were significant prognostic factors. Monthly income only had marginal effects on survival at 2.5 years. For discrimination ability, our model has Somner’s D statistics of 0.76, 0.76, and 0.75 for 6-months, 1-year, and 2.5-years survival, respectively.

Conclusions: Three prognostic models with same covariates for short-term and long-term survival in HD patients were found in this study. The consistency in model performance helps clinicians and patients to make decision.

Funding: Government Support - Non-U.S.

FR-PO684
Twice Weekly Treatment Eligibility for Incident Hemodialysis (HD) Patients
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Background: KDOQI guidelines advise that hemodialysis treatments constitute a conservative criteria, half of these were judged ineligible because of US requirements or HD-induced symptoms. Opportunity exists for incremental HD in a significant number of incident patients.

In the 225 patients who could achieve the target stdKT/V with 2/week HD, the mean spKT/V required was 0.83±0.36. A total of 105 or 25% of patients with measured Kru met all 4 criteria.

Conclusions: Urine collections disclosed that 225 or approximately 30% of 734 incident patients were eligible for 2/week HD based on solute kinetics alone. Using conservative criteria, half of these were judged ineligible because of US requirements or HD-induced symptoms. Opportunity exists for incremental HD in a significant number of incident patients.

FR-PO685
The Relationship of Diabetes and Congestive Heart Failure to Costs of Care in End Stage Renal Disease Patients
Sheetal Chaudhuri, Jane Brzozowski, Hao Han, Len A. Usyut, John W. Larkin, Mahathi Mothali, Terry Ketchersid, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

Background: Many Medicare patients (Pts) with end stage renal disease (ESRD) are known to have co-morbidities of diabetes mellitus (DM) and/or congestive heart failure (CHF). Total costs of care for ESRD Pts are likely to be dependent on patient comorbidities and likely to vary by geography. We investigated the relationship of DM and CHF based on Pts’ geographic location.

Methods: ESRD Pts with evidence of dialysis at any time during Jan 1, 2010 through Dec 31, 2011 and Medicare as their primary payer were analyzed. Pts were stratified based on Metropolitan Statistical Areas (MSA) and Medicare Part A and B costs were calculated from 100% Medicare data. T-test comparisons were performed for quartiles of total cost of care for four groups: based on vintage (incident [≥90 days on dialysis] or prevalent [≥3 years on dialysis]), as well as, comorbidities (no DM and no CHF, DM and no CHF, no DM and with CHF and with both DM and CHF).

Results: Claims for 107,659 Pts were analyzed. Total cost of care increased significantly as the percent (%) of Pts with CHF and DM increased; cost of care declined significantly as the % of Pts with neither DM nor CHF increased by MSA. Cost of care did not change with the increase in % of Pts without DM and with CHF. Yet, costs of care declined as % of Pts with DM and without CHF increased by MSA. These patterns were observed in both incident and prevalent Pts.

Figure 1. Costs of care by MSA (per member per month)

Incident Patients
Prevalent Patients

Results: These results identify differences in association between ESRD related co-morbidities and total costs of care: the % of Pts with both DM and CHF is higher in areas with higher total costs. Surprisingly, costs of care are lower in areas where the % of Pts with DM but without CHF is higher. Risk Adjustments should be considered.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO686
Long Term Outcomes Over 2 Years following a Dialysis Adequacy Quality Improvement Initiative
Sajida Yousoufi, Philip A. Karla, Janet Hegarty. 1,2
1 Royal Free NHS Foundation Trust; 2 Manchester Academic Health Sciences Centre.

Background: Dialysis adequacy is known to correlate with clinical outcomes such as mortality. Evidence based guidelines recommend that haemodialysis patients should achieve a urea reduction ratio of >65%. UK Renal Registry data shows wide variation in facility attainment of target URR. In 2010 the Salford Renal Network implemented an ambitious programme to uplift attainment of key quality of care indicators to within the top 10% in the UK; dialysis adequacy was a target in 2 phases of improvement in 2010-2012.

Methods: Our network implemented a quality improvement programme using collaborative methodology. We set four teams a different clinical indicator to work on over 12 months cycles for 2 successive years, guided by QI facilitation input. Unit A worked on URR in phase 1 and developed a package of changes using plan-do-study-act (PDSA) testing that was used for improvement by Unit B in phase 2. We analysed the long-term outcomes in these units for a further 2 years until May 2014.

Results: Both units reached their aim of >90% of patients achieving target URR>65% within their improvement year. Both units sustained the improvements for 2 years with no additional resource input after the collaborative. Changes included protocolled nurse-led changes to dialysis prescriptions, multidisciplinary review of vascular access, a nurse-led anticoagulation protocol, blood sampling protocol, and monthly reports.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Longer term outcomes from QI interventions are underreported with limited evidence on sustainability. We implemented multifaceted interventions to improve dialysis adequacy in our network to within the top 10% in the UK. Implementing evidence-based changes led by frontline staff trained in QI has sustained these improvements for 2 years after a formal QI intervention, improving quality of care for our patients.

FR-PO687
Clinical Effectiveness of Intermittent Infusion Hemodiafiltration (I-HDF) Compared with Conventional Hemodialysis: A Multicenter Clinical Trial
Michio Mineshima, Kei Eguchi. Clinical Engineering, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Intermittent infusion hemodiafiltration (I-HDF) using backfiltration of an ultrapure dialysis fluid has been developed to improve the peripheral circulation of the patient receiving a typical hemodialysis (HD) with repeated intermittent infusion by an automated dialysis machine, GC-110N (JMS Co. Ltd., Tokyo, Japan). In a typical HD treatment, excessive water removal often induces hypotension and muscle spasm. In the I-HDF, some 200-300 mL ultrapure dialysis fluid was infused into the blood component through the dialysis membrane at a rate of 100 mL/min, every 30 min. I-HDF, namely, means a HDF treatment with small amount of infusion volume, 1.4 to 2.1 L (200-300 mL × 7 times)/session.

Methods: In this paper, clinical effectiveness of I-HDF was evaluated in comparison with conventional HD (CHD) during a multi-center clinical trial that twenty chronic renal disease patients participated.

Results: A significantly lower value for time-averaged blood volume reduction was obtained with I-HDF compared with CHD in spite of there being no difference in the total amount of water removal. It was due to a higher plasma refilling rate in I-HDF. In addition, increasing peripheral blood flow rate in the patient’s toe was detected by a laser flowmeter for each infusion in many patients. The cleared space value defined as amount of normalized solute removal during a treatment were higher with I-HDF than CHD for many patients.

Conclusion: Intermittent Infusion HDF using an automated dialysis machine was effective for improvement of the peripheral circulation of patients receiving conventional HD.

FR-PO688
Impact of Post-Hospital Phone and Telehealth Care Management to Reduce Admissions: Experience from 28 US Dialysis Clinics
Rachel L. Wingard, Billie Axley, Kathryn A. McDougal, Andrew D. Howard, Joelle Heilemann, Perry Parlier, Sophia Rosen, Len A. Usvyat, Alexis Porras, Franklin W. Maddux. 1Fresenius Medical Care, Waltham, MA; 2Metropolitan Nephrology Associates, Clinton, MD.

Background: 2012 day 30 readmissions for hemodialysis (HD) patients (pts) were high at 35% in 2012 (USRDS). The Right Trac (RT) program aimed to address readmissions by telephone calls and dialysis team visits. In 28 clinics from Feb-Nov ‘14, RTCMs attempted weekly phone calls to pts at home or dialysis clinic, or via telehealth in the clinic for 30 days post hospitalization.

Results: In 28 clinics from Feb-Nov ‘14, RTCMs attempted weekly phone calls to pts at home or dialysis clinic, or via telehealth in the clinic for 30 days post hospitalization. RTCM rates ranged between 2.5 to 95%. RTCM calls during 30 days post-hospital showed significantly lower 60-day readmits ppy for pts with initial and >=1 follow-up calls. Telehealth also had lower 90-day readmits ppy vs. phone calls, although not significant. Further study is needed, especially in view of high RTCM rates.

FR-PO689
Reduced Hemodialysis (HD) Patient Hospital Admissions and Readmissions Associated With Right Trac™ Care Transitions Program
Rebecca L. Wingard, Billie Axley, Kathryn A. McDougal, Andrew D. Howard, Cathleen Ockee, Sharon Deluca, Janice B. Sitzlar, Len A. Usvyat, Franklin W. Maddux. 1Fresenius Medical Care, Waltham, MA; 2Metropolitan Nephrology Associates, Clinton, MD.

Background: 30-day readmissions for HD patients (pts) are high at 35% in 2012 (USRDS). The Right Trac (RT) Program addressed factors in the complex process of care transitions, with the aim to reduce hospital admissions and readmissions.

Methods: 26 HD clinics (3682 pts) were in RT. Interventions deployed in 3 phases (Apr ’13-Nov ’14). I: Pre- and post-hospital checklists for clinicians to manage pt teaching, anemia, nutrition, medications, and dry weight. II: Telephonic case management for 30 days post-discharge. III: Dialysis Link™ centralize clinical info exchange among providers, admission and readmit data from per pt per year (ppy) for “baseline year” (2012) vs. “full intervention year” (2014) were compared to 18 control clinics (2449 pts) matched for clinic size, admission and readmission rate, and urban vs. rural location at baseline. Poisson models with random effects for pty and clinic, adjusted for age, vintage, race, gender, ethnicity, DM, CHF, and COPD were constructed to assess the difference between baseline and intervention and between RT and control clinics.

Results: 30-day readmissions ppy declined from baseline to full intervention year in RT (0.88 to 0.65, p<0.001) and controls (0.73 to 0.6, p<NS); comparison of the change between groups was not significant (Fig 1). Admissions ppy declined from 2.5 to 95 for RT (p<0.001), and 2.14 to 1.9 for controls (p<NS); comparison of the change between groups was significant with greater decline for RT (p<0.001, Fig 2).

Conclusions: RTCM calls during 30 days post-hospital showed significantly lower 90-day readmits ppy for pts with initial and >=1 follow-up call. Telehealth also had lower 90-day readmits ppy vs. phone calls, although not significant. Further study is needed, especially in view of high RTCM rates.

FR-PO690
Predicting Early Mortality Among Hemodialysis Patients Using USRDS Data
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Background: Higher early mortality of hemodialysis (HD) is recognized. We sought to quantify the risk of early mortality and develop a robust prediction model which could potentially guide clinical decision-making.

Methods: The 2007-2012 data from the United States Renal Data System (USRDS) on incident HD patients, age >18 years, were randomly split as ‘training’ and ‘validation’ samples. Cox proportional hazards model with piece-wise constant coefficients was used to model all-cause mortality during day 0-90 and day 91-365 of HD. Those transferred to peritoneal dialysis or transplantation were censored. The resulting model was validated by C statistic.

Results: The mean age (n=611,094) was 63.61±14.9 years, with 130,473 deaths during the first year of HD. Mortality rates were 35 per 100 person-years in the first 90 days and 21 per 100 person-years during day 91-365. The discrimination p-values for day 0-90 and day 91-365 showed very good ability involved 23 variables including demographics characteristics, pre-ESRD care, laboratory values, co-morbidities as well as institutionalization status. In adjusted analyses, selected variables with significant time-varying effects are listed in the Table.
FR-PO691

Recent Evidence on the Impact of Medicare’s Bundled, Prospective Payment System for Renal Dialysis

Richard Hirth1, Tammine A. Nahra1, Adam S. Wilk1, Marc Turenne2, John Wheeler1, Kathryn Sleeman1, Wei Zhang1, Jonathan H. Segal1

1University of Michigan; 2Arbor Research Collaborative for Health.

Background: Medicare implemented an expanded prospective payment system (PPS) in 2011, including services previously paid by fee-for-service. One intent of the PPS was to incentivize providers to be more efficient in the mix of services provided.

Methods: We used Medicare claims to assess monthly trends from 1/2010-12/2014 for injectable drugs that were previously billed separately. For 2010, we assessed actual spending. For 2011-14, we projected spending based on reported utilization.

Results: ESA use declined in the months immediately pre- and post-PPS, continuing to decline through 2012. In 2013, ESA use leveled off. Use of iron products, often improving medication utilization overall and the use of lower cost therapies. These incentives seem to incentivize providers to be more efficient in the mix of services provided.

Conclusions: The expanded bundle dialysis PPS provided incentives for both lower medication utilization overall and the use of lower cost therapies. These incentives seem to have motivated an immediate movement toward lower cost methods of care. Facilities have been able to maintain a lower cost of care over the last two years. CMS continues to monitor facility costs and will continue to make a reduction to the ESRD PPS Market Basket through CY 2018, in accordance with section 217 of PAMA.

Funding: Other U.S. Government Support

FR-PO692

Effect of Medicare’s Payment Adjustment for Low-Volume Dialysis Facilities on Facility Closures

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Background: Small dialysis facilities may face higher per-treatment costs due to economies of scale. Since 2011 a low-volume payment adjustment (LVPA) raised Medicare payments to facilities with <4000 treatments in each of the 3 prior calendar years. A goal of this policy is to preserve access to care by preventing the closure of small facilities.

Methods: We tested the hypothesis that the LVPA prevented closures by examining the year-to-year closure rates of U.S. dialysis facilities during 2007-2013, before and after the policy, comparing facilities providing <4000 and >4000 annual treatments. Analyses with linear regression relate facility outcomes to prior year size, ownership, for-profit status, hospital affiliation, patient mix, regional location, modality mix and county characteristics, to examine the effect of the LVPA on 8 of treatments provided by facilities.

Results: Among low-volume facilities, year-to-year closure rates declined from 3.8%, 4.9% and 4.0% pre-LVPA, falling to 1.1%, 0.5% and 0.8% post-LVPA. Among facilities with >4000 treatments, closure rates also decreased, but to a much smaller extent (from 1.0%, 1.2% and 0.8% pre-LVPA to 0.6%, 0.2% and 0.3% post-LVPA).

Conclusions: In Medicare’s bundled payment system, closure rates decreased overall, with a much larger absolute reduction among small facilities. The gap in closure rates between small and large facilities fell from about 3% points before the policy to about 0.5% points after. LVPA appears to have helped prevent small dialysis facility closures, but it may also motivate some small facilities to avoid growing in order to retain the LVPA. Emphasizing a dialysis facility’s importance for patient access rather than size alone may help inform payment policy modifications.

Funding: Other U.S. Government Support

FR-PO693

Delayed Thrombectomy Increases Risk for Dialysis Catheter Placement

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Background: Arteriovenous dialysis accesses (fistulas or grafts) are associated with significant rates of thrombosis. Though timely thrombectomy may have a significant impact on immediate and long-term access survival, it is not always readily available. The goal of this study was to evaluate whether delayed thrombectomy increases risk for loss of dialysis access and subsequent placement of a dialysis catheter.

Methods: All patients at the Fairview Health System with thrombectomy as the primary reason for admission between January 2008 and April 2015 were included in this retrospective observational study. The electronic medical record was reviewed to evaluate type of access, timing of admission and declot, and access on discharge and 6 and 12 months after discharge. Baseline characteristics and proportions were determined for the overall population as well as stratified by tertile of time to thrombectomy, defined as the time from admission to the declot procedure. The outcomes of interest included need for dialysis catheter at discharge and 6 and 12 months after discharge. Logistic regression was used to evaluate the risk for delay of thrombectomy catheter use adjusting for prior intervention, access type, and time to thrombectomy.

Results: Of 444 patients identified using procedural codes, 122 were admitted primarily for thrombectomy. The mean age was 60.4 years, 65% were male, and 44.3% utilized arteriovenous fistula for access. Mean time to thrombectomy was 0.45 days (range: 0.05-1.13 days). Fifteen patients utilized a catheter for hemodialysis on discharge. Delayed thrombectomy was associated with a two-fold increase in requirement for catheter at discharge (OR 2.02; CI 1.19-3.43) and at 6 months (OR 2.04; CI 1.20-3.48). This association remained present at 12 months (OR 1.75; CI 1.02-3.00).

Conclusions: In this study of patients cared for within a large academic health system, a one day delay in thrombectomy doubled the risk for need for a dialysis catheter at discharge and 6 and 12 months after discharge. These results indicate that a clotted dialysis access should be considered a medical emergency.

Funding: Other U.S. Government Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

520A
Intradialytic Body Weight Reduction and Outcome of Vascular Access: Analysis of Data from the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS)  
Manabu Asano,1 Kenichi Oguchi,2 Akira Saito,3 Yoshihiro Onishi,1 Yosuke Yamamoto,4 Shunichi Fukuhara,5 Takashi Akiba,6 Tadao Akizawa,7 Busei Hospital, Saitama, Japan; J-DOPPS Research Group, Japan; 1Hope International, Kyoto, Japan; 2Inst for Advancement of Clinical and Translational Science, Kyoto Univ Hospital, Kyoto, Japan.

Background: There is no doubt that large-volume ultrafiltration is one of the important risk factors for vascular access (VA) thrombosis in hemodialysis patients. However, the relationships between intradialytic body weight reduction and VA patency are still in the middle of being discussed. We tried to determine whether large-volume ultrafiltration was practically associated with VA failure by means of the results obtained from the phase 3 and 4 J-DOPPS.

Methods: Referring data from the phase 3 and 4 J-DOPPS, the current analyses were limited to 2736 patients who were evaluable for VA patency and body weight change during dialysis. They were assigned to one of the following three groups according to the tertiles (T1-T3) of intradialytic fluid removal per body weight: T1, -9.5% to 3.8%; T2, 3.8% to 5.1%; and T3, 5.1% to 13.7%. The hazard ratio of VA failure was compared across these tertile groups using Cox regression models. The models were adjusted for the following risk factors: age, gender, BMI, diabetes, phosphorus, potassium, ESA use, and antplatelets use. Primary VA survival was defined as the days until the first VA intervention. Secondary VA survival was defined as the days until new VA creation.

Results: The incidence rates (events/100 person-years) of primary and secondary VA events were 4.7 ± 1.3 for T1, 6.4 ± 3.7 for T2, and 7.9 ± 4.3 for T3, respectively. The adjusted hazard ratios versus T1 for primary VA patency were 1.16 (95% confidence interval [CI], 0.88 to 1.52) for T2 and 1.41 (95% CI, 1.07 to 1.87) for T3. The hazard ratios versus T1 for secondary VA patency were 1.29 (95% CI, 0.78 to 2.13) for T2 and 1.45 (95% CI, 0.86 to 2.45) for T3.

Conclusions: This study shows that large-volume ultrafiltration during dialysis tends to increase VA failure in hemodialysis patients.

FR-PO695

Post-Endovascular Intervention Venous Access Pressure Ratio (VAPR) Predicts Access Survival  
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Background: The vascular access pressure ratio test identifies vascular access (VA) dysfunction in hemodialysis patients when 3 consecutive VA pressure (VAPR)MAP measurements are >0.55. We hypothesized that a post-interventional VAPR decline predicts VA outcomes in patients with VA dysfunction.

Methods: Retrospective analysis of all VA procedures from 09/2013 to 04/2015. Data collection included demographics, comorbidities, VA features, mean VAPR <30 days pre- and post-procedure, time-to-next-procedure, and access type. Kaplan-Meier arteriovenous graft (AVG) and fistula (AVF) survival curves were compared by the log-rank test. A Cox-proportional hazard model was used to determine the association of VAPR Δ% (Pre-Post)/Pre>100% with access survival.

Results: Analysis of 92 subjects [females 57% (n=53); black 88%; and diabetes mellitus 61% (n=56)] included 46 AVG with 94 procedures and 46 AVF with 86 procedures. Mean VAPR Δ% was 26 ± 61% (SD) and 16 ± 54% for AVG and AVF, respectively. VAPR decline was absent in 13 AVG. AVG with no VAPR decline (<0%) post-intervention when compared to AVG with any decline (>0%) required more subsequent procedures (64% vs 47%), with fewer days to next procedure (75 vs 149 d), and lower survival (p = 0.002). For AVG, a post-intervention VAPR decline >10% (p = 0.04) projected AVG survival. 34% of AVG procedures had <10% decline (n=30) and required more subsequent procedures than AVG with >10% decline (64% vs 39%). AVG without VAPR decline had a 3-fold greater risk of failure (p = 0.003). The risk of failure was 2.0-fold greater (p = 0.04) for AVG with <10% decline.

Conclusions: A 10% post-intervention reduction of VAPR in AVG and any VAPR reduction in AVF predicts greater VA survival.

FR-PO696

Abnormalities in Mineral Metabolism and Dialysis Arteriovenous Fistula Thrombosis in the HEMO Study  
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Background: Vitamin D deficiency and fibroblast growth factor 23 (FGF23) excess are highly prevalent among patients requiring chronic hemodialysis. This study aims to determine the association of 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), and FGF23 serum levels with arteriovenous fistula (AVF) thrombosis in hemodialysis patients.

Methods: The HEMO Study was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum 25(OH)D, 1,25(OH)2D, and intact FGF23 levels were measured in stored serum samples obtained at baseline in 881 patients in this cohort. Cox proportional-hazards models were used to examine the association of 25(OH)D, 1,25(OH)2D, and FGF23 serum levels with time to first AVF clotting event after controlling for important clinical covariates in the HEMO Study.

Results: Patients had a mean age of 57 ± 14 years, 55% were females, and 46% were white. During a median follow-up of 3.0 years, 111 AVF clotted. Median (IQR) serum 25(OH)D, 1,25(OH)2D, and FGF23 levels were 19.1 (14.2, 26.6) ng/mL, 6.3 (2.9, 14.5) pg/mL, and 3118 [726, 12928] pg/mL. Among patients with levels in the highest tertile compared to the lowest tertile, both 1,25(OH)2D and FGF23 were significantly associated with an increased risk of clotting in adjusted analyses, hazard ratio (HR) 2.79 (95% CI, 1.21-6.46) and HR 1.35 (95% CI, 1.02-1.83), respectively. No statistically significant associations were observed between 25(OH)D serum levels and AVF thrombosis.

Conclusions: Calcitriol and FGF23 excess were associated with an increased risk of AVF thrombosis among chronic hemodialysis patients.

Funding: NIDDK Support, Veterans Administration Support

FR-PO697

Ultrasound-Guided Evaluation of New AV Fistulas Safely Decreases Time to First Cannulation  
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Background: The use of bedside ultrasonography (USG) in various medical specialties has exploded over the last decade. For the past year, we have been using bedside USG for earlier AV fistula utilization and for diagnosing potential problems. Prior to the use of USG, cannulation was based on physical exam. We were interested to see whether use of bedside USG helps in early cannulation of AVF.

Methods: USG procedures from February 2014 to February 2015 were reviewed. Time to cannulation in the year prior to the introduction of USG (2013 - 2014) was calculated and compared to similar data with USG use. By week 4 all new fistulas underwent the first USG exam. Examinations were performed by the renal attendings and fellows each exam lasting about 5 minutes. Sonosite M-Turbo ultrasound machine was used.

Results: Total of 44 USG examinations were performed on 14 patients while monitoring new AVF maturation. In 10 patients USG-guided cannulation occurred at an average of 6.2 ± 0.9 weeks compared to 10.2 ± 0.9 weeks prior to USG use (P = 0.006). There were no complications seen with using the earlier USG-guided cannulations. Subsequent cannulations by the nursing staff were successful without USG. In 4 patients failure of maturation was diagnosed by USG at an average of 3.8 ± 0.9 weeks vs 9.6 ± 1.2 weeks prior to USG (P = 0.08). Antibiotic dosing occurred 21 times prior to USG compared to 11 times with USG, despite the similar cannulator rates for both years.

Conclusions: USG use facilitates early AVF cannulation with decreased time to first use. Identification of potential AVF issues and their referral are accomplished earlier. This may translate to earlier catheter removal and fewer infections.

FR-PO698

Arteriovenous Grafts Reduce Cather Dependence in the Elderly  
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Background: Arteriovenous fistulas (AVF) are the permanent access of choice. The benefits of AVF, durability and longevity, are minimized in the elderly where more than 40% of patients will die within their first year of initiating hemodialysis. We investigate an expanded role for primary arteriovenous grafts (AVG) in this population.
Methods: We retrospectively review consecutive patients over the age of 70 who underwent upper extremity access creation from January 2008 to July 2014. Data collection included demographics, past medical histories, subsequent interventions, volume flows, access usage, and patient survival.

Results: We performed 366 AVF and 124 AVG creations in 442 patients over the age of 70 (197 women, 245 men). There were no significant differences in the comorbidities between the two access types. The AVG group was significantly older and more likely to be female, 79.2 yo vs. 77.2 yo (p<0.001) and 60% vs. 41% (p<0.001) respectively. Patients with AVF were significantly more likely to never use their permanent access, 25% vs. 11% (odds ratio 3.6, p=0.002) and if utilized, cumulated significantly later, 3.6 ± 0.2 months vs. 1.3 ± 0.1 months (p<0.001). Catheter dependence at 6 months was 40% for AVG and 28% for AVF. (Figure 1) Secondary patency at 18 months was 64% for AVF and 63% for AVG.

Conclusions: Prosthetic grafts should be considered as the preferred permanent access type in the elderly. Better predictors of mortality, including frailty scores, should be investigated for determining the best choice of permanent access in elderly patients.

FR-PO699
Anticoagulation-Free Dialysis Is Not Associated with Failure to Meet Ultrafiltration Target: A Single-Center Inpatient Dialysis Study
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Background: Conventional outpatient hemodialysis utilizes various forms of anticoagulation to prevent access and extracorporeal circuit clotting. In contrast, to reduce the risk of bleeding events, inpatient dialysis units do not frequently use anticoagulation. We aimed to investigate the consequences of anticoagulation-free dialysis and the factors associated with failure to achieve ultrafiltration target (UFT) in our inpatient unit.

Methods: We performed a retrospective analysis of 250 consecutive hemodialysis treatments in 125 chronic patients. Patients were excluded if they were admitted for initiation of dialysis or required systemic anticoagulation. We looked at both instances of successful achievement and failure of UFT. We looked at the following factors: type of access, episode of intradialytic hypotension (IDH), episode of access clotting, and episode of extracorporeal circuit clotting. No anticoagulation was used in the HD treatments. Correlation analyses were performed and categorical data was analyzed using chi-square test. STATA, version 11, was used for statistical analyses.

Results: Overall the incidence of failure to meet UFT was 35%. Association of failure to meet UFT and IDH was noted (p=0.002). Access clotting and IDH were associated with failure of UFT. We looked at the following factors: type of access, episode of intradialytic hypotension (IDH), episode of access clotting, and episode of extracorporeal circuit clotting. No anticoagulation was used in the HD treatments. Correlation analyses were performed and categorical data was analyzed using chi-square test. STATA, version 11, was used for statistical analyses.

Conclusions: Our study of 250 anticoagulation-free hemodialysis treatments suggests that access and extracorporeal circulation were not associated with failure to meet ultrafiltration target. However, the failure to achieve ultrafiltration target was significantly associated with intradialytic hypotension. Larger cohort, multi-center prospective trials should be performed to look at causality of failure to meet ultrafiltration targets in the hospitalized patient.

FR-PO700
Evaluation of the Ability of Transonic Monitoring to Predict Dialysis Access Stenoses
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Background: Patency of vascular access is critical to successful maintenance hemodialysis. It is well established that lesions are easier to treat if they can be identified prior to thrombosis. Non-invasive evaluation of access blood flow with the Transonic device is established for this purpose. We previously analyzed its performance after two years and demonstrated >99% sensitivity and specificity. We now seek to extend that work by looking at performance over a fifteen-year period.

Methods: Transonic studies are performed on approximately 1500 maintenance dialysis patients with AV grafts or fistulae in our 7 clinics in New York City. Transonic flow rates <600 cc/min or decreases by >10% from prior readings prompt referral to Interventional Radiology or Vascular Surgery. We report on the sensitivity, specificity and predictive values for patients treated between 1998 and 2012.

Results: Sensitivity was 42%; specificity 72%. Positive predictive value (PPV) was 20%; negative predictive value (NPV) was 85%.

We evaluated our ability to predict stenosis based on decreased dialysis clearance: for Kt/V, PPV was less than 10% and NPV less than 80% for different cutoff points; for URR, NPV was less than 10% and PPV less than 80%.

Conclusions: We hypothesize that the large numbers of false positive and false negative results were caused by scheduled referrals to Interventional Radiology, which have become routine. This study suggests that routine Transonic studies may no longer be as important as they were in 2000; however, Transonic studies provide better predictive ability than reductions in urea-based dialysis clearance.
FR-PO702
Association of Bacteremia with Arteriovenous Access Failure in Hemodialysis Patients
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Background: Obesity, female sex, diabetes, peripheral vascular disease, and pacemakers are known risk factors for arteriovenous fistula (AVF) and arteriovenous graft (AVG) failure. We examined whether bacteremia in hemodialysis (HD) patients with AVF/AVG represents an additional, independent risk factor for subsequent AVF and AVG failure.

Methods: We conducted a retrospective observational study among 29,571 U.S. patients from the United States Renal Data System who started HD with AVF and AVG between 1/1/2009 and 9/30/2010. We used inpatient ICD-9 codes after dialysis start to define bacteremia and AVF/AVG failure. We then used a multivariable Cox proportional hazards model to assess relationship between exposure to bacteremia and time to access failure.

Results: Overall, 12.2% of patients with bacteremia experienced an access failure, compared to 4.0% of patients without bacteremia (P<0.001). This difference persisted over a median follow-up of 582 days. With adjustment for known confounders, patients who had bacteremia after dialysis start were at ~3-fold greater risk of subsequent access failure, relative to those who did not (HR=3.18, 95% CI: 1.71 – 5.95).

Conclusions: This observational study indicates that decreased AVF and AVG survival may be associated with exposure to bacteremia among HD patients.

FR-PO703
Comparison of Loss of Vascular Access Patency in Hemodialysis Patients with End-Stage Renal Disease due to Systemic Lupus Erythematosus versus Other Causes
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Background: Previously we found that U.S. patients with systemic lupus erythematosus (SLE) and end-stage renal disease (ESRD) were 40% less likely than other ESRD patients to have a permanent vascular access in place at the start of dialysis. Here, we examine whether subsequent loss of patency differs in SLE vs. other ESRD patients who have a permanent vascular access.

Methods: A cohort of 106,993 U.S. patients starting hemodialysis with an arteriovenous fistula (AVF) or graft (7/05-9/11) was identified from a national registry of treated ESRD (United States Renal Data System). Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to estimate the association between SLE vs. other ESRD (by provider-reported attributed cause at start of dialysis) and the time to first inpatient ICD-9 codes after dialysis start to define bacteremia and AVF/AVG failure. We then used a multivariable Cox proportional hazards model to assess relationship between exposure to bacteremia and time to access failure.

Results: Overall, 12.2% of patients with bacteremia experienced an access failure, compared to 4.0% of patients without bacteremia (P<0.001). This difference persisted over a median follow-up of 582 days. With adjustment for known confounders, patients who had bacteremia after dialysis start were at ~3-fold greater risk of subsequent access failure, relative to those who did not (HR=3.18, 95% CI: 1.71 – 5.95).

Conclusions: This observational study indicates that decreased AVF and AVG survival may be associated with exposure to bacteremia among HD patients.

FR-PO704
The Placement of Tunneled Central Venous Catheters Through Percutaneous Puncture of Superior Vena Cava in Hemodialysis Patients
Tianlei Cui, Xiaoxi Zeng, Yuhuan Feng, Ping Fu. Nephrology Dept, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.

Background: After the exhaustion of traditional insertion sites of tunneled central venous catheters (IVCVCs), it can be challenging to place the IVCVCs in exotic locations. A retrospective case series in West China Hospital was studied to assess the placement of IVCVCs through percutaneous puncture of superior vena cava (SVC) in patients with inimate veins occlusion.

Methods: Sixteen patients (male: 62.5%; mean age: 64.7 years; mean duration of HD: 5 years) who underwent placement of IVCVCs through percutaneous puncture of SVC were retrospectively analyzed. They had either exhausted IV access sites or chosen not to undergo other vascular access placement. All of the patients had occlusion in innominate veins on both sides. The outcomes were function measurements of IVCVCs, and safety parameters. The technique: With patients supine, following the guidance of fluoroscopy, a S-F catheter was placed at the distal end of SVC through the femoral vein, iliac vein or hepatic vein, serving as a fluoroscopic target. Later, guided by fluoroscopy vertically and horizontally, the puncture needle and sheath were placed into SVC through a percutaneous route with the insertion site at 0.5-1.0 cm lateral-inferior to the clavicle head of sternocleidomastoid, allowing the access of the guidewire and the placement of a IV catheter.

Results: The procedure succeeded in all of the patients. During the follow-up (mean: 12 months, range: 3-36 months), access failure due to thrombosis was observed in one patient, and the failure was treated by aspirin and Clopidogrel. The remaining continued to function well until the end of the follow-up or until the death of the patients (n=3). The procedure was generally safe. No pneumothorax occurred. The most common complication was mediastinal hematoma after the failure of SVC puncture. The fluoroscopy could reveal the hematoma during the procedure. The largest hematoma was 2cm in diameter in the current series and it resolved spontaneously.

Conclusions: In patients with inominate veins occlusion and exhaustion of the conventional insertion sites, the IVCVCs can be safely placed through SVC puncture using percutaneous route.

FR-PO705
Analysis of Survival of Cardiac Function in Maintained Hemodialysis Patients with Arteriovenous Fistula and Tunneled Cuffed Catheter
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Background: Until now, there is little data of cardiofunction regarding to different type of vascular access. This study was to investigate survival of patients with arteriogenous fistula and tunneled cather group. The baseline anthropometric and laboratory parameters were measured. The time and cause of mortality were documented. The survival of patients with arteriogenous fistula and tunneled cather group in terms of cardiac function was compared to the survival of patients with arteriogenous fistula and tunneled cather group.

Methods: Total of 219 patients who received maintained hemodialysis were included in this study. Patients were divided into two groups: arteriogenous fistula group and tunneled catheter group. The baseline anthropometric and laboratory parameters were measured. The time and cause of mortality were documented.

Results: There were significant difference of left ventricular hypertrophy [x^2=6.645, P=0.001], left ventricular diastolic dysfunction [x^2=4.007, P=0.045], between two groups. But there was no significant difference of left ventricular diastolic dysfunction between two groups. Kaplan-Meier survival curves showed that the mortality was enhanced among tunneled cather group.
Patients with left ventricular hypertrophy, left ventricular systolic dysfunction, left ventricular diastolic dysfunction in arteriovenous fistula group have a high survival rate compared with tunneled catheter group. Furthermore, iPTH, calcium, systolic blood pressure and diastolic blood pressure were the independent risk factors of mortality for patients on maintained hemodialysis by Cox regression model.

Conclusions: Development of vascular access may have influence on mortality in patients on maintained hemodialysis. Those with tunneled catheters have lower survival rate when left ventricular dysfunction occurred.

FR-PO706
A Retrospective Study of Preferable Alternative Sites to Right Internal Jugular Vein for Tunneled Hemodialysis Catheters Insertion: Right External Jugular Vein versus Left Internal Jugular Vein
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Background: It has been recommended by the KDOQI guidelines that right internal jugular vein (RIJV) is a preferred insertion site for hemodialysis (HD) catheters, and both right external jugular vein (REJV) and left internal jugular vein (LIJV) are alternative sites for those who have encountered severe thrombosis and/or occlusion of RIJV. The retrospective study aimed to determine if superiority exists in the two alternative sites by comparing the outcomes of tunneled (cuffed) dialysis catheters (TDCs) through REJVs versus LIJVs in HD patients who had failed RIJV.

Methods: From January 1, 2013 to December 31, 2014, 28 LIJ-TDCs and 21 REJ-TDCs were inserted in our hospital. All events were recorded from patient charts until May 31, 2015. Using SPSS 22.0 software, data were analyzed by the Fisher exact test or chi-square test. Event-free catheter survival was estimated by the Kaplan-Meier method. Multivariable Cox hazards analysis was fitted to detect the independent risk factors of events. A P-value of <0.05 was considered statistically significant.

Results: A total of 20924 (LIs, 11782; REJs, 9141) catheter-days were evaluated and the mean was 427.02 days. Most of the patients (53.1%) were older than 65 years with an average dialysis time of 25.3 months. The event-free catheter survival time was (516.20±55.60)±1 in REJ-TDCs and (343.91±40.63)±1 in LIJ-TDCs (P=0.038). Mean effective blood flow was higher in REJ-TDCs than in LIJ-TDCs (270.95±24.93 vs 244.82±30.35 ml/min, P=0.02). A substantial positive trend toward statistical significance was found between two groups in incidence of all events, including death, death related to catheter complication and catheter removal. The total historic catheters indwelling time was identified as an independent risk factor for severe TDC events by Cox regression hazards test (P=0.01).

Conclusions: REJ might be superior to LIJ as an alternative insertion site for TDC placement in HD patients who had failed RIJV.

FR-PO707
Haemodialysis Recirculation in Patients with Catheter Access: Damien Ashby, Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom.

Background: Recirculation is a well described impairment of the haemodialysis circuit which reduces dialysis dose and electrolyte clearance. Catheter tips are designed to minimise recirculation based on in vitro experiment, with most designs having a tip separation of 25 mm, but clinical studies of catheter-related recirculation have not been published.

Methods: In a group of stable adult patients receiving haemodialysis by tunneled catheters, recirculation was calculated by 3-sample urea measurement, and analysed in 25 mm, but clinical studies of catheter-related recirculation have not been published. Defining thresholds to avoid high recirculation (>5%) with tip separation over 25 mm high recirculation was seen in 6 patients. Increasing threshold tip separation to 30mm reduced the number of patients with high recirculation to 2. The same was achieved using a weight-based tip separation threshold of 0.5 mm/kg. High recirculation was associated with high erythropoietin requirement (R=0.29, p=0.030) but not with low Kt/V (p=0.26).

Conclusions: Significant recirculation affects a significant minority of patients dialysing on tunneled catheters, and is closely related to tip separation. A tip separation threshold of 25 mm may be inadequate to avoid high recirculation, and 30mm or perhaps a weight-based threshold may be superior. Erythropoietin resistance is a possible consequence of this type of haemodialysis recirculation.

Funding: Clinical Revenue Support

FR-PO708
Risk Factors for Fatal Dialysis Access Haemorrhage
Nicole M. Lioufas, Jonathan E.H. Ling, Gail Theresa Read, Matthew D. Jose, Royal Hobart Hospital, Hobart, Tasmania, Australia; School of Medicine, The Univ of Tasmania, Australia.

Background: Haemodialysis requires access to the circulation via an arteriovenous fistula or graft, or a synthetic vascular catheter. Annually there are deaths associated with catastrophic bleeding from dialysis vascular access.

Methods: A systematic search strategy including data from the National Coronial Information System (NCIS, containing coroner’s reports from all Australian states and New Zealand), the Australian and New Zealand Dialysis and Transplant registry (ANZDATA), published cases from Australia and New Zealand, individual renal units and State Renal Network reports. Data was analysed for all deaths where cause of death was reported as being due to dialysis access haemorrhage from 1st January 2000.

Results: A total of 83 patients (mean age 67 years (range 30 – 89), 55% female) receiving renal replacement therapy died due to dialysis vascular access haemorrhage. These were identified through NCIS 54, ANZDATA 64, State networks 3, Publications 2, and individual unit units. Most deaths occurred within the access itself (66%) with complications including infection (22%), dialysis catheter problems (17%), recent access intervention (15%) or use of a thig arteriovenous fistula (11%). Bleeds commonly occurred at home in people treated with satellite haemodialysis. Modality at the time of death was home haemodialysis in 12 people. Use of Warfarin or cognitive impairment was identified in only 1 death each. Coronial inquests and Root Cause Analyses were identified in only 7 deaths with recommendations involving communication, staffing, clinical policy, practice changes and equipment modifications.

Conclusions: Death due to dialysis access haemorrhage is an uncommon, catastrophic, but potentially preventable event. A number are preceded by vascular access infection, vascular access complications or recent intervention. Only a minority of deaths have been investigated, but where they have, critical recommendations for optimising future care are presented.

FR-PO709
Subcutaneous Implantable Electronic Devices in Chronic Kidney Disease and Hemodialysis Patients

Background: While epicardial leads have been reported to bypass central venous stenosis, their placement is much more invasive and requires the services of a cardiac thoracic surgeon. Recent data have demonstrated successful defibrillation using a subcutaneous ICD (SICD). While the use of these devices is expanding, their insertion in advanced renal failure and hemodialysis patients is somewhat limited. In this analysis, we present 9 cases of SICD implantation in haemodialysis patients treated successfully with an SICD. Demographic characteristics revealed; male–8, diabetes–8, hypertension–13, coronary artery disease–10, peripheral vascular disease–8. Two of the four hemodialysis patients had an AVF while two were dialyzing with a tunneled dialysis catheter. Mean GFR for the CKD patients was 40.3 ± 6.6 ml/min. Patients received the SICD device for primary prevention of sudden cardiac death (cardiomyopathy with low ejection fraction). 3/13 patients had non-ischemic cardiomyopathy (CMP) with an ejection fraction of <25%, while 10/13 suffered from ischemic CMP with an EF of <30%. There were no procedure-related complications in 20 patients. Death due to dialysis access haemorrhage is an uncommon, catastrophic, but potentially preventable event. A number are preceded by vascular access infection, vascular access complications or recent intervention. Only a minority of deaths have been investigated, but where they have, critical recommendations for optimising future care are presented.

Methods: Retrospective evaluation of SICD in patients with CKD and ESRD.

Results: Thirteen patients with CKD and ESRD on dialysis received successful SICD. A total of 83 patients (mean age 67 years (range 30 – 89), 55% female) receiving renal replacement therapy died due to dialysis vascular access haemorrhage. These were identified through NCIS 54, ANZDATA 64, State networks 3, Publications 2, and individual unit units. Most deaths occurred within the access itself (66%) with complications including infection (22%), dialysis catheter problems (17%), recent access intervention (15%) or use of a thig arteriovenous fistula (11%). Bleeds commonly occurred at home in people treated with satellite haemodialysis. Modality at the time of death was home haemodialysis in 12 people. Use of Warfarin or cognitive impairment was identified in only 1 death each. Coronial inquests and Root Cause Analyses were identified in only 7 deaths with recommendations involving communication, staffing, clinical policy, practice changes and equipment modifications.

Conclusions: Death due to dialysis access haemorrhage is an uncommon, catastrophic, but potentially preventable event. A number are preceded by vascular access infection, vascular access complications or recent intervention. Only a minority of deaths have been investigated, but where they have, critical recommendations for optimising future care are presented.

FR-PO710
Modified Non-Transposed Brachio basilic Arteriovenous Fistula for Hemodialysis: A Randomized Controlled Study
Yanrong Hu, Chunyu Zhou, Chandra Mohan, Changbin Li, Jie Tang, Ai Peng, Shanghai Tenth People’s Hospital, Tongji Univ School of Medicine, Shanghai, China; Univ of Houston, Houston, TX; DHHA-Univ of Colorado School of Medicine, Aurora, CO.

Background: Transposed brachiobasilic arteriovenous fistula (BBAVF) is technically challenging. It not only associates with severe arm swelling and pain, but also takes longer to be ready for use. Here we introduce a novel modified non-transposed BBAVF (mNT-BBAVF), and compare its outcomes those of the standard brachiobasilic arteriovenous fistula (BCAVF).

Methods: From January 2010 to December 2012, 74 incident hemodialysis patients with suitable basilic and cephalic veins were randomized equally into mNT-BBAVF and
Management of Catheter Related Bacteraemias: New Insights into an Old Problem

Methods: We retrospectively reviewed all blood cultures taken from our institution’s dialysis patients for 1 year (October 2013 and September 2014). The records of patients with positive cultures were reviewed to ascertain if the infection was related to their access. Data was then collected on the type of organism grown, management of the episode, recurrence rate, and any long term complications.

Results: 1014 cultures were taken from approximately 930 haemodialysis patients. 45% of these were dialysing via a catheter. There were 52 instances of CRB giving a CRB rate of 0.34 per 1000 catheter days. 65% were due to gram-positive organisms, 29% were due to gram-negative organisms and 6% were fungal related. The overall recurrence rate of 0.34 per 1000 catheter days. 65% were due to gram-positive organisms, 29% were due to gram-negative organisms and 6% were fungal related. The overall recurrence rate was 26%.

Conclusions: We observed significantly more infective complications with gram-negative organisms compared with gram-positive. This probably reflects the underlying characteristics of these patients rather than the pathogenicity of the organisms per se (19% of patients with gram-negative infections were intravenous drug users). Never the less our data suggests that gram negative infections are a risk factor for complications and clinicians should consider further investigations in these cases. Our CRB rate was low compared to quoted rates in the literature; this may reflect routine the use of citrate lock in our catheters.

Assessment of Arteriovenous Fistula Access Flow Using Video Image Processing Technology

Background: Vascular stenotic lesions are the main cause of failure in arteriovenous fistula (AVF). Routine measurement of access flow (AF) is important in the timely detection of changes and planning interventions. The aim of this pilot study was to investigate whether video image processing (VIP) techniques can be used to detect AVF motion and explore the relationship between motion patterns and AF.

Methods: Skin above the AVF was imaged for 1 minute using a digital single lens reflex camera prior to HD. The video was processed using Eulerian video magnification (Wu et al. ACM Trans. Graph. 31(4), 2012) to amplify AVF motions. Thereafter the motion-amplified video was converted to quantitative waveform data using an algorithm based on change in color of each image (Matlab Image Processing Toolbox). Monthly AF measurements were recorded and correlated with the post-processed AVF waveform pattern.

Results: We studied 12 hemodialysis patients (51.5±11.3 years, 50% male) with a mean:SD AF 150±392ml/min (N=9; AF was unavailable in 1 subject). Amplitude of skin displacement was 0.069±0.04mm (N=9; technical issues occurred in 2 subjects). While amplitudes of that size are hardly visible to the naked eye, they were clearly discernible in post-processed amplified videos. Amplitude was notably smaller in subjects with lower AF (Fig. 1). Amplitude analysis of the amplified video indicates a relationship with AF (R=0.73, p<0.01; N=9).

Conclusions: Our proof-of-concept study demonstrates this video imaging and analysis technique has potential to provide a quick, noninvasive, low cost way to obtain quantitative information related to AF. Research is underway to assess the impact of clinical interventions on the amplitude pattern.
In the control profile, real-time Kt/V (Fig 1a, solid line) closely followed the target line (Fig 1a, dashed line) and was associated with normal \( P_t \) and \( P_r \). In patients with high access recirculation, real-time Kt/V tracking line deviated widely from the target line (High Recirc Kt/V Profile; Fig 1b, c, d) and remained deviant throughout the treatment session. Fig 1d demonstrates a case wherein the initial low Q (High Recirc Kt/V Profile; Fig 1b, c, d) and remained deviant throughout the treatment session. It was noted that the initial low Q (High Recirc Kt/V Profile; Fig 1b, c, d) and remained deviant throughout the treatment session.

**Results:** 49 stents were inserted during 45 procedures in 39 patients. 12 had diabetes. Mean age was 64.5±25.5 yrs, median dialysis vintage was 1162±1504 days (range 5–5027). Median time from access creation (82% arteriovenous fistula) to stent insertion was 318±926 days (range 31–3752). 34 stents were inserted peripherally (cephalic arch and distally), the majority in the cephalic arch. Equal numbers of covered and bare-metal stents were inserted. 4 stents were placed in thrombosed access. 7 procedures were due to surveillance alone, a further 8 due to surveillance and pressure/flow problems. 12 stents were inserted for rupture or dissection (overall access procedure complication rate 1%). Median time from first stent to access failure/ceded HD was 333±653 days, assisted by median 2 (range 0-11) further procedures. Treatment for rupture was not associated with significantly shorter access longevity. Only 10 patients’ access failed following follow-up. Our overall HD definitive access prevalence rate was 86-90%.

**Conclusions:** Appropriate HD access is essential in minimising HD morbidity. We recommend stent insertion for fibre-requiring stenosis or rupture during endovascular procedures. Our data suggest that appropriate, judicious stent insertion in an appropriately structured pathway results in access durability and longevity.

**FR-PO715**

Recurrent Vascular Access Stenosis as a Novel Marker for Cardiovascular Outcome in Hemodialysis Patients

Hyo Jin Kim, Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Yon Su Kim, Curie Ahn, Kwon Wook Joo. *Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea.*

**Background:** Vascular access (VA) is essential component and its stenosis is a major complication in hemodialysis (HD) patients. Nevertheless, there are few data for outcomes of patients who had recurrent VA stenosis. We have explored the influence of recurrent VA stenosis on cardiovascular (CV) event, patient death, and VA failure.

**Methods:** This is a single-center, retrospective study. Patients who had VA operation at Seoul National University Hospital between January 2009 and March 2014 were enrolled. Patients who had two or more instances of percutaneous angioplasty or revision operation within 180 days were categorized recurrent group. The primary outcome was CV event, as coronary artery or heart failure or cerebrovascular, and or peripheral vascular events. The secondary outcomes were all-cause mortality (ACM), composite of ACM or CV events, and VA failure. The two groups were compared before and after matching with propensity scores (PSM).

**Results:** A total of 766 patients (59.7% male, age 59.6 ± 14.3 years) were analyzed. Recurrent group patients (n = 77; 10.1%) were older and had higher underlying CV disease and dyslipidemia. A total 213 patients (14.2% in non-recurrent, 71 in recurrent group) were selected by PSM. During 28.7±13.5 months follow-up, 46 patients (21.6%) had CV outcomes, 30 patients (14.1%) died, and 14 patients (6.6%) experienced vascular access failure. After adjustment, recurrent group was an independent risk factor for CV events (adjusted hazard ratio [HR] 2.66; 95% confidence interval [CI] 1.46–4.86, \( p < 0.001 \)) and composite of ACM or CV events (adjusted HR 1.99; 95% CI 1.21–3.27, \( p = 0.007 \)). However, it was not associated with increased ACM and VA failure.

**Conclusions:** Recurrent VA stenosis was a novel independent risk factor for CV event in HD patients, rather than VA failure. For patients suffered from recurrent vascular stenosis, diligent monitoring should be warranted not only for VA patency but also for CV events.

**FR-PO716**

Stent Insertion Is an Important Tool in Maintaining Arteriovenous Access Patency

Stephen G. John,1 Kumar Abayasekara,2 Peter M. Bangay,3 Mario De Nunzio,4 James E. Kirk,4 John Graham Pollock,5 Peter D. Tharley,6 Paul J. Owen,1 Richard J. Fluck,1 Lindsay J. Chesterton,1 1Nephrology, Royal Derby Hospital; 2Vascular Surgery, Royal Derby Hospital; 3Radiology, Royal Derby Hospital, Derby, United Kingdom.

**Background:** Definitive access for haemodialysis (HD) remains the cornerstone of optimal dialysis. However, HD patients are becoming older, access attempts more problematic and vein preservation remains critical. Clinical examination and access monitoring enable appropriate, timely, endovascular intervention. Stents may be inserted for recurrent stenosis or after endovascular rupture, but their role remains debatable. We report on our single-centre experience of access surveillance and endovascular intervention, highlighting the role of stent insertion.

**Methods:** Electronic hospital records were retrospectively analysed in all access-related stents inserted from 2006-2014 by 5 vascular radiologists.

**Results:** 49 stents were inserted during 45 procedures in 39 patients. 12 had diabetes. Mean age was 64.5±25.5 yrs, median dialysis vintage was 1162±1504 days (range 5–5027). Median time from access creation (82% arteriovenous fistula) to stent insertion was 318±926 days (range 31–3752). 34 stents were inserted peripherally (cephalic arch and distally), the majority in the cephalic arch. Equal numbers of covered and bare-metal stents were inserted. 4 stents were placed in thrombosed access. 7 procedures were due to surveillance alone, a further 8 due to surveillance and pressure/flow problems. 12 stents were inserted for rupture or dissection (overall access procedure complication rate 1%). Median time from first stent to access failure/ceded HD was 333±653 days, assisted by median 2 (range 0-11) further procedures. Treatment for rupture was not associated with significantly shorter access longevity. Only 10 patients’ access failed following follow-up. Our overall HD definitive access prevalence rate was 86-90%.

**Conclusions:** Appropriate HD access is essential in minimising HD morbidity. We recommend stent insertion for fibre-requiring stenosis or rupture during endovascular procedures. Our data suggest that appropriate, judicious stent insertion in an appropriately structured pathway results in access durability and longevity.

**FR-PO717**

Association of Vascular Access Flow and Volume Status on Fistula Arm by Bio-impedance Analysis in Hemodialysis Patients

Hun Jeong,1 Hyung Jong Kim,2 Eun jung Ko,1 Younhee Lee.1 1Internal Medicine, CHA Bundang Medical Center, CHA Univ, Seongnam, Korea; 2Internal Medicine, Seoul Bukbu Hospital, Seoul, Korea.

**Background:** Multi-frequency bioimpedance is a tool of body composition measure and can monitor changes in extracellular volume during dialysis. Arterio-venous fistulae(AVF) could potentially affect fluid retention in the arm. We investigated whether multi-frequency bioimpedance could detect AVF stenosis or association of AVF with fluid retention in the AVF arm.

**Methods:** We measured the extracelluar (ECW) and total body water (TBW) in AVF arm following hemodialysis by multi-frequency bioimpedance(biohyd S10®) using an eight-electrode contact technique. We measured AVF flow by transonic ultrasonography using an ultrasound dilution technology (HD 03®) in hemodialysis.

**Results:** Total 28 patients (male 13 patients) were enrolled and the mean age of patients was 54.8± 13.21 years. ECW/TBW ratio of fistula arm was a significantly higher than ECW/TBW ratio of non-fistula arm(0.389 ± 0.01 vs 0.382 ± 0.001, \( p<0.05 \)). ECW/TBW ratio of fistula arm was a significantly negative correlation with access flow level (mL/min) on fistula(\( p=0.05 \)). The 5KHz reactance of fistula arm was a significantly positive correlation with access flow level (mL/min) on fistula(\( p<0.05 \)).

**Conclusions:** Absolute and relative extracellular fluid volumes are increased in the fistula arm of hemodialysis. We thought that extracellular fluid volumes in the fistula arm were associated with access flow level (mL/min) and/or relative fistula stenosis. We suggest that multi-frequency bioimpedance can be a useful assistant tool of vascular access flow measure.
FR-P0719


Background: Complications of long-term use of tunneled catheters for hemodialysis involve a high risk of infection, thrombosis, hospitalization and expense. This study reviews a single center experience to identify factors that may contribute to the high rate of patients initiated with tunneled HD catheters.

Methods: We conducted a 13-question survey of 47 CKD patients who had been newly initiated on dialysis through a tunneled central vein dialysis catheter during their hospital admission in a university hospital from December 2013-May 2015.

Results: Of 47 subjects, 27 were male and 20 female. Subjects’ mean age was 60 years old. Demographics included 26/47 (55%) African Americans, 7/47 (15%) Hispanics, 12/47 (26%) Caucasians and 2/47 (4%) Asian. Ninety-six % of patients (45/47) had been seen by a physician within the past year, and had been told their kidney function was poor. Eighty-three % of patients (39/47) were referred to a nephrologist. Thirty-six % patients saw a nephrologist and, of those patients, only 13 patients were referred to a surgeon for access. Of the patients who saw a nephrologist, twenty two % (6/28) did not follow through with access placement secondary to noncompliance. Thus, of 47 patients starting hemodialysis with a catheter, only 7 had actually seen a surgeon for access placement. The largest drop off in the continuum of care of the patient is between seeing the nephrologist and seeing the surgeon. Since half of the patients surveyed received care elsewhere, it indicates this finding is not unique to our institution.

Conclusions: There are numerous points in the path to arteriovenous access where attrition occurs. Nephrologists and primary care physicians must oversee proper follow up and follow through to assure successful access placement. In our study, we found that there is a big attrition point from nephrology to surgery referral. A coordinator to help follow up patients or a joint clinic are options to improve this problematic step.

FR-P0720

The Association of Overhydration Status with Megafistulas in End-Stage Renal Disease Patients on Hemodialysis Mihaly T. Tapolcai, Maria Faludi, Melinda Forr, András Tisler, Tibor Fulop, Klara Berta. Dept of Dialysis, Semmelweis Medical Care Semmelweis Univ, Budapest, Hungary; Nephrology, Semmelweis Univ, Budapest, Hungary; Nephrology, Univ of Mississippi, Jackson, MS.

Background: Megafistulas are tortuous dilated fistulas that fold upon themselves and become visible on the arm and shoulders all the way to the clavicle. They may exacerbate low cardiac output, as well as represent a problematic dilatation of the dialysis access. We sought to investigate the association of bioimpedance apparatus (BCM) measured extracellular fluid volume overhydration (OHV) and the presence of megafistulas.

Methods: In a cross sectional study we compared the pre-dialysis BCM-measured OHV% in 12 prevalent chronic dialysis patients with megafistulas (MEGA) who had negative angiographies with that of 52 control dialysis patients (CONTR).

Results: 10/12 MEGA patients had OHV% >16% as compared to 20/52 CONTR patients (Chi square p = 0.02).

**Megafistula and Overhydration**

![Graph showing degree of overhydration vs. megafistulas](image)

The degree of OHV% was 20.2 ± 7.4% among the MEGA vs. 14.4 ± 7.1% in the CONTR group (Student t p = 0.01), representing 4.2 ± 3.2 vs 2.8 ± 1.6 L of excess fluid (p = 0.03). MEGA patients took an average of 1.7 ± 1.4 vs. 0.8 ± 0.8 (p = 0.002) antihypertensive medications compared to the CONTR patients yet their blood pressure was 156/91 vs 141/78 mmHg (p = 0.03/0.0001). We found no difference in fistula vintage, body mass index, age, inflammatory markers, diabetes status or diuretic use. The odds ratio of overhydration being associated with a megafistula is 5.3 (p = 0.01).

Conclusions: There is an association of BCM-measured overhydrated clinical state with the presence of megafistulas; either as an increased volume capacitance or as a potential cause.

FR-P0721

The Observation of the Tunneled Cuffed Catheter Insertion Through Right Innominate Vein in Hemodialysis Patient Yanhuang Feng, Tianlei Cui, Peng Fu. Div of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.

Background: The routine vascular access for hemodialysis is often available due to thrombosis and occlusion after frequent cannulation, which leads to an increase in cost and difficulty of catheterization or recanalization. Further catheterization may accelerate the exhaustion of vascular resources. We inserted cuff catheter through right innominate vein in patients with thrombosis or occlusion of right internal jugular vein and subclavian vein so as to preserve precious vascular access at other parts of body. Here we report our observation of right innominate vein catheterization.

Methods: We enrolled patients who had been receiving regular HD in our center and to whom catheter cannot be inserted due to thrombosis or occlusion of internal jugular vein and subclavian vein. We performed cuff catheter insertion by puncturing right innominate vein in 8 patients and recorded their clinical features, lesion position, and efficacy of the treatment.

Results: Among the 8 cases, where mean age is 67.6 years (range from 54-78), 3 of them are male and 5 are female. All the patients received central venous catheterization for more than 2 times, with median time of having a catheter for 36 months. The vascular ultrasound and CTA reveals that all of them suffered thrombosis or occlusion of right internal jugular vein and subclavian vein. By puncturing right innominate vein, all the patients’ vascular accesses have been successfully established, with the end of cuff catheter located in the right atrium, superior vena cava (SVC) or SVC/ right atrial junction. No obvious discomfort has been reported, nor did complications such as hematoma and pneumothorax recorded. The mean follow-up period lasts for 12 months, all vascular access of these cases are patent.

Conclusions: For HD patients with limited vascular resources such as thrombosis or occlusion of right internal jugular vein and subclavian vein, the application of tunneled cuffed venous catheter through innominate vein has been proved to be safe and effective. It could preserve vascular access by bypassing the stenotic lesion internal jugular vein or subclavian vein, and reduce the incidence of vascular access exhaustion.

Funding: Government Support - Non-U.S.

FR-P0722

Tunneled Hemodialysis Catheter and Hemodialysis Outcomes Vedran Pasara, Mladen Knotek. Dept of Medicine, Renal Div, Univ of Zagreb, Merkur Hospital, Zagreb, Croatia.

Background: Studies have reported that tunneled dialysis catheter (TDC) is associated with inferior hemodialysis (HD) patient (pt) survival, as compared to arteriovenous fistula (AVF). Since many cofactors may also affect survival of HD pts, it is unclear whether the risk for the worse survival arises from TDC per se, or from associated conditions. Therefore, the aim of this study was to determine the long-term outcome of HD patients, with respect to vascular access (VA).

Methods: This retrospective case-control study included all 156 TDC with 57 AVF from 2010 to 2012 at Clinical Hospital Merkur. Control group consisted of 97 pts dialyzed through AVF. The groups were matched according to dialysis unit and time of VA placement. The site of choice for the placement of TDC was right jugular vein. Kaplan-Meier analysis with log-rank test was used to assess pt survival. A multivariate Cox regression analysis was used to determine independent variables associated with the pt survival.

Results: Cumulative one-year survival of pts who were dialyzed exclusively through TDC was 86.4 % and of those who were dialyzed exclusively through AVF the survival was 97.1 % (p<0.002). In a multivariate Cox regression analysis, male sex and older age were independently negatively associated with the survival of HD pts, while shorter duration of HD before the creation of the observed VA, hypertension renal disease and glomerulonephritis were positively associated with survival. TDC turned to be an independent negative risk factor for survival of HD pts (HR 23.037, 95% CI 6.221-85.308).

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<th>TDC</th>
<th>AVF</th>
<th>P</th>
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<th>Patient age at current VA creation (yrs)*</th>
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<tr>
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<td>536 (230,1399)</td>
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<tr>
<td>19.9%</td>
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*mean ± SD; ** median with IQR

Conclusions: TDC is an independent negative risk factor for the survival of patients on HD.

Funding: Government Support - Non-U.S.
FR-PO723

Carpal Tunnel Syndrome Is Associated with Arteriovenous Fistula in Hemodialysis Patients

Il Young Kim,1 Min Jung Kim,1 Joon Hui Kim,1 Dong Won Lee,2 Soo Bong Lee,1 Su Min Park,1 Jong Man Park,2 Woo Jin Jung,2 Sang Heon Song,2 Eun Young Seong,2 Harin Rhee,2 Ihm Soo Kwak.2 1Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea; 2Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea.

Background: Carpal tunnel syndrome (CTS) is associated with various systemic diseases such as rheumatoid arthritis, hypothyroidism, peripheral neuropathy and diabetes mellitus (DM). In hemodialysis patients, several factors can contribute to CTS, including amyloid deposition, generalized fluid retention, increased synovial volume, edema around the nerve, and an ischemic or ‘steal’ effect distal to a dialysis access. This study aimed to evaluate the influence of arteriovenous fistula (AVF) dysfunction on the development of CTS.

Methods: The study included 43 patients (23 male & 20 female) on maintenance hemodialysis via AVF and 97 healthy controls. The median nerves of study population were examined by ultrasonography. Cross-sectional area (CSA) of the median nerve was measured at the distal wrist (CSA-D), and proximal forearm (CSA-P), and wrist-to-forearm ratio (WFR; CSA-P/CSA-D) was calculated for each hand. We also investigated the history of percutaneous transluminal angioplasty (PTA) in them.

Results: The mean age of hemodialysis patients was 60.4 ± 16.0 years. The mean duration on hemodialysis was 48.3 ± 39.6 months. The WFRs in hemodialysis patients were higher than those in healthy controls (1.37 ± 0.45 vs. 1.21 ± 0.25, P < 0.05). The hands with AVF (n = 43) showed higher WFR than those without AVF (n = 43) in hemodialysis patients (1.35 ± 0.47 vs. 1.25 ± 0.26, P < 0.05). The WFRs in patients with a history of PTA were higher than those in patients without a history of PTA (1.46 ± 0.56 vs. 1.23 ± 0.32, P < 0.05).

Conclusions: In maintenance hemodialysis patients, WFR of median nerve was significantly increased in the hand with AVF. Moreover, development of CTS was related not only to AVF itself, but also to AVF function.

FR-PO724

Factors Affecting Patency of Haemodialysis Arterio-Venous Fistulae and Grafts

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Background: Arterio-venous fistulae (AVF) are the preferred access for haemodialysis (HD), and where these cannot be created, arterio-venous grafts (AVGs) are the next best option. AVFs/AVGs however, not uncommonly fail to mature. The causes of this are varied, but loss of patency due to thrombosis and/or significant stenoses are major causes. We investigated the factors affecting patency of AVFs/AVGs in order to identify whether there were any characteristics which were predictive of this.

Methods: All AVFs/AVGs created in our unit between 2006 and 2014 were reviewed. Reasons for loss of primary patency were obtained from the dialysis access database. Characteristics reviewed were age, gender, co-morbidity score, diabetes status and site of AVF. Patients were grouped as follows: patency <30 days, patency <90 days, patency >90 days and patency >365 days.

Results: There were 1897(1) AVFs and 251(2) AVGs created. 649 (34.2%) of AVFs were lower arm, all the AVGs were upper arm, or lower limb. 1346 (62%) were male. The main reasons for AVF loss were clotted/stenosed vessels in 76% of cases. There was no association between ethnicity or gender with regard to patency rates. Other variables are shown in table 1.

Conclusions: We did not find any definite predictive factors for loss of primary patency in the variables we studied. In particular, co-morbidity score, age and diabetes showed no association with poorer outcomes. There is quite a significant ‘drop off’ in primary patency at 12 months. In the majority of cases, this was due to thrombosis of the HD access. This highlights the importance of close surveillance, as measures to maintain patency (surgical or radiological) are more likely to be required in this period.

FR-PO725

Drug-Eluting Stents versus Bare-Metal Stents During Percutaneous Coronary Intervention in Patients on Dialysis

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Background: In patients undergoing percutaneous coronary intervention (PCI), drug-eluting stents (DES) reduce the need for repeat revascularization (RR) compared with bare-metal stents (BMS). The effects on death and MI are more controversial, with mixed results from observational studies and generally null results from clinical trials. However, few previous studies have focused patients with end-stage renal disease (ESRD). We compared the effectiveness of DES with BMS in a representative cohort of US patients on dialysis.

Methods: Using the US Renal Data System, we identified 36,117 patients on dialysis with Medicare Parts A+B who had PCI with stenting after DES became available in the US (4/23/03 – 12/31/10). We used propensity-score matching (PSM) and inverse probability of treatment weighting (IPTW) with Cox regression to examine the association of DES versus BMS on the following 1-year outcomes: death, death or MI, and death, MI or RR. Due to concerns about residual indication bias, we conducted a second, temporal analysis that leveraged the large changes in the prevalence of DES use during three distinct eras: Transitional (4/23/03 – 6/30/04); Liberal (7/1/04 – 12/31/06); and Selective (1/1/07 – 12/31/10).

Results: In the PSM and IPTW analyses, DES was associated with lower risks of all three outcomes compared with BMS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;30 days</th>
<th>&lt;90 days</th>
<th>&gt;90 days</th>
<th>&gt;365 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVF % patent</td>
<td>88%</td>
<td>70%</td>
<td>70%</td>
<td>39%</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>72 years</td>
<td>72 years</td>
<td>70 years</td>
<td>71 years</td>
</tr>
<tr>
<td>AVG % patent</td>
<td>88%</td>
<td>75%</td>
<td>62%</td>
<td>35%</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>70.5 years</td>
<td>70.5 years</td>
<td>66.8 years</td>
<td>67.1 years</td>
</tr>
<tr>
<td>Diabetic</td>
<td>31%</td>
<td>36%</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>Davies Co-morbidity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (no co-morbidities)</td>
<td>17.3%</td>
<td>13.1%</td>
<td>14.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td>1 (1-2 co-morbidities)</td>
<td>60.3%</td>
<td>62.3%</td>
<td>60.9%</td>
<td>64.2%</td>
</tr>
<tr>
<td>2 (3 or more co-morbidities)</td>
<td>11%</td>
<td>13.1%</td>
<td>13.8%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

Conclusions: Adoption of DES for PCI was associated with improved outcomes in US patients with ESRD on dialysis.

Funding: NIDDK Support

Table: Hazard ratios (95% CI) for DES vs BMS

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Death/MI</th>
<th>Death/MI/RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSM</td>
<td>0.82 (0.78-0.86)</td>
<td>0.84 (0.91-0.87)</td>
<td>0.87 (0.84-0.91)</td>
</tr>
<tr>
<td>IPTW</td>
<td>0.82 (0.79-0.85)</td>
<td>0.85 (0.82-0.87)</td>
<td>0.88 (0.85-0.90)</td>
</tr>
</tbody>
</table>

DES use varied by era: Transitional=56%, Liberal=85%, and Selective=62%. In the temporal analysis, outcomes in the Liberal DES era were significantly better than in the Transitional Era, but not consistently better than in the Selective Era.
FR-PO726

Eleven Year Trends in Myocardial Infarction and Stroke in the Incident and Prevalent Dialysis Populations

**Background:** Myocardial infarction (MI) and cerebrovascular (CVA) events are highly prevalent in the chronic dialysis population. We aimed to quantify the annual incidence and trends of MI and CVA events from 2004 to 2014 in a large dialysis population.

**Methods:** We analyzed 600,000 patients receiving chronic dialysis from a large dialysis provider from January 2004 to December 2014. For each calendar year, we calculated the incidence of MI and CVA (event per 100 patient-years) identified by ICD9 code for the population in the first 120 days of chronic dialysis (incident period) and in the subsequent period after the first 120 days (prevalent period). Linear regression was used to quantify statistically significant trends in MI and CVA rate of the eleven year period.

**Results:** Over an eleven year period in the incident population, the mean incidence of MI and CVA was 3.3 and 3.2 events per 100 patient years respectively. Among the prevalent population, the mean incidence of MI and CVA was 1.9 and 1.8 events per 100 patient years respectively. Using linear regression models, the incidence of MI and CVA was found to decrease by 0.14 (p<0.05) and 0.11 (p=0.0009) per year among incident patients. Similarly, the incidence of MI and CVA was found to decrease by 0.06 (p=0.0007) and 0.10 (p<0.0001) per year among prevalent patients. See Figure 1.

**Conclusions:** Both MI and CVA rates are decreasing among incident and prevalent dialysis populations over the past eleven years.

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FR-PO727

Relationship of Ticagrelor Dose and Platelet Reactivity in Patients with End Stage Renal Disease on Hemodialysis

**Background:** In our previous study, ticagrelor has superiority on platelet inhibition than clopidogrel in patients with end stage renal disease (ESRD) on hemodialysis (HD). One study compared two doses of ticagrelor (90 or 60mg) and placebo, reported that ticagrelor significantly reduced the risk of cardiovascular death, MI, or stroke and increased the risk of bleeding. The rate of bleeding is more frequent in 90mg group. We hypothesized there was some relationship between ticagrelor dose and platelet inhibition. We investigated efficacy and safety of standard and low dose ticagrelor, and clopidogrel in ESRD patients on HD.

**Methods:** In a single-center, prospective, randomized study, 50 ESRD patients were randomly assigned to receive clopidogrel (75mg once daily), standard dose ticagrelor (90mg twice daily) or low dose ticagrelor (90mg once daily) for 14-days. Platelet function assessment which included transmittance aggregometry, and VerifyNow TM P2Y12 assay were then used to serially measure. Maximal platelet aggregation (MPA), inhibition of platelet aggregation (IPA), and P2Y12 reaction units (PRUs) were evaluated. Results: Baseline characteristics, and concomitant medication of three groups were not significantly different. The standard dose ticagrelor showed significant lower MPA and higher IPA as compared with clopidogrel at 1.5 and 48 hours, and 14-days after (p<0.05). Low dose ticagrelor showed significant lower MPA and higher IPA at 48 hours after (p<0.001). Although there was no statistical significance, after 1,48hours and 14-days revealed lower MPA and higher IPA, as compared with clopidogrel. There was no significant difference between two ticagrelor doses. Two doses of ticagrelor showed significant lower PRUs, as compared with clopidogrel (p<0.001). 2 patients of standard dose ticagrelor and 1 patient of clopidogrel discontinued study because of bleeding. There was no bleeding in low dose ticagrelor.

**Conclusions:** Low dose ticagrelor may result in greater platelet inhibition than clopidogrel in ESRD patients on HD. Further studies with large number and various doses of medicine are needed.
**FR-PO731**

**Temporal Trends in Myocardial Infarction Incidence and 30-Day Mortality in U.S. Dialysis Patients**

**Background:** Acute myocardial infarction (MI) is a catastrophic event in dialysis pts. Few data exist on current MI hospitalization rates. We assessed trends in type of MI (ST-elevation MI [STEMI], non-ST-elevation MI [NSTEMI], and unclassifiable MI [other]), demographics, and death rates by type of MI in 2005-2011.**

**Methods:** Using Medicare claims data, we created yearly cohorts of dialysis pts point prevalent on January 1 of each year 2005-2011. We assessed STEMI, NSTEMI, and other MI hospitalization rates, and calculated annualized 30-day death rates following MI.

**Results:** In 2005 there were 10,275 NSTEMI, 1,892 STEMI, and 1,918 other MI vs 2011 16,235 NSTEMI, 1,269 STEMI, and 1,634 other MI. Demographics: mean age 67; 5% < 45, and 6% > 84 yr; 47% female; 48% white, 32% black; 55% ESRD from DM. While overall MI rate increased slightly from 2005-2011 (80.1/1,000 PY in 2005 vs 91.2 in 2011), STEMI and other MI decreased by 44% and 29% respectively, while NSTEMI increased by 31%. Short term mortality was relatively unchanged for NSTEMI (295 deaths/1000 PY), increased slightly for STEMI (495/1000 PY in 2005 to 565/1000 PY in 2011), and was highest following other MI (881/1000 PY in 2005 and 915/1000 PY in 2011).

**Conclusions:** In the recent treatment era there has been little change in either rates of overall MI hospitalization or 30-day mortality. The increase in NSTEMI rates may be due to greater utilization of more sensitive cardiac biomarkers (cardiac troponins) for MI diagnosis. MI remains a catastrophic event for dialysis pts. Aggressive interventions to reduce the burden of ischemic heart disease and to improve its prognosis in dialysis pts are warranted.

**FR-PO732**

**Risk of Acute Coronary Events and Coronary Interventions for Overweight and Obese Patients versus Normal Weight Patients Undergoing Dialysis – A National Study**

**Background:** Although elevated body mass index (BMI) is associated with increased risk of cardiovascular events in the general population, it is suggested that the converse may hold true for patients on dialysis.**

**Methods:** We tested this hypothesis in a national cohort of 1,072,737 incident Medicare-eligible US patients, who began dialysis between 5/1995 and 12/2008. Hospitalizations attributed to first myocardial infarction (MI) (ICD 9 codes: 410) and major coronary interventions (coronary angioplasty, stent, and coronary bypass surgery) following first MI were obtained from the US Renal Data System. Multivariable Cox regression compared hazard ratios [HR] of MI and subsequent coronary interventions among BMI categories.

**Results:** The adjusted HR of MI was highest for underweight patients and lowest for morbidly obese patients, decreasing significantly with increasing BMI category. Overweight patients were significantly more likely to receive a coronary intervention post-MI compared to normal weight individuals but this benefit did not extend to morbidly obese or underweight patients.

**Conclusions:** In contrast to the general population, higher BMI is associated with lower risk of major coronary events in US dialysis patients suggesting a protective effect. Furthermore, access to coronary interventions following a major coronary event is not equal across BMI categories.

**FR-PO733**

**Propensity-Based Comparison of Haemodialysis and Peritoneal Dialysis with Risk of Haemorrhagic and Ischaemic Stroke Among New Dialysis Patients**

**Background:** The risk of stroke is between 6-10 fold higher in dialysis patients compared to the general population. It is hypothesised that the choice of dialysis modality at initiation may influence the risk of stroke.**

**Methods:** We tested this hypothesis in a national cohort of 1,097,747 US patients (n=86,168 on PD) who were Medicare eligible and began dialysis between 5/1995 to12/2010 and followed until 9/2011. Hospitalizations attributed to first Haemorrhagic Stroke (H-CVA) and Ischaemic stroke (I-CVA) were obtained from the US Renal Data System files and merged with data from the medical evidence, treatment history and mortality files. Multivariable Cox regression compared the hazards ratio [HR] of H-CVA and I-CVA for PD versus HD with a propensity-matched intent-to-treat (ITT) approach and as-treated analysis. Patients were censored at transplantation, death, recovery of kidney function, or end of study (Sept 2011). Approval was received from University Hospitals Ethics Committee.

**Results:** The adjusted PD/HD HRs for first hospitalized H-CVA using the intent-to-treat model was 0.89 (0.83-0.95) and this decreased from 0.73 (0.61-0.87) in the period 1995-1998 to 0.64 (0.51-0.80) in the period 2007-2010. In contrast, overall HRs for I-CVA were 1.15 (1.12-1.18) and this decreased from 1.20 (1.13-1.27) in the period 1995-1998 to 1.06 (0.97-1.15) in the period 2007-2010. The as-treated model suggested more favourable outcomes for H-CVA with overall HR of 0.61 (0.57-0.67) and for I-CVA with a HR 0.96 (0.89-1.03) in 2007-2010 period. Patients who switched from PD to HD or HD to PD had significantly higher HR of H-CVA, while patients who switched from PD to HD had higher HR of I-CVA.

**Conclusions:** PD and HD contribute differentially to the overall risk of I-CVA and H-CVA among new dialysis patients. While PD is similar to HD with regard to hazards of I-CVA, it appears to protect against the hazard of H-CVA. These associations should be taken into consideration when choosing treatment options for new dialysis patients.

**Funding:** Other NIH Support - Health Research Board & Irish Heart Foundation
FR-P0734

Predictors of Sudden Cardiac Death in Hemodialysis Patients with and without Previous Arrhythmia – Results from a Multinational Cohort Viviane Calice-Silva,1 Stephen Thijssen,2 Xiaolong Ye,2 Aileen Grassmann,3 Daniele Marchel,2 Bernard J. Canaud,2 Peter Kotanko,1 Pedro Recuerto-Filho.1 1Pontifícia Univ Católica do Pará, Brazil; 2Renal Research Inst; 3 Fresenius Medical Care, Germany.

Background: Cardiac dysfunction, rapid electrolyte shifts and high ultrafiltration rates during hemodialysis (HD) are associated with increased vulnerability to arrhythmogenic events. Patients with previous arrhythmia (ARR) are at a higher risk of sudden cardiac death (SCD – Herzog et al, 2011). Our aim was to analyze predictors of SCD in HD patients with and without previous ARR.

Methods: Incident HD patients from the Monitoring Dialysis Outcomes (MONDO) cohort who received in-center treatment between 1/2006-12/2011 and survived at least 90 days on HD were included and followed until 12/2012. Causes of death were classified as SCD according ICD-10/ICD-9. Patients with comorbidity or prior hospitalization due to ARR and/or ARR predisposition were identified. Cox proportional hazard models were constructed to explore associations between baseline parameters and SCD.

Results: We studied 19,129 patients (16 countries). 7,538 patients with complete data were included in the models, 613 died of SCD. Mean age 62.7±15.5 years, 58.1% male, 48.4% diabetics. Age, ischemic heart disease, albumin, serum sodium, interdialytic weight gain in % of post-HD weight and pre-HD-systolic blood pressure were identified as predictors of death in both subgroups. Distinct predictors are shown below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCD with ARR Hazard Ratio(P&lt;0.05)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bicarbonate [mmol/L]</td>
<td>0.07(0.04)</td>
<td>0.04</td>
</tr>
<tr>
<td>Leukocytes [1000/mm³]</td>
<td>0.02(0.005)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin [g/dL]</td>
<td>0.11(0.04)</td>
<td>0.005</td>
</tr>
<tr>
<td>Dialysate sodium [mmol/L]</td>
<td>0.093(0.03)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Cadherin as vascular access</td>
<td>0.41(0.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: Despite the small sample size, some predictors of SCD seem to differ depending on the presence or absence of arrhythmia history or predisposition. These findings may assist the identification of patients at high risk for SCD. Further studies have to be done to corroborate these results.

FR-P0735

The Risks of Acute Health Events After Incident Atrial Fibrillation in Older Hemodialysis Patients Medha Ary1, Benjamin A. Goldstein,2 Mark A. Hlatky,3 Nisha Bansal,3 Alan S. Go, Wolfgang C. Winkelcmaier,1 Baylor College of Medicine, Houston, TX; 2Duke Univ, Durham, NC; 3Stanford Univ, Palo Alto, CA; 4Univ of Washington, Seattle, WA; 5Kaiser Permanente Northern California, Oakland, CA.

Background: Limited data exist about whether incident atrial fibrillation/flutter (AF) impacts the risks of major acute health events in patients with ESRD undergoing hemodialysis (HD).

Methods: From the US Renal Data System, we studied older (≥67 years) adults with ≥2 years of uninterrupted Medicare A+B coverage before starting HD (2006-11) and no known AF prior to ESRD. Incident AF was ascertained from ICD-9 diagnosis codes (427.3x) in inpatient claims. We used extended Cox regression adjusted for sociodemographic characteristics and key comorbidities to estimate hazard ratios (HR [95% confidence interval]) for death, ischemic stroke, myocardial infarction (MI), and hip fracture (as a negative control outcome). AF was treated as a time-varying covariate, with time since first AF diagnosis further categorized as ≤10, 11-30, 31-90, and >90 days. Patients were censored at time of kidney transplant or end of data (12/31/2011).

Results: We identified 85,377 eligible HD patients; 16.7% developed incident AF and 58.2% died during follow-up. Incident AF was associated with higher adjusted mortality: 8-fold higher during the first 30 days (HR=8.2 [7.9-8.6]), 4-fold higher between 31-90 days (HR=4.2 [4.0-4.4]), and 2-fold higher beyond 90 days after AF diagnosis (HR=2.2 [2.1-2.2]). Incident AF also increased the adjusted rate of ischemic stroke 1.5-2.5-fold during the first 30 days (HR=2.1 [1.6-2.7]), 31-90 days (HR=2.5 [2.0-3.0]), and beyond 90 days (HR=1.5 [1.3-1.7]). Quantitatively similar findings were obtained for MI. However, the adjusted rate of hip fracture was only marginally increased following AF diagnosis (≈30 days: 1.0 [1.0-1.6]; 31-90 days: 1.1 [1.0-1.3]; >90 days: 1.2 [1.1-1.4]). All associations were attenuated when requiring incident AF to be indicated as principal discharge diagnosis.

Conclusions: While AF was independently associated with higher risks of ischemic stroke, MI, and hip fracture in older ESRD patients on HD, it was more strongly associated with excess all-cause mortality.

Funding: NIDDK Support

FR-P0736

The CRASH-ILR Study: Half a Million Hours of Continuous ECG Monitoring in a Hemodialysis Population Robert Lewis,1 Darren Green,2 Philip A. Kalra,3 Donah Zachariah,3 Paul Kalra,3 Paul R. Roberts.4 1Portsmouth Hospitals NHS Trust, Portsmouth, United Kingdom; 2Salford Royal NHS Trust, Salford, United Kingdom; 3Royal Bournemouth Hospital, Bournemouth, United Kingdom; 4Southampton Univ Hospitals Trust, Southampton, United Kingdom.

Background: Sudden cardiac death (SCD) may cause ≥25% of all hemodialysis (HD) patient deaths. Multiple potential mechanisms may contribute to the risk of life-threatening arrhythmias in this population. The CardioRenal Arrhythmia Study in Hemodialysis has continuously monitored patients using an Implantable Loop Recorder (ILR) for more than 500,000 hours.

Methods: 30 patients (60% male) aged 67±12 years on established HD for 39±44 months with varied etiology of CKD (diabetes 37%, hypertension 23%) and ejection fraction of 56±8% were implanted with a Reveal XT ILR (Medtronic, MN, USA). Patients transmitted data at each HD session and were asked to activate their ILR if symptomatic with palpitations, dizziness or syncope.

Results: Patients were monitored for an average of 17,810±8,108 hours performing 94±92 transmissions. 6 patients (20%) died during the study. The final arrhythmia was VF in 2 patients and agonal bradycardia in 3. One patient died from SCD 2 weeks after device explantation due to infection. All 3 bradycardic deaths occurred in patients during end-of-life care. 1 VF death occurred during a GI bleed: the other was unheralded. A surviving patient received a biventricular pacemaker for 2:1 block detected by ILR. Atrial arrhythmias (AA) were noted in 7 (25%), 4(13%) of which were incident. 1 patient had asymptomatic sustained VT managed with antiarrhythmic drugs. Frequent ectopy was recorded in 2 patients. There were 19 symptomatic activations in 6 patients all corresponding to sinus rhythm (or AA in cases of permanent AF). 6 patients had device explantation, 4 after renal transplantation and 2 due to device infection.

Conclusions: CRASH-ILR is the longest ILR follow up in HD patients to date and provides new insights into arrhythmia and SCD. Arrhythmias occurred in 15% (50%) of the study population. Mortality was high, but this was due to SCD as an expected end-of-life event in 5 of 6 patients.

Funding: Pharmaceutical Company Support - Medtronic, MN, USA

FR-P0737

Revisiting Ultrafiltration Rate (UFR), Treatment Time (TT) and Mortality in Thrice Weekly Hemodialysis Jennifer L. Bragg-Gresham, Brett W. Platter, Debabrata Ray, Yi Li, Rajiv Saran. KECC, Univ of Michigan, Ann Arbor; MI.

Background: UFR and TT are two potentially modifiable practices for improving outcomes in HD. UFR > 13 ml/kg/hour has been associated with higher mortality. We re-examined this association, focusing on the effect of higher UFR at TT ≥ 4 hours, as longer TT has been claimed to be ‘protective’, even though TT >4 hours is logistically difficult to implement in the prevailing US practice setting.

Methods: Using recently available national data from CROWNWeb (CW), we analyzed 10,699 adults on thrice-weekly, in-center HD. Baseline CW data was extracted from June 2012. Patients were followed through December 31, 2013. Cox regression was used to examine the association between UFR (calculated as the intradialytic weight loss / TT and expressed in ml/kg post HD-weight/hr) and mortality, adjusting for demographics, co-morbidities, dialysis vintage, intradialytic weight gain (IDWG) and dialysis dose (Kt/V), stratified by TT. Average follow-up was approx 1 year.

Results: Individuals receiving TT ≥ 240 were younger, more likely to be black and male, and had larger BMI. In both strata of TT (< 240 and ≥ 240) those patients with UFR > 13 tended to be younger, non-black race, have a lower BMI, longer HD vintage, higher Kt/V and higher IDWG than patients with UFR < 13. Congestive heart failure was more prevalent in patients with UFR ≥ 13 regardless of TT. In both strata of TT, patients with a UFR > 13 had higher hazard of mortality, with a larger risk found in those with TT ≥ 240.

Funding: NIDDK Support

Conclusions: A higher UFR (>13) was associated with higher mortality irrespective of TT category. The association was surprisingly strong among those receiving longer TT. In the US, longer TT is prescribed in order to achieve small solute targets (confounding-by-indication) and not necessarily to lower the UFR, as high UFR is a consequence of high IDWG and the average shorter TT.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

531A
FR-PO738

Sudden Death and Dialysate Potassium in Hemodialysis: Results from the Dialysis Outcomes and Practices Pattern Study (DOPPS)

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Background: Sudden death (SD) is common in hemodialysis (HD) patients. We investigated trends in dialysate (DK) and pre-dialysis serum (SK) potassium across the Dialysis Outcomes and Practices Pattern Study (DOPPS) phases 1-5 (1996-2015) and evaluated whether the risk of SD is higher with lower DK.

Methods: 67,263 patients in 21 countries were studied. Instrumental variable methods were used to model the effect of DK on SK. Adjusted Cox regression was used to test the associations of baseline DK and SK with all-cause death, and an arrhythmia composite (AC) of SD or arrhythmia-related hospitalization.

Results: In the US, DK and SK (mEq/L) have been stable over time (70% DK=2, 25% DK=3; mean±SD SK=4.7±0.7). In Europe, DK has increased (currently 15% DK=1-1.5, 45% DK=2-3, 33% DK=3) while mean SK has decreased from 5.2 to 4.9. SK was only 0.08 mEq/L higher per 1 mEq/L higher DK. SK ≥ 6 (ref 4.5-4.9) was associated with death (HR=1.12, 95% CI: 1.05-1.19) and AC (HR=1.17, 1.04-1.33). Compared to DK=2, DK=3; mean (AC) of SD or arrhythmia-related hospitalization.

Conclusions: The risk of incident AK among patients on HD is increased after a stroke, MI, or hip fracture. Risks were highest in the first 90 days after the event, and remained elevated >90 days after an ischemic stroke or MI, but not after a hip fracture.

Funding: NIDDK Support

FR-PO740

Arrhythmias as a Potential Cause of Dizziness and Syncpe in Patients with End-Stage Renal Disease

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Background: It is unknown how often arrhythmias underlie dizziness and syncpe in end-stage renal disease. We launched a study to implant subcutaneous loop recorders for their estimation.

Methods: Data is shown for 40 patients (62.4±8.2 years [mean±SD], range 39 to 78 y, 26 M) with stage 4 or 5 renal failure and F-to-F of ≥ 2 months. Main kidney diseases were diabetic (18), polycystic disease (8) and chronic glomerulonephritis (6). One patient was pre-dialytic, five had peritoneal dialysis, and rest were on hemodialysis. Median time since the start of dialysis was 1.6 years. Seven patients (18%) had either chronic or paroxysmal atrial fibrillation (AF) prior to the implantation of the recorder, being in line with published data.

Results: During the F-to-F of 14±7 months, recorder revealed bradyarrhythmia in six (15%) patients with an R-R arrest >5.0 sec with a max. of 9.0 sec; two patients with symptoms thus far received a pacemaker. AF occurred in 21 (53%) patients. The median time to detect new AF was 235 days. Four patients (10%) had non-sustained ventricular tachycardia unknown before the recorder data.

Conclusions: Arrhythmias are more typical than estimated in patients with severe kidney disease. Particularly, symptomatic bradycardia is relatively common and can be easily treated with a pacemaker. AF is three times more common than known before. These findings may change diagnostics and treatment of dizziness in these patients.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO739

Acute Health Events and the Risk of Incident Atrial Fibrillation in Older Patients Undergoing Maintenance Hemodialysis

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Background: Acute health events might increase the risk of developing atrial fibrillation (AF). We examined the incidence of new onset AF relative to several acute events in patients with ESRD initiating hemodialysis (HD).

Methods: From the USRDS, we studied older (67+ years) patients with 2 years of Medicare A&B coverage prior to initiating HD (2006-11) who had no documented diagnosis of AF, or claims indicating ischemic stroke, myocardial infarction (MI), or hip fracture prior to ESRD. We used time-varying Cox regression to estimate adjusted hazard ratios for incident AF relative to the acute events of interest, adjusted for socio-demographics and baseline comorbidities. The incidence of AF after either an acute MI, or hip fracture was modeled in time-varying fashion, during the periods of 0-30, 30-90, and >90 days after the acute event. Patients were censored at kidney transplantation or end of database (12/31/2011).

Conclusions: Arrhythmias are more typical than estimated in patients with severe kidney disease. Particularly, symptomatic bradycardia is relatively common and can be easily treated with a pacemaker. AF is three times more common than known before. These findings may change diagnostics and treatment of dizziness in these patients.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO741

Blood Pressure and Risk of Cardiovascular Events Among Hemodialysis Patients: The CRIC Study

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Background: Among hemodialysis (HD) patients, previous studies have reported a U-shaped association between systolic blood pressure (SBP) and risk of mortality. However, the shape of the association between SBP and risk of cardiovascular events (CVD) is not well characterized.

Methods: We studied participants on HD in the Chronic Renal Insufficiency Study (CRIC). SBP was measured at the dialysis unit (“dialysis-unit SBP”, N=803) and at the CRIC study visit (“out-of-dialysis-unit SBP”, N=326). We studied the association of SBP

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

Underline represents presenting author.
Conversely, the association between out-of-dialysis-unit-SBP was linear, with the highest quartile having greater than 2-fold risk of CVD than the lowest quartile.

Conclusions: Among HD patients, the association of SBP measured in the dialysis unit with CVD is U-shaped, while the association of SBP measured outside the dialysis unit with CVD is linear, similar to what has been reported for mortality (Bansal et al., Hypertension 2015). Targeting SBP measured outside the dialysis unit may improve CVD outcomes in HD patients.

Funding: NIDDK Support

FR-PO743

title

Choosing the Right Analysis of Repeated Events for Clinical Trials in Dialysis

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Background: Cardiovascular (CV) events are a leading cause of morbidity and mortality in hemodialysis (HD) patients. There is a paucity of randomized clinical trials (RCT) in nephrology and fewer positive ones, perhaps due to incorrect choice of endpoints or inadequate power. We simulated RCTs with repeated CV events and competing non-CV death to determine how different analytic methods affected study power (sample size).

Methods: We simulated 1000 RCTs of 1100 patients, with frequency and timing of CV events (CV death, MI, stroke, PVD, CV revascularization, and leg amputation) based on real observations in an Ontario HD administrative cohort (n=9647) from 2004-2011. In simulations, patients were randomized to placebo or a treatment with a known effect and censored at 4 years or non-CV death. We analyzed this data with 1) a Cox model for time to first event, 2) a model with non-CV death as a competing risk, 3) a negative binomial (NB) model and 4) several adaptations of the Cox model for repeated events (e.g., Wei, Lin and Weissfeld, WLW). To check for 2 potential problems (finding a difference when there was none and missing a true difference), we ran simulations in 2 scenarios: 1) with zero treatment effect, we calculated the false positive rate; 2) when the treatment delayed CV event by 33%, we calculated the true positive rate (power) based on the 1000 simulations.

Results: In the source (real) data, 45% of patients had >2 CV events; the overall CV event rate was 0.26/yr. When there was no effect of treatment, the NB model had a false positive rate of 11%; for all other models, it was the expected 5%. For the time to first event, competing risk and the WLW marginal Cox model, power was similar (72%) and notably higher than for the remaining Cox-type models (52%-61%).

Conclusions: The WLW Cox model for repeated events was as powerful as models for time to first event but has the advantage of assessing the impact on all (repeated) events a patient experiences. This highlights the importance of choosing the appropriate analytic method when designing a clinical trial in HD patients to maximize the likelihood of both a positive and a meaningful result.

Funding: Government Support - Non-U.S.

FR-PO744

Routine Predialysis Measurements of Systolic Blood Pressure Are Higher Than Predialysis Standardized Measurements of Systolic Blood Pressure

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Background: Measurement of systolic blood pressure (SBP) in the dialysis unit does not follow American Heart Association recommendations. We determined the differences between predialysis SBP (SBP) measured in routine practice versus a standardized procedure.

Methods: The Blood Pressure in Dialysis Study is a pilot, multicenter, randomized clinical trial that assesses treatment of hypertensive HD patients to two BP targets. Measurement of predialysis SBP is done after 5 minutes rest, 3 readings 1 minute apart, with attention to cuff size, placement and patient positioning. We compared the 2-week averaged routine predialysis SBP (RDUSBP) taken immediately prior to enrollment with the 2-week averaged predialysis standardized SBP (SDUSBP) in the first 2 weeks of baseline. The within subject variability in SBP, (s

Results: We studied 186 patients. The week averaged RDUSBP was a mean (SD) 10.3 (16.6) mm Hg higher than 2 week averaged SDUSBP (p<0.001).

The RDUSBP was ± 5 mm Hg of the SDUSBP in 20% of patients, 6-15 mm Hg higher in 30%, 15-25 mm Hg higher in 17%, >25 mm Hg higher in 17% and >5 lower in 16%. Estimating treatment effect, for RDUSBP (15.7) and SDUSBP (19.6) were not significantly different, (p<0.99). Differences between RDUSBP and SDUSBP tended to be greatest among those with a high body mass index.

Conclusions: SDUSBP were, on average, 10 mm Hg lower than RDUSBP measured in the dialysis unit. Reliance on routine BP measurements may lead to overtreating hypertensive HD patients. More attention to the measurement of BP in dialysis unit is needed.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc.
Comparison of Central and Peripheral Blood Pressure in Predicting Cardiovascular Surrogates in Patients with End-Stage Renal Disease

**Background:** Hypertension is an established cardiovascular (CV) risk factor and is closely related with mortality in end-stage renal disease (ESRD) patients. Recent studies have demonstrated that central blood pressure (cBP) is a significant predictor of CV disease in the dialysis population, because cBP reflects the hardening conditions of the coronary and cerebral arteries and vascular damage. Therefore, we investigated the association between cBP and CV surrogates compared with peripheral blood pressure (pBP) in patients with ESRD.

**Methods:** A cohort of 92 ESRD patients from the Cardiovascular and Metabolic Disease Etiology Research Center between November 2013 and February 2015 was selected. cBP was measured by Sphygmocor noninvasively. CV surrogates were determined by carotid intima-media thickness, pulse wave velocity (PWV) and left ventricular mass index (LVMI). Linear regression analysis and Steiger’s Z test were used to compare predictive utility of cBP and pBP for CV surrogates.

**Results:** The mean age was 53.2 years and 52 (56.5%) were male. Mean systolic cBP (eSBP) and central pulse pressure (cPP) was 140.2±28.9 and 57.1±22.8 mmHg. Mean systolic pBP (pSBP) and peripheral pulse pressure (pPP) was 145±25.8 and 65.8±22.2 mmHg. There was an independent association of eSBP and pSBP with PWV (β=0.408, P<0.01; β=0.322; P=0.001) and LVMI (β=0.370, P=0.001; β=0.382, P=0.001). cPP and pPP also were independently associated with PWV (β=0.381, P<0.001; β=0.353, P=0.001) and LVMI (β=0.411; P<0.001; β=0.497; P<0.001) after adjustment for confounding factors. However, there were no significant differences in the predictive value of cSBP and pSBP for estimating PWV (adjusted R², 0.494 vs. 0.431, P=0.07) and LVMI (adj R², 0.215 vs. 0.220, P=0.885). No significant difference was found for cPP and pPP for predicting PWV (adj R², 0.451 vs. 0.429, P=0.546) and LVMI (adj R², 0.220 vs. 0.265, P=0.320).

**Conclusions:** Although cBP values were closely associated with CV surrogates, these values did not provide additional information beyond pBP in predicting CV risk in patients with ESRD.

**FR-P0743**

Early Mortality in Hemodialysis Patients Anticoagulated for Atrial Fibrillation

**Background:** Atrial fibrillation (AF) is prevalent in the Hemodialysis (HD) population and portends a high mortality rate. AF also causes embolic stroke and is treated with lifelong oral anticoagulation (OAT). We have previously shown early increased mortality in HD patients receiving OAT without significant stroke reduction (JASN, 25:609A, 2014). It is unclear why OAT increased early mortality in these patients. To address this question, we queried the USRDS for unique risk factors for mortality in this cohort.

**Methods:** All incident adult HD cases from the USRDS for 2005-2008 were queried for demographics, access type, risk factors before dialysis, and mortality. Data were derived from ICD9 and CPT codes, or Form 2728. Proportional hazards models were used to estimate the hazard ratio (HR) for death within 90 days.

**Results:** 34,522 incident HD patients with AF were identified, 6664 (19.3%) of whom died within 90 days of the initiation of dialysis. For the entire group, demographics showed: 83.1% Caucasian, mean age 57.4 years (SD=9.0), and 41.5% female. When controlling for diabetes, cardiomyopathy TIA, pulmonary hypertension, aortic stenosis, CHF, MI, cancer, obesity, cardiac device, age and access type the HR for death in the OAT group was 1.10 (95% CI 1.04 - 1.16). The 1-, 2- and 3-month mortality rates were 6%, 83.1% Caucasian, mean age 75.4 years (SD=9.0), and 41.5% female. When controlling for demographics, access type, risk factors before dialysis, and mortality. Data were derived from ICD9 and CPT codes, or Form 2728. Proportional hazards models were used to estimate the hazard ratio (HR) for death within 90 days.

**Conclusions:** OAT therapy in HD patients with AF may contribute to the increased death rate observed during the first 90 days of dialysis, but not apparently due to bleeding. We speculate that OAT use may be associated with non-hemorrhagic complications that may lead to increased mortality in the HD population. Defining this level of clinical detail is beyond the scope of an administrative dataset like the USRDS. Future studies addressing non-hemorrhagic effects of OAT may provide new insights on possible causes of early mortality in these patients.

**Funding:** Private Foundation Support

**FR-P0746**

Reduced Temperature Hemodialysis Augments Dialysis Induced Improvement of Cardiac High Energy Phosphate Levels

**Background:** Reduced temperature hemodialysis was significantly associated with increased PWV (36.5°C/64.5°C/66°C vs. 35.0°C; R²=0.03). At both temperatures, hemodialysis was significantly associated with increased mean LV ejection fraction (36.5°C/cp 64.5°C/66°C post 70.9±6.8% vs. 0.002;35.0°C/cp 69.0±6.1% post 72.4±6.3% vs. P<0.01). P<0.05 was highly significant compared with basal condition (P<0.01) and reduced temperature hemodialysis (P=0.03: ). Mean increase in P<0.05 was higher after reduced temperature compared to normothermic hemodialysis (+51.5% vs +74.1% respectively).

**Risk Grading by CHADS2_Vasc Score Is Useful in Non-Dialysis Subjects with Atrial Fibrillation while It Is Not Useful in Dialysis Patients Because of Their Very High CHADS2_Vasc Scores**

**Background:** Whether CHADS2_Vasc score is useful for predicting the risk of outcomes has not been sufficiently examined in dialysis patients with AF. **Methods:** Two prospective studies of 1,109 dialysis patients (AF group (n=35); non-AF group (n=1,074)) and 26,469 community dwellers (AF group (n=25,058); non-AF group (n=411)) living in the same area were conducted. Subjects were subdivided into four groups according to CHADS2_Vasc score (G1: CHADS2_Vasc score = 0; G2: score = 2; G3: score = 3; G4: score = 4). Crude mortality rates of all-cause and cardiovascular death and crude incidence rates of stroke (per 1000 person-years) were estimated in each group.

**Results:** Results were shown in the table.
Conclusions: CHA2DS2_Vasc score is useful for predicting the risk of outcomes in non-dialysis subjects with AF and dialysis subjects without AF. Dialysis patients with AF already had very high scores and the risk grading by CHA2DS2_Vasc score is not useful.

Funding: Government Support - Non-U.S.

FR-PO749

Post Stroke In-Hospital Disability Deterioration and Mortality of Community-Onset Stroke in Patients with and without End-Stage Renal Disease

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Background: Increasing evidence suggests that end-stage renal disease is associated with higher risk and severity of cerebrovascular disease. However, the risk factors for post stroke disability and mortality is not clear. We examined the association between risk factors including dialysis treatment and disability deterioration and mortality during hospital stay of community-onset stroke.

Methods: The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data of about 50% of all acute-care inpatients in Japan. Using this database, we extracted data of inpatients age >20 years old, admitted within 3 days after community-onset stroke between July 2010 and March 2013. Disability level was divided into modified Rankin Scale (mRS) 0-1, 2-3, 4-5, and 6 (death). Disability deterioration was defined as an increase in disability level. The odds ratio (OR) for in-hospital disability deterioration and mortality was calculated using a logistic regression model.

Results: Out of 438,569 patients, 7,633 (1.7%) had dialysis therapy. The median length of stay was 24 and 20 days for patients with and without dialysis, respectively. During the hospital stay, there were 101,024 (23.0%) disability deterioration and 46,029 (10.5%) death. The patients with dialysis had higher rate of disability deterioration (26.7%) and mortality (13.0%) compared to those without. After adjustment with age, gender, BMI, mRS, Activities of Daily Living, smoking habits, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular complications, antipatelet, anticoagulant, and thrombolytic medications, multivariate-adjusted ORs of dialysis for deterioration of disability was 1.57 (95%CI 1.48-1.66) and in-hospital mortality was 1.72 (95%CI 1.59-1.86).

Conclusions: Dialysis treatment was an independent risk factor for in-hospital disability deterioration and mortality of community-onset stroke.

FR-PO750

Proportion of Treatments with Low Systolic Blood Pressure and Short Term Mortality in Incident Hemodialysis Patients

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Background: Prior studies have associated low mean predialysis systolic blood pressures (preSBP) with increased 120 day risk for mortality in incident hemodialysis (iHD) patients (Maddux et al., ASN 2014). This study aimed to investigate how the percent (%) of low mean preSBP during the prior weeks’ hemodialysis (HD) treatments affects the short term risk of mortality in iHD patients.

Methods: For this study, 56,525 iHD patients at Fresenius Medical Care North America (FMCNA) clinics were investigated from 1/1/2004 to 12/31/2010. From the first date of outpatient chronic dialysis (FDD), the % of the prior weeks’ mean preSBP <110 mmHg was calculated for the first 4 months of HD. Mortality risk in the following week (7 days) was analyzed by the % of the prior week’s mean preSBP <110 mmHg at weeks 2, 4, 6, 12, and 16 from FDD.

Results: We observed that the short term risk for mortality in the following week increases in iHD patients as the % of the prior week’s mean preSBP <110 mmHg increases at weeks 2, 4, and 6 from the FDD; the risk for mortality was found to be the greatest at week 2 and was slightly reduced by week 6. Conversely, by week 12 and 16 from FDD, the % of the prior week’s mean preSBP <110 mmHg was not found to be related with the risk of mortality in the next week.

Conclusions: This study demonstrates that increases in the % of low mean preSBP during the prior weeks’ hemodialysis (HD) treatments is associated with heightened short term risks of mortality during the first 6 weeks of iHD, but not during weeks 12 and 16 from the FDD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO751

The Possibility of Faster Progression of Brain Atrophy in Patients on Peritoneal Dialysis Compared with Hemodialysis

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Background: Brain atrophy has been reported in chronic kidney disease (CKD) patients, especially in hemodialysis (HD) patients. Recently, we reported faster decline in normalized gray matter volume (GMV) in peritoneal dialysis (PD) patients compared with non-dialysis-dependent CKD (ND) (Tsuruya, et al. Am J Kidney Dis, 2015). However, it has not been reported on the comparison of the progression rate of brain atrophy between PD and HD patients. In the present study, we compared it among PD, HD, and ND patients.

Methods: A total of 151 patients of 38 PD patients aged 60 ± 12 years (men 23, diabetes 11), 24 HD patients aged 64 ± 6 years (men 18, diabetes 9), and 89 ND patients (CKD stage 3a, 34; stage 3b, 31; stages 4-5, 24) were recruited and underwent MRI scanning at baseline and after two years. T1-weighted MRI images were analyzed with statistical parametric mapping software. Total gray matter, total white matter, and cerebrospinal fluid were segmented and each volume was quantified. Normalized GMV was calculated as percentage of intracranial volume to normalize for head size variability. We compared the annual change in normalized GMV among CKD stages.

Results: Annual change in normalized GMV was significantly higher in PD patients than other CKD patients. This finding remained significant even after adjustment for potential confounding factors.

Conclusions: Progression of brain atrophy is significantly higher in PD patients than other CKD patients including HD patients, independent of age, gender, diabetes, and blood pressure level.
FR-PO752

In Centre Nocturnal Haemodialysis: Improving Outcomes and Experience for Patients
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Background: Extended periods of haemodialysis (HD) improve patient outcomes. Home HD schedules can deliver extended dialysis, but there are patient and physician related barriers that make home therapies impossible for many. We explored in centre nocturnal HD (INHD) as a method of offering extended periods of HD to patients unsuitable for home therapy.

Methods: Ten prevalent HD patients switched from standard HD (3x4 hours) to INHD (3x5 hours) for four months. Mean ultrafiltration (UF) volumes (L), relative UF rates (ml/kg/hour) and absolute UF rates (ml/hour) were calculated. Additional, biochemical and haematological data, data on dialysis adequacy and blood pressure control were collected. Changes in quality of life (QoL) were assessed using SF12, EQ-5D and the Hospital Anxiety and Depression Score (HADS) questionnaires.

Results: Seven patients completed four months of INHD. Mean dialysis time per session was 355 minutes (SD±34.92). Mean total UF volume increased from 2.0±0.5L to 2.6±3.4L (p=0.02), but there was a reduction in absolute mean UF rates from 513±121ml/hour on standard dialysis, to 356±66 ml/hour on INHD (p=0.03) and a decrease in mean relative UF rates from 6.5±1.7ml/kg/hr to 4.6±1.6ml/kg/hr (p=0.03). Adequacy measured by urea reduction ratio improved from 72±2% to 80±3% (p<0.001), with a trend towards improved phosphate control to within therapeutic targets, from 1.7±0.6mmol/L to 1.2±0.2mmol/L (p=0.08). In addition, there were improvements in all QoL scores. Mean EQ-5D visual analogue score improved from 48.16±9.2 to 72±13.2 (p=0.003). Mean HADS anxiety score decreased from 9±5.83 to 3.57±3.04 (p=0.03). SF12 physical component score improved from 31.3±3.32 to 41.69±10.19 (p=0.005).

Conclusions: Despite an increase in total UF volume, extended INHD led to an overall reduction in UF rate that has been shown to abrogate HD induced cardiac injury. Other physiological benefits included improved urea clearance and better phosphate control. There were also significant improvements in patient QoL measures over four months.

FR-PO753

Association of Multiple Strokes on Mortality in Incident Hemodialysis Patients: An Application of Multistate Model to Determine Transition Probabilities
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Background: Little is known about the effect of multiple, or subsequent, ischemic strokes in patients receiving dialysis.

Methods: A retrospective cohort study of incident hemodialysis patients with Medicare Parts A and B coverage who had experienced a first ischemic stroke was performed. A multistate model with Cox proportional hazards was used to predict transition probabilities from first ischemic stroke to subsequent stroke or to death. Demographic and clinical factors associated with the respective transition probabilities were determined.

Results: Overall, 12,054 individuals (mean age 69.7 years, 41.3% male, 53.0% Caucasian and 34.0% African-American) experienced a first stroke. Female sex was associated with an increased risk of having a subsequent stroke (adjusted hazard ratio 1.37, 95% confidence intervals 1.20 – 1.56, P < 0.0001), African-Americans, as compared to Caucasians, had lower likelihood of dying after a first stroke (0.81, 0.77 – 0.85, P < 0.0001). A subsequent stroke trended towards having a higher likelihood of transitioning to death compared to a first new stroke on dialysis (1.72, 0.96 – 3.09, P = 0.071). The probability of transitioning to a subsequent stroke increased over the first 6 months, peaked at approximately 12 months, then declined steadily over time (Figure). When a subsequent stroke occurs at 24 months, probability of survival dropped >15%, in absolute terms, from 0.254 to 0.096, with substantial drops observed at subsequent time points such that the probability of survival was more than halved.

Conclusions: Likelihood of subsequent ischemic stroke and of survival in dialysis patients appears to vary by sex and race.

FR-PO754

Electrocardiographic Manifestation in End-Stage Renal Disease Patients with Different Renal Replacement Treatment
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Background: End-stage renal disease commonly coexists with certain type of cardiovascular diseases, partially reflects the burden of cardiac in uremic state and dialysis methods. Hemodynamic changes are different between predialysis state, hemodialysis (HD), peritoneal dialysis (PD) and post-kidney transplant (Post-KT) patients. This study aimed to investigate the cardiac disorders using electrocardiographic (ECG) features between each stage of CKD patients, including HD, PD and Post-KT.

Methods: ECG records were analyzed retrospectively in 974 participants, including (a) 48 Early CKD (CKD stage 1-2), (b) 188 Advanced CKD (CKD stage 3, 4 and 5), (c) 567 Hemodialysis (HD), (d) 112 chronic ambulatory peritoneal dialysis (PD) and (d) 59 post-kidney transplant (KT) patients. ECGs were analyzed by two examiners for major ECG abnormalities.

Results: A few ECG abnormalities were observed in Early CKD, but highly frequent QTc prolongation and first degree atrio-ventricular block (AVB) were detected in Advanced CKD. PD patients developed more left ventricular hypertrophy (LVH) and premature ventricular contraction than HD counterparts.

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536A
Conclusions: Prolonged QTc, first-degree AVB, LVH and PVC were prevalent in ESRD and dependent on renal replacement therapy method. The physicians should be cautious and promptly treat to the fatal arrhythmias.

Funding: Government Support - Non-U.S.

FR-PO755

The Relation Between Sclerostin, Peripheral Vascular Calcification, and Cardiovascular Events in ESRD Patients Young Ja Na, Sang Yoon Lim, Myung-gyu Kim, Sang-Kyung Jo, Won-Yong Cho. Nephrology, Korea Univ Hospital, Seoul.

Background: Sclerostin, a negative regulator of Wnt signaling pathway produced by osteocyte, is a potent regulator of bone metabolism and a novel candidate for the bone vascular axis in chronic kidney disease patients. Although sclerostin is known as an inhibitor of vascular calcification, recent studies demonstrated conflicting results about the association between sclerostin and cardiovascular events or mortality. In this study we tested the association between sclerostin, peripheral vascular calcification, and cardiovascular events in end stage renal disease (ESRD) patient starting peritoneal dialysis.

Methods: In this prospective study, we included 45 ESRD patients admitted to Korea University Anam Hospital for starting peritoneal dialysis. Circulating sclerostin level was measured in all patients before the start of peritoneal dialysis. Simple vascular calcification score (SVCS) was measured using plain radiographic films of both hands and the pelvis. Median follow up period was 36 months.

Results: Higher sclerostin level was associated with male sex, diabetes mellitus, higher left ventricle (LV) mass index, and lower LV fractional shortening in univariate analysis. ESRD patients with severe vascular calcification (SVCS ≥3) had significantly higher prevalence of diabetes mellitus. They had higher pulse wave velocity, alkaline phosphatase, and lower cholesterol levels, LV fractional shortening and in multivariate analysis, the presence of diabetes mellitus (OR, 44.59, p=0.023), lower cholesterol levels (OR, 0.94, p=0.032) were independent risk factors predicting severe vascular calcifications. In multivariate Cox regression model, higher pulse wave velocity (HR 1.63, p=0.028) was a significant predictor for cardiovascular events. In addition higher sclerostin group (HR 9.82, p=0.094) and lower albumin levels (HR 0.25, p=0.081) display a strong tendency of increased cardiovascular events.

Conclusions: This study showed the possible important role of sclerostin in the development of vascular calcification and cardiovascular events in PD patients. Longer term follow up with larger sample size will be needed to clarify this issue.

FR-PO756

Use of Anticoagulants in Patients with Atrial Fibrillation and End Stage Renal Disease: A Study of Real World Data Lloyd P. Haskell,1 Chris Knoll,2 Patrick Ryan,3 Zhong Yuan.1 1Cardiovascular, Janssen R and D, Raritan, NJ; 2Epidemiology, Janssen R and D, Raritan, NJ; 3Epidemiology, Janssen R and D, Titusville, NJ.

Background: End stage renal disease (ESRD) in patients with atrial fibrillation (AF) is a significant cause of morbidity and mortality. While these patients are at high risk for stroke, there are limited data with respect to use of anticoagulants in clinical practice and current guidelines are not clear on how to manage them.

Methods: US-based, four large healthcare databases (Truven MarketScan Commercial Claims/Encounters [CCAE], Medicare Supplemental [MDCR], Medicaid [MDCD] and Optum Clininformatics [Optum]) were used to establish cohorts of patients with AF and ESRD, who were identified using ICD-9 codes. The first encounter with evidence of both conditions during the inception period of 2010-2012 was the index date; patients must have had at least 1 year enrolment prior to and after the index date to be eligible for the study. The use of anticoagulants was examined during the follow-up period.

Results: Table 1 shows patient demographics and use of anticoagulants by data source. As expected, the privately-insured patient populations (CCAE and Optum) as well as the Medicaid population (MDCD) were younger as compared with the Medicare eligible (MDCR). Across study cohorts, approximately 37% to 40% of patients with AF and ESRD received at least one dispensing of warfarin, with the exception of the Medicaid population (14%). About 3% to 4% of patients (except for Medicaid) received at least one dispensing of novel oral anticoagulant therapy (rivaroxaban, apixaban, or dabigatran).

Table 1: Use of Anticoagulants in Patients with AF and ESRD

<table>
<thead>
<tr>
<th>Datassource</th>
<th>N</th>
<th>Mean Age [S.D.]</th>
<th>Male, %</th>
<th>Novle Oral Anticoagulants</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>3650</td>
<td>56 [7.7]</td>
<td>66.2%</td>
<td>2.5%</td>
<td>37.7%</td>
</tr>
<tr>
<td>Medicare</td>
<td>9866</td>
<td>77 [7.7]</td>
<td>59.7%</td>
<td>3.4%</td>
<td>40.1%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>5663</td>
<td>64 [3.7]</td>
<td>41.6%</td>
<td>0.6%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Optum</td>
<td>2825</td>
<td>65 [12.4]</td>
<td>66.8%</td>
<td>4.1%</td>
<td>37.5%</td>
</tr>
</tbody>
</table>

Conclusions: Less than 40% of patients with AF and ESRD received anticoagulant therapy. As these are high risk patients, anticoagulant therapy may be underutilized. Further research is necessary to investigate clinical outcomes associated with anticoagulation in these patients.

FR-PO757

Factors Determining Changes in Mortality Rates in Incident Hemodialysis Patients Jochen G. Raimann,1 Len A. Usvyat,2 Dugan Maddux,2 Jeroen Kooman,3 Frank van der Sande,3 Kevin Chan,2 Franklin W. Maddux,2 Peter Kotanko.1,4 1Renal Research Inst; 2 Fresenius Medical Care North America; 3 Maastricht Univ Medical Centre; 4 Icahn School of Medicine at Mount Sinai.

Background: The higher risk of death for incident hemodialysis (HD) patients decreases during the first year (Chan, 2011). Next to vintage, risk is also affected by patient characteristics and the evolution of clinical and laboratory parameters. We analyzed how mortality rates change in different age groups, levels of albumin, in black and white, and in diabetic and non-diabetic patients after HD initiation.

Methods: We analyzed patients commencing HD in Fresenius Medical Care North America clinics between 1/1/2005 and 11/30/2014. We calculated proportions of patients dying from all causes in diurnal intervals starting with the first day on HD up to 1000 days. Only patients who had their first outpatient treatment on day 1 of their first ever HD were analyzed. We analyzed differences in mortality in the following strata: a) age groups (<40, between 40 and 65, and >65 years), b) serum albumin greater and below 3.8 g/dL, c) black and white; and d) diabetic and non-diabetic patients. We fitted penalized B-splines with 95% CIs through all available daily rates.

Results: We studied 334,880 patients. For all groups, mortality rates dropped within the first year. There were differences between groups of age, albumin and between white and black patients, but none between diabetic and non-diabetic patients.

Conclusions: Mortality rates decrease substantially once patients initiate HD. After approximately one year on HD, mortality remains consistent in all groups, but remains lower for those with higher albumin, younger age and black race. Diabetes appears to not affect mortality. Since only patients starting in an outpatient setting were included, selection bias may apply differently to the patient groups.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America
FR-PO759

Survival in Elderly on Dialysis and Impact of Institutionalization Amarpali Brar, David Kau, Moto O. Salliu, Mary C. Mallappallil. Renal, SUNY Downstate, Brooklyn, NY.

Background: We hypothesized that in the very elderly dialysis patients in the United States, institutionalization in nursing homes would increase mortality in addition to age alone.

Methods: Data was obtained from the U.S. Renal Data System. Incident dialysis patients from 2001 to 2008 above the age of 70 were included. Follow-up period was from incident dialysis date to either death or last follow up on September 30, 2009. Patients above 70 were categorized into four groups according to age as 70-75 years, 76-80 years, 81-85 years, greater than 85 years and further divided into institutionalized and non-institutionalized.

Results: A total of 349,440 patients were identified above the age of 70 years at the time of initiation of dialysis. Major causes of end stage renal disease were diabetes, hypertension, glomerulonephritis, cystic kidney disease, and urological causes. Mean survival for non institutionalised patients was 3.15 ± 0.01 years for those between 70-75 years of age, 2.55±0.01 years for 76-80 years of age, 2.12±0.01 years for 81-85 years of age and 1.64:±0.01 years for those above 85 years at the time of initiation of dialysis respectively. For institutionalized patients, mean survival was significantly lower, 1.71±0.03 years for 70-75 years old, 1.44±0.02 years for 75-80 years old, 1.25±0.02 years for 81-85 years old and more than 85 years and 1.04±0.02 for > 85 years age group, p<0.001. The oldest group in non-institutionalized over the age of 85 years had a similar survival as the institutionalized ESRD patients 70-75 years old.

Conclusions: There was increased mortality in institutionalized elderly patients as compared to non institutionalised elderly patients in the same age group. Keeping with the increased frailty and decreased benefits of therapies in the very elderly especially in those with additional co-morbidities besides age, palliative and end of life care should be considered.

FR-PO760

Geriatric Nutritional Risk Index Is a Simple Predictor of Mortality in Chronic Hemodialysis Patients Kosaku Nitta, Ken Tsuchiya. Dept of Medicine, Kidney Center, Tokyo Women’s Medical Univ, Shinjuku-ku, Tokyo, Japan.

Background: Malnutrition is common in hemodialysis (HD) patients, and it is associated with increasing risk of mortality. The geriatric nutritional risk index (GNRI) has been developed as a tool to assess the nutritional risk. The aim of the present study was to examine the reliability of the GNRI as a mortality predictor in a Japanese HD cohort.

Methods: We prospectively examined the GNRI of 332 maintenance HD patients aged 40-49, 50-59, 60-69, ≥ 70 years of age. The patients were further divided into quartiles (Q) according to GNRI values (Q1: <91.6, Q2: 91.7-97.0, Q3: 97.1-102.2, Q4: >102.3). Predictors for all-cause mortality were examined using Kaplan-Meier and Cox proportional-hazards analyses.

Results: The GNRI presented a normal distribution. During the follow-up period of 36 months, a total of 76 patients died. The overall mortality at the end of the 3-year observational period was 22.3 %. At the 3-year follow-up period, Kaplan-Meier survival rates for all-cause mortality were 72.3%, 79.3%, 84.9%, and 92.6% in Q1, Q2, Q3, and Q4, respectively (p = 0.0067). Multivariate Cox proportional-hazards analysis demonstrated that the GNRI was a significant predictor of adjusted all-cause mortality (HR 0.958; CI 0.929–0.9, p = 0.001).

Conclusions: The results of the present study demonstrate that the GNRI is a strong predictor of overall mortality in HD patients. However, cardiovascular mortality was not associated with GNRI values, and it did not differ among the GNRI quartiles. The GNRI score can be considered a simple and reliable marker of predictor for mortality risk in Japanese HD patients.

FR-PO761

Frailty and Clinical Outcomes in Chronic Dialysis Patients Dong Ho Yang,1 Eun jung Ko,1 Hye yun Jeong.1 1Internal Medicine, CHA Bundang Medical Center, Seongnam, Republic of Korea; 2Internal Medicine, CHA Gumi Medical Center, Gumi, Republic of Korea.

Background: Frailty is a biological syndrome of decreased reserve and resistance to stressors and is independently associated with mortality and hospitalization in the general population. We investigated the relationship between frailty and clinical outcomes in chronic dialysis patients.

Methods: In this prospective study, 1,658 patients receiving chronic dialysis were enrolled. Chronic dialysis was defined as dialysis for more than 6 months. Of the 1,658 patients, 1,255 received hemodialysis. The remainder received peritoneal dialysis. Fried’s criteria for frailty as modified by Woods et al. was used. A trained interviewer asked study participants about 5 frailty phenotypes (slowness, weakness, exhaustion, shrinking, and physical inactivity) using the RAND 36-item Short Form.

Results: The mean age was 55.2±11.9, and 55.2% were male. Overall, 577 (34.8 %) patients met the study definition of frailty. Another 755 (45.7%) patients were pre-frail. Table 1 shows the prevalence of frailty and its components by age group. During the 30-month follow-up period, 607 patients (79 non-frail, 249 pre-frail, and 279 frail) were hospitalized; and 87 patients (10 non-frail, 24 pre-frail, and 53 frail) died (P<0.001). Frailty was strongly associated with hospitalization (adjusted hazard ratio [HR] 1.80, 95% CI 1.4 to 2.3) and mortality (HR 2.37, 95% CI 1.11 to 5.0) in multivariate analysis. The relationship between frailty and hospitalization was strongest among patients age 40 to 49, with a HR of 3.02 (95% CI 1.48 to 6.20).

Table 1. The prevalence of frailty and its components by age.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frail, %</th>
<th>Pre-frail, %</th>
<th>Slowness/Weakness, %</th>
<th>Exhaustion, %</th>
<th>Inactivity, %</th>
<th>Shrinking, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>21.1</td>
<td>57.8</td>
<td>33.0</td>
<td>60.8</td>
<td>58.3</td>
<td>13.7</td>
</tr>
<tr>
<td>50-59</td>
<td>20.6</td>
<td>55.9</td>
<td>35.2</td>
<td>66.2</td>
<td>45.6</td>
<td>7.6</td>
</tr>
<tr>
<td>60-69</td>
<td>38.0</td>
<td>47.2</td>
<td>41.0</td>
<td>80.2</td>
<td>42.8</td>
<td>9.8</td>
</tr>
<tr>
<td>≥ 70</td>
<td>63.8</td>
<td>26.5</td>
<td>34.6</td>
<td>50.6</td>
<td>35.6</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Conclusions: We found a high prevalence of frailty in chronic dialysis patients across all age groups. The risk of hospitalization and mortality in the 30-month follow-up period significantly increased in frail chronic dialysis patients.
FR-PO763

1- and 2-Year Mortality Prediction Models for Patients Starting Chronic Dialysis
Mikko Haapio,1 Jaakko Helve,1 Carola Gronhagen-Riska,1,2 Patrik Finne,1,2 1Nephrology, Univ of Helsinki and Helsinki Univ Hospital, Helsinki, Finland; 2Finnish Registry for Kidney Diseases, Helsinki, Finland.

Background: Mortality risk of patients with end-stage renal disease (ESRD) is highly elevated compared to patients without ESRD. Taking into account our limited nephrological care resources and the simultaneously increasing number of ESRD patients there is a great need for means of mortality risk estimation to assist both in individualized patient care as well as in sound use of resources. Some mortality prediction models already exist, but many have shown a lack of comprehensiveness in data or in patient recruitment in their development.

Methods: Our objective was to design a prediction model for 1- and 2-year all-cause mortality in patients starting chronic renal replacement therapy. In addition, we aimed to build an easy-to-apply model consisting of only a few variables. We used the comprehensive data of the Finnish Registry for Kidney Diseases with complete coverage of Finnish ESRD patients. Model training group included all incident adult patients who started chronic dialysis in Finland from 1 January 2000 to 31 December 2008 (n=4335). The external validation cohort consisted of all those who started dialysis from 1 January 2009 to 31 December 2012 (n=1768). Prediction algorithms for 1- and 2-year mortality were developed using multivariate logistic regression with stepwise selection of variables. Our primary analyses included 32 variables, from which the most important ones were selected.

Results: Both final prognostic models, including only 6-7 variables, showed adequate discrimination (c-statistic 0.77 and 0.74 for 1- and 2-year mortality, respectively). Because of a significantly lower mortality in the newer (validation) cohort, both models somewhat overestimated mortality risk.

Conclusions: Mortality prediction algorithms could be more widely implemented into clinical treatment-planning of ESRD patients. Our prediction models perform sufficiently and are convenient to use, and could assist in individualized risk-stratification and, furthermore, in equal and fair sharing of limited health care resources.

FR-PO764

Comorbidity Burden at Dialysis Initiation and Mortality: A Retrospective Cohort Study
Alywn Titus Gomez,1 Bryce A. Kibed,1 Talal A. Alfaadhel,2 Brenda Hemmelgarn,3 Karthik T. Tennukore,1 1Medical, Dalhousie Univ, Halifax, NS, Canada; 2Medicine, Univ of Toronto, Toronto, ON, Canada; 3Medicine, Univ of Calgary, Calgary, AL, Canada.

Background: Contemporary assessments of the validity and prognostic value of comorbidity indices in dialysis are lacking. We sought to assess the validity of two comorbidity indices used for dialysis patients and to determine if a high degree of comorbidity was associated with mortality.

Methods: We conducted a retrospective cohort study of incident chronic dialysis patients in a tertiary care institute from 2006-2013. The Charlson Comorbidity Index (CCI) and End-Stage Renal Disease Comorbidity Index (ESRD-CI) were calculated in all patients at dialysis initiation. These indices combine individual medical conditions into an overall score. Comorbid conditions were ascertained using electronic records. The primary outcome was all-cause mortality.

Results: The cohort consisted of 771 patients. Most were male (62%) and Caucasian (91%). Patients had a high prevalence of diabetes (48%) and history of myocardial infarction (31%). The c-index was 0.61 for the CCI, and 0.63 for the ESRD-CI. In an adjusted analysis, ESRD-CI scores of 4, 5 and ≥6 were associated with a similar mortality risk (Table 1). There was a small increased mortality risk for CCI scores of 4, 5 and ≥6.

Conclusions: The CCI and ESRD-CI had a limited ability to discriminate risk of death for incident dialysis patients. Although a higher comorbidity burden was associated with mortality, increases in index scores did not considerably change the risk of death.

Table 1. Multivariable Cox survival analysis for the ESRD-CI and CCI

End-Stage Renal Disease Comorbidity Index

<table>
<thead>
<tr>
<th>Score</th>
<th>Relative Hazard [95% Confidence Interval]</th>
<th>6/1</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.63 [1.12 to 2.36]</td>
<td>2</td>
<td>Reference</td>
</tr>
<tr>
<td>3</td>
<td>1.28 [0.84 to 1.92]</td>
<td>3</td>
<td>Reference</td>
</tr>
<tr>
<td>4</td>
<td>1.95 [1.34 to 2.85]</td>
<td>4</td>
<td>Reference</td>
</tr>
<tr>
<td>5</td>
<td>1.89 [1.25 to 2.36]</td>
<td>5</td>
<td>Reference</td>
</tr>
<tr>
<td>≥6</td>
<td>1.99 [1.41 to 2.81]</td>
<td>≥6</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Charlson Comorbidity Index

<table>
<thead>
<tr>
<th>Score</th>
<th>Relative Hazard [95% Confidence Interval]</th>
<th>6/1</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.76 [1.10 to 2.82]</td>
<td>2</td>
<td>Reference</td>
</tr>
<tr>
<td>3</td>
<td>1.86 [1.22 to 2.83]</td>
<td>3</td>
<td>Reference</td>
</tr>
<tr>
<td>4</td>
<td>2.38 [1.53 to 3.72]</td>
<td>4</td>
<td>Reference</td>
</tr>
<tr>
<td>≥5</td>
<td>2.71 [1.81 to 4.06]</td>
<td>≥5</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, cause of end-stage renal disease, type of dialysis (hemodialysis or peritoneal dialysis), estimated GFR, albumin, phosphate and hemoglobin

FR-PO765

Cumulative Risk of Death in Propensity-Matched Incident Dialysis Patients: A Nationwide Prospective Multicenter Cohort Study in Korea
Hee-Yeon Jung,1 Sukyung Lee,1 Ji-Young Choi,1 Se-Hee Yoon,2 Jung-Hee Cho,1 Sun-Hee Park,1 Chan-Duck Kim,1 Yong-Lim Kim.1 1Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; 2Internal Medicine, Konkuk Univ, Danjeon, Republic of Korea.

Background: Our previous study reported the superior outcome of peritoneal dialysis (PD) than hemodialysis (HD) in the early dialysis period. This study investigated the impact of dialysis modality after the early period of incident dialysis patients.

Methods: Incident dialysis patients were enrolled from Korean nationwide prospective cohort from September 2008 to December 2013. The patients were stratified by modality at day 90 after the first dialysis or the modality at dialysis initiation if death occurred prior. The survival of PD and HD patients were compared by propensity score matching analysis. Relative risk of death was estimated using the cumulative hazard ratio from the stratified Cox proportional hazard model adjusted for residual confounding.

Results: A total of 1348 patients were matched from 2658 incident dialysis patients with mean follow-up of 29.9 ± 14.1 months. All clinical parameters including baseline residual renal function were comparable between PD and HD patients. The cumulative risk of death was significantly lower in PD than HD from 6 months after dialysis initiation. The cumulative hazard ratio for death was 0.70 (95% confidence interval [CI] 0.41-0.98) at one year for PD compared with matched HD and 0.68 (95% CI 0.46-0.90) at two years. The cumulative survival probability was higher in PD patients for up to 3.5 years on dialysis, with no difference after the period.

Conclusions: Overall survival in maintenance dialysis patients favored PD in the early period of dialysis and the survival advantage lasted to 3-5 years after initiation of dialysis. However, PD and HD patients had similar survival outcomes thereafter.

FR-PO766

Inflammation and Fluid Overload a Complex Interaction: Results from the International MONDO Initiative
Marijke J.E. Dekker,1 Len A. Usvyat,2 Daniele Marcelli,1 Frank van der Sande,3 Constantijn Konings,1 Peter Kotanko,2 Jeroen Kooman.3 1Catharina Hospital Eindhoven; 2Renal Research Inst; 3Fresenius Medical Care; 4Maastricht Univ Medical Center.

Background: In hemodialysis (HD) patients, the presence of inflammation or fluid overload (FO) is associated with increased mortality. The combined presence of these two is associated with even a greater risk of death. This study aims to unravel the temporal relationship between fluid status alterations and inflammation.

Methods: We conducted a longitudinal study (baseline and follow-up 3 months each) in a European subset of the MONDO-Initiative. Fluid status was assessed by multifrequency bioimpedance and inflammation by C-reactive protein (CRP). We divided patients into 4 groups based on fluid- and inflammation status. FO was defined as overhydration above >2.5L. Inflammation was defined as CRP >10mg/L.

Results: We included 5954 patients (56.1% male, age 63 years, vintage 5.1 years). At baseline inflammation and FO were jointly present in 1092 (18.3%) patients. 141 (11.8%) developed inflammation during follow up. Of the 1192 (20%) patients with inflammation but with normal fluid status at baseline, 111 (10.2%) had FO during follow up. Inflammation at baseline predicted FO during follow up (odds ratio(OR) 1.2095% CI 1.05-1.37)). Likewise, FO during baseline predicted inflammation during follow up (OR 1.30 95% CI 1.15-1.47)). However, in a minor of patients the presence of FO and/or inflammation appears to be a relatively stable condition. The presence of both inflammation and FO during baseline was associated with an increased mortality risk compared to the absence of both.

Conclusions: FO and inflammation are associated in prevalent HD patients. FO is a predictor for inflammation and vice-versa inflammation predicts FO. The combined presence of FO and inflammation is associated with poor survival.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO767**

**Blood Volume Analysis as a Guide for Dry Weight Determination in Chronic Hemodialysis Patients**

**Line Malha,1,2,3 Hassan Fattah,1 Frank Modersitzki,1 David S. Goldfarb,1,2,4**

**Background:** Volume overload and depletion both lead to high morbidity and mortality. Achieving euvolemia is a challenge in patients with end stage kidney disease (ESKD) on hemodialysis (HD). Blood volume analysis (BVA) uses radio labeled albumin to determine intravascular blood volume (BV). The measured BV is compared to an ideal BV (validated in healthy controls). We hypothesized that BVA could be used in HD to evaluate the adequacy of the current clinically prescribed “estimated dry weight” (EDW) and to titrate EDW in order to improve overall dry weight status. We were also interested in the reproducibility of BVA results in ESKD. This is the first longitudinal study of BVA in HD patients.

**Methods:** 12 adults on chronic HD were recruited; 10 completed the study. BVA (Daxor, Norwood, MA) was used to measure BV at baseline. EDW was kept the same if the patient was deemed to be euvoicmic by BVA otherwise, the prescribed EDW was changed with the aim that measured BV would match ideal BV. A second BVA measurement was done 1-3 months later in order to measure BV again.

**Results:** Based on BVA, 6/10 patients were euvoicmic at baseline and 5/10 were euvoicmic at the second measurement. When comparing patients who had their prescribed EDW changed after the initial BVA to those who did not, both groups had similar differences between measured and ideal BV (P=0.75). BV values were unchanged at the second measurement (P=0.34) and there was no linear correlation between BV change and initial EDW change (r=0.04).

**Conclusions:** This pilot study is the first longitudinal measurement of BVA in HD patients. It revealed that changing weight did not proportionally change intravascular BV. BV remained stable for 1-3 months. BVA may not be helpful in clinically stable HD patients but studies on patients with hemodynamic instability and uncertain volume status are needed.

Funding: Pharmaceutical Company Support - Daxor provided BVA equipment and supplies but was not involved in study design or execution and did not participate in the analysis of data or preparation of the manuscript.

**FR-PO768**

**Effects of Physician Payment Reform on Provision of Home Dialysis**

**Kevin E. Erickson,1 Wolfgang C. Winkelmayer,1,2 Glenn Matthew Chertow,1,2 Jay Bhattacharya,1**

**Background:** Patients with end-stage renal disease can receive dialysis at home or in-center. In 2004 the Centers for Medicare and Medicaid Services reformed physician payment for in-center hemodialysis care from a capitated to a tiered fee-for-service model, augmenting physician payment for frequent in-center visits. We evaluated whether payment reform influenced dialysis modality assignment.

**Methods:** Using a national cohort of patients starting dialysis in the US in the three years before and after payment reform, we conducted difference-in-difference analyses comparing patients with Traditional Medicare coverage (who were affected by the policy) to others with Medicare Advantage (who were unaffected by the policy). We also examined whether the policy had a more pronounced influence on dialysis modality assignment in areas with lower costs of home vs. in-center dialysis.

**Results:** Patients with Traditional Medicare coverage experienced a 12% (95% CI, 2% to 21%) reduction in home dialysis use following payment reform compared to patients with Medicare Advantage. Patients living in areas with larger dialysis facilities (where payment reform had made in-center hemodialysis comparatively more lucrative for physicians) experienced a 16% (95% CI, 8% to 23%) reduction in home dialysis use following payment reform compared to patients living in areas with smaller facilities (where payment reform made in-center hemodialysis comparatively less lucrative for physicians).

**Conclusions:** National physician payment reform intended to improve the quality of dialysis care resulted in fewer patients receiving home dialysis. This highlights a major failure of the policy and the importance of considering unintended consequences of future physician payment reform efforts.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Support. Other NIH Support - Funding: F32 HS019178 from AHRQ (Dr. Erickson); D08RS446 (Dr. Chertow); Dr. Winkelmayer receives research and salary support through the endowed Gordon A. Cain Chair in Nephrology at Baylor College of Medicine. Dr. Bhattacharya would like to thank the National Institute on Aging for support for his work on this paper (R37 150127-054662-002).

**FR-PO769**

**Characteristics and Outcomes Amongst Patients Who Switch Dialysis Provider**

**Scott Reule,1 Paul E. Drawz, Robert N. Foley. Dept of Medicine, Univ of Minnesota, Minneapolis, MN.**

**Background:** Associations between provider switch and inferior clinical outcome have been demonstrated in primary care settings. It is plausible that similar associations extend into those on renal replacement therapy (RRT) as nephrology care often extends beyond that of RRT management alone. There is a paucity of literature available describing the characteristics and outcomes amongst those whom switch dialysis provider.

**Methods:** Using USRDS data, a change in provider will be defined to the presence of any non-continuous facility codes while receiving maintenance RRT. As patients transitioning to maintenance RRT may experience early adverse outcomes, only those patients having initiated RRT with a vintage of at least 1 year were included in the analysis. Means and proportions were calculated for continuous and categorical variables, respectively. Logistic regression was used for adjusted comparisons with adjustments for baseline demographic characteristic including age, sex, and race. All estimates with p-value < 0.05 were considered significant.

**Results:** Applying these criteria, a total of 187,510 (9.1%) of prevalent patients requiring RRT were identified as having changed provider at least once. The mean age of those who have changed provider (vs. no change) was 41.3 years (vs. 57.3 years), 57% were male (vs. 55.1%), 51.3% were white (vs. 49.1%), diabetes as comorbidity in 29.9% (vs. 21.1%), and 23% were < 65 years of age at initiation (vs. 7.95%). Risk of death was lower in those who change provider (OR 0.69; CI 0.68 – 0.70) and odds were higher for both listing for (OR 2.9; CI 2.9 – 3.0) and receipt of renal transplantation (OR 4.1; CI 4.0-4.2).

**Conclusions:** Patients who switch dialysis providers constitute a distinct population of patients who are younger and lack comorbid conditions frequently observed in those on dialysis. Compared to those who do not switch providers, those who switch are more likely to be listed for and receive renal transplant.

**FR-PO770**

**Effects of Sildenafil in Dialysis Patients with Erectile Dysfunction: A Systematic Review and Meta-Analysis**

**Anaawin Sanzuanque,1,2 Sikarin Upala,1,2 Internal Medicine, Bassett Medical Center and Columbia Univ College of Physicians and Surgeons, Cooperstown, NY;1 Preventive and Social Medicine, Faculty of Medicine Sirivaj Hospital, Mahidol Univ, Bangkok, Thailand.**

**Background:** Erectile dysfunction (ED) is prevalent in dialysis patients. Sildenafil, a PDE-5 inhibitor, has been shown to be very effective against ED in general population. However, there is some evidence that dialysis patients are resistant to sildenafil treatment. We performed this meta-analysis to evaluate efficacy of sildenafil in dialysis patients with ED compared with control.

**Methods:** We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published RCT comparing sildenafil therapy to placebo or controls on ED in patients with dialysis. The primary outcome was change in International Index of Erectile Function (IIEF) score. The diagnosis of ED was confirmed with a score of ≥ 21 or less in IIEF.

**Results:** From 153 full-text articles, 3 studies involving 153 dialysis patients were included in the meta-analysis. All included studies were RCT comparing sildenafil with active control in either hemodialysis or peritoneal dialysis patients. A meta-analysis using fixed-effects model was performed. Those who received sildenafil had a significant improvement in IIEF score with a MD of 10.48 (95% CI: 9.96 to 11.00, p-value<0.01).

**Conclusions:** This is the first meta-analysis to show that sildenafil is effective in dialysis patients with erectile dysfunction compared with control. Further study comparing other benefits and side effects of PDE-5 inhibitor in dialysis patients should be conducted.

**FR-PO771**

**Validation of Screening Questionnaires for Sleep Apnea in Hemodialysis Patients**

**Farahnah Yousaf,1 Mitesh K. Patel, Saw H. Mu, Alla Goldberg, Chaim Charytan, Bruce S. Spinowitz, New York Hospital Queens.**

**Background:** Sleep apnea hypopnea syndrome (SAHS) is common in end stage renal disease (ESRD). We investigated the validity of Berlin and STOP-BANG questionnaires against nocturnal oximetry in identifying high risk hemodialysis patients for SAHS.

**Methods:** After obtaining local IRB approval, adult hemodialysis patients who were undergoing regular chronic hemodialysis for at least 3 months were consented and asked to complete Berlin and STOP-BANG questionnaires. Nocturnal oximetry from hemodialysis night using Pulsox 300i wristwatch was also completed. The saturation recordings were downloaded and analyzed using Profox software. The first hour of recording was deleted in effect as saturation recording period from sleep time only. Saturation data were also excluded from analysis. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds, per hour. Sensitivity, specificity, positive and negative predictive values were calculated for the Berlin and STOP-BANG questionnaires.

**Results:** Twenty HD patients (11 males and 9 females) aged 54 ± 5.8 years had a mean body mass index of 25.5 ± 6.7 kg/m² and neck circumference of 38.4 ± 5.8 cm.

**Conclusions:** This is the first meta-analysis to show that sildenafil is effective in dialysis patients with erectile dysfunction compared with control. Further study comparing other benefits and side effects of PDE-5 inhibitor in dialysis patients should be conducted.

**FR-PO772**

**Validation of Screening Questionnaires for Sleep Apnea in Hemodialysis Population**

**Erickson F,1 Modersitzki F,2 Wolfrum H,2 Tschander C,1 Winkelmayer WC.1 Preventive and Social Medicine, Faculty of Medicine, Stanford Univ, Palo Alto, CA;2 Medicine, Baylor College of Medicine, Houston, TX.**

**Background:** Sleep apnea hypopnea syndrome (SAHS) is common in end stage renal disease population. Reliable screening tools for SAHS in ESRD population are limited.

**Methods:** Both Berlin and STOP-BANG questionnaires lack specificity to be utilized in this setting. The inclusion criteria were published RCT comparing sildenafil therapy to placebo or controls on ED in patients with dialysis. The primary outcome was change in International Index of Erectile Function (IIEF) score. The diagnosis of SAHS was confirmed with a score of ≥ 21 or less in IIEF.

**Results:** From 153 full-text articles, 3 studies involving 153 dialysis patients were included in the meta-analysis. All included studies were RCT comparing sildenafil with active control in either hemodialysis or peritoneal dialysis patients. A meta-analysis using fixed-effects model was performed. Those who received sildenafil had a significant improvement in IIEF score with a MD of 10.48 (95% CI: 9.96 to 11.00, p-value<0.01).

**Conclusions:** This is the first meta-analysis to show that sildenafil is effective in dialysis patients with erectile dysfunction compared with control. Further study comparing other benefits and side effects of PDE-5 inhibitor in dialysis patients should be conducted.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
FR-PO772
Moderate to Severe Nocturnal Hypoxemia and Executive Dysfunction in Patients Undergoing Maintenance Hemodialysis Farahnaz Youssaf, Mitsesh K. Patel, Chaim Charytan, Alla Goldberg, Bruce S. Spinowitz. New York Hospital Queens.

Background: Nocturnal hypoxemia and executive dysfunction is common in end stage renal disease. We investigated the impact of moderate to severe nocturnal hypoxemia on executive function in patients undergoing maintenance hemodialysis.

Methods: Following local IRB approval, adult hemodialysis patients were consented to complete 1 night of nocturnal oximetry using Pulsiox 300T wristwatch. The first hour of recording was deleted in efforts to capture oximetry reading from sleep time only. Oxygen desaturation index (ODI) was defined as the number of desaturations ≥ 3% from baseline lasting ≥ 10 seconds per hour. Trail making tests A and B were also completed during dialysis session. Trail making test A and B performance was compared using t-test in patients with ODI < 15 versus those with ODI ≥ 15. Executive dysfunction was defined as trail making A and B completion time > 75 seconds and 180 seconds, respectively.

Results: Nine of 20 patients aged 45 ± 12 years with a mean body mass index (BMI) of 23 ± 3 kg/m² and neck circumference of 35 ± 4 cm had ODI < 15. The remaining eleven patients aged 60 ± 12 years with a mean BMI of 28 ± 5 kg/m² and neck circumference of 41 ± 6 cm had ODI ≥ 15. Patients with ODI ≥ 15 took significantly longer (77 ± 34 sec) to complete trail making test A versus patients with ODI < 15 (45 ± 23 sec). Five of 11 (45%) patients with ODI ≥ 15 required > 75 seconds to complete trail making test A compared to only 1 patient out of 9 (11%) with ODI < 15. Mean duration for completion of trail making B test was also longer in patients with ODI ≥ 15 (157 ± 87 seconds) compared to ODI < 15 (117 ± 67 seconds) [p<0.03]. Two of 11 patients with ODI ≥ 15 and 2 of 9 patients with ODI < 15 required > 180 seconds to complete trail making test B.

Conclusions: Patients with ODI < 15 performed better on trail making test A, were younger with a smaller BMI and neck circumference, compared to those with ODI ≥ 15. Additional research is warranted to confirm these findings. Whether treatment of moderate to severe nocturnal hypoxemia may slow or prevent executive decline in patients undergoing maintenance hemodialysis remains to be determined.

FR-PO773
Indoxyl Sulfate (Indican) and Sleep Disorders in Hemodialysis Patients: The Retained Solutes Outcomes and Clinical Studies (ROSCO) Study Yunnuo Zhu,1 Tanushree Banerjee,1 Tariq Shafi,2 Timothy W. Meyer,2 Michael L. Melamed,3 Thomas H. Hostetter,4 Neil R. Powe,51 UCSF; 2JHU; 3Stanford; 4Albert Einstein; 5Case Medical Center.

Background: Although sleep disorders are common in dialysis patients, the pathophysiology of sleep disturbance is unclear. Protein-bound solutes inadequately removed during dialysis may contribute to sleep disorders.

Methods: We examined the association of total and free levels of IS with sleep disorder in 1,241 prevalent dialysis patients from the HEMO study. IS levels were measured using mass spectroscopy and modeled as tertiles. Sleep disorder was assessed using a 5-level categorical question in the Short Form (36) Health Survey. We used ordinal logistic regression to assess the relation of IS with sleep disorder, adjusting for confounders including age, race, gender, ICED score, body mass index, diabetes, congestive heart failure, serum albumin, creatinine, and phosphate levels. The lowest tertile of IS was the reference group. Effect modification was tested for IS levels with Kt/V and gastrointestinal (GI) disease (due to IS’s GI origin).

Results: Patients were on average 57.5 years old, 62.8% were black, and 43.2% were male. There was a significant association between increasing tertiles of free IS and more severe sleep disorder in both unadjusted [OR 1.44 (95% CI: 1.1-1.89)] and adjusted models [1.78 (1.24-2.58)]. There was effect modification by Kt/V (p=0.03) but none by GI disease (p=0.17). Similar results were observed with total IS and sleep disorder [2.09 (1.37-3.19)]. Stratified analyses by Kt/V did not show an association between higher tertiles of free IS and sleep disorder in the high Kt/V group [0.72 (0.45-1.14)]. However greater odds of sleep disorder with higher tertile of IS were noted in the low Kt/V group. This relation was also present for total IS; those with low Kt/V had greater odds of sleep disorder with the highest total IS tertile [2.11 (1.29-3.45)] but not with the high Kt/V group [0.91 (0.61-1.35)].

Conclusions: Higher levels of IS are significantly associated with sleep disorder. Patients with a lower dialysis dose may be more susceptible. Further research on whether removal of IS improves sleep outcomes is needed.

FR-PO774
Quantifying Physical Activity Levels and Sleep in Hemodialysis Patients Using a Commerially-Available Activity Tracker Maggie Han,1 Schanel Williams,1 Anna Meyring-Wosten,1 Viviane Callico-Silva,2 Melissa Mendoza,1 Hanjie Zhang,1 Xiaoling Ye,1 Tariq Shafi,2 Deborah S. Evans,1 Deborah A. Benner.1 1DAVita HealthCare Partners Inc, Denver, CO; 2Apex Health Innovations, Simi Valley, CA.

Background: Unemployment rates are high among dialysis patients; a 2011 study found approximately 71% of working-age dialysis patients are unemployed.1 Another study found that dialysis negatively impacts employment status and has the largest effect between dialysis years 1 and 2.2 We examined whether prolonged dialysis (dialysis vintage) affects employment status.

Methods: Dialysis vintage data and mean age were obtained from a sample of 16,069 employed patients from a large dialysis organization (Nov 2014-April 2015). Employment status was defined as regular full-time (35 hrs/ wk), regular part-time (<35 hrs/wk), and per diem (≤24 hrs/wk).

Results: Regular full-time employed patients were older (52.6 yrs) than part-time (49.1 yrs) and per diem (49.0 yrs) patients. Employment status was highest among all patients for all categories of employment during year 1 of dialysis (35.7%) and dropped significantly by year 2 (14.4%) [Table]. Employment status continued to drop as vintage
Conclusions: Our study found that dialysis vintage negatively impacts employment status and has the largest effect between years 1 and 2. Further study is needed to reveal if a similar rate of increase toward this threshold exists. It appears that these patients should alert dialysis staff that support and intervention may be needed to help patients employed. References: 1) Muehler RJ et al. Clin J Am Soc Nephrol. 2011;6(3):489-496. 2) van Manen JG et al. Peri Dial Int. 2001;21(6):595-601.

FR-PO777

Provider Visit Frequency During Hemodialysis and Its Effect on End Stage Renal Disease Comorbidities
Juan E. Echeverri, Joslyn Wiley, Hazem Abu Grara, Rene Armando Garcia, Alberto J. Sabucedo, Marco A. Ladino-Avellaneda. Div of Nephrology, Miami VA Medical Center/Univ of Miami, FL.

Background: In the United States, patients with End Stage Renal Disease (ESRD) on hemodialysis visit their Nephrologist one to four times per month during their dialysis sessions. Medicare reimbursement policy encourages frequent provider visits for patients on ESRD on hemodialysis. We believe that increasing the number of face-to-face provider visits improves the care and clinical outcomes of comorbidities related to ESRD (hypertension, hyperphosphatemia, and hyperkalemia). Methods: We used a Pre and Post-test pilot study design to evaluate the effect on laboratory measurements and blood pressure by increasing the frequency of Nephrologist face-to-face visits at the Miami VA Medical Center. Seventeen patients that were evaluated during a period of six months were included in the analysis. In the initial three months, the patients were evaluated four times per month (usual care). The number of face-to-face visits was increased to eight times per month (or twice weekly) for the following three months. Results: A paired-sample t-test was conducted to compare the mean systolic blood pressure measure before and after the intervention. Additional provider face-to-face visits per month were associated with a significant difference in the systolic blood pressure before and after the intervention (p = 0.004, t=3.303, Mean=8.235, and Standard Deviation=16). In addition, we found improvement of the phosphorus levels with a difference that was statistically significant (p = 0.028, t=2.419, Mean=5.512, and Standard Deviation=16). Patients reported increased perceived quality of care when they had the opportunity of seeing the Nephrologist more frequently.

Conclusions: Hypertension and electrolyte abnormalities are known risk factors that increase morbidity and mortality in patients with End Stage Renal Disease. Adherence to medications may improve in patients on Hemodialysis therapy. Increasing the number of visits per month with the Nephrologist during Hemodialysis sessions increases adherence to a renal diet, medication use and patient satisfaction.

FR-PO779

Response Rate of Hepatitis B Virus Vaccination in Various Stages of Chronic Kidney Disease
So Mi Kim, Eun kyong Lee, Yun Jung Oh. Div of Nephrology, Dept of Internal Medicine, Jeju National Univ Hospital, Jejudo, Republic of Korea; Dip of Nephrology, Dept of Internal Medicine, Dankook Univ Hospital, Cheonan, Chungnam, Republic of Korea; Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Jejudo, Republic of Korea.

Background: Although hepatitis B virus (HBV) vaccination is recommended for all dialysis patients, the response rate of HBV vaccination in dialysis patients is very low. Therefore, we tried to investigate the necessity of early HBV vaccination in pre-dialysis patients analyzing the response rate of vaccination in various stages of chronic kidney disease (CKD).

Methods: A total of 87 patients in 3 different stages of CKD was enrolled in this study. Patients in stage 3 (n=30) and 4 (n=28) were received the HBV vaccine as standardized schedule, consisting of 1 mL of the recombinant vaccine, Hepavax-gene TF at 0, 1, and 6 months. And then, the patients with stage 5 (n=29) were received the same vaccine for dosing doses at 0, 1, 2, 3, 4, 5, and 6 months. Three months after each of the last vaccination, serum level of Anti-HBs was measured in all patients.

Results: There was no significant difference in baseline characteristics including age, sex, presence of DM among the 3 groups. The overall seroconversion rate after vaccination was 79.4%. The seroconversion rate was significantly higher in patients with stage 3 than other patients (stage 3: 94%, stage 4: 79%, stage 5: 66%, p<0.01). Analyzing based on dialysis, seroconversion rate was also significantly higher in pre-dialysis patients than in dialysis patients (pre-dialysis group: 86%, dialysis group: 65%, p=0.02). There was no significant factor to contribute seroconversion in multivariate analysis.

Conclusions: Our study showed the high seroconversion rate after HBV vaccination in CKD patients with stage 3 and pre-dialysis. Therefore, the HBV vaccination should be considered in early CKD stages.

FR-PO780

Outbreaks of Hepatitis C Infection Infected Reported in U.S. Hemodialysis Facilities, 2008-2014

Background: Hepatitis C virus (HCV) infection is more prevalent among hemodialysis (HD) patients than the general population. HCV transmission in dialysis units may contribute, and is difficult to detect due to lack of symptoms and systematic screening. We summarized HCV outbreaks reported to CDC to characterize their frequency and factors contributing to transmission in HD facilities.

Methods: We defined a healthcare-associated outbreak as '2 new HCV infections (positive anti-HCV; E1 year after negative anti-HCV, or positive anti-HCV with acute hepatitis) in the same facility.' We reviewed outbreaks in 2008-2014 reported to CDC. For HD unit outbreaks, we summarized type of facility, number of new cases, number of patients notified for HCV testing, infection control lapses identified, and results of HCV molecular testing. Infection control transmission was confirmed if there was epidemiological and molecular evidence of transmission.

Results: During 2008–2014, 22 outbreaks of HCV infection in healthcare settings were reported to CDC; 11 (50%) of these outbreaks occurred in outpatient HD clinics. Seventy-nine (median 4, range 2–21) new HCV infections were identified. More than 1,800 HD patients were notified and screened for HCV in outbreaks facilities. Infractivity HCV transmission was confirmed in all 11 outbreaks. New cases had treatment time and location overlap with their HCV-infected source patient. For 9 outbreaks, lapses in infection control were identified, including environmental disinfection (8), hand hygiene (5), and injectable

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medication handling (3), separation of clean and contaminated workspaces (2), and vascular access care (1). Multiple lapses were identified in 7 outbreaks. No specific infection control lapses were identified at the time of the investigation in 2 outbreaks. 

Conclusions: Outpatient hemodialysis clinics remain a common setting for healthcare-related HCV outbreaks. Infection control lapses were frequently identified in reported outbreaks. Rigorous adherence to recommended infection control practices is needed to protect patients and prevent future outbreaks in this setting.

Funding: Other U.S. Government Support

FR-PO781
Influenza and Outcomes in ESRD Patients David T. Gilbertson,1 Anne C. Beaubrun,2 Kenneth J. Rothman,1 Jiannong Liu,1 Brian D. Bradbury,1 Akhtar Ashfaq,1 Charles A. Herzog,2 Allan J. Collins,1 Chronic Disease Research Group, MMRF;3 Ctr for Observational Rsrch, Amgen;4 RTI Health Solutions.

Background: Yearly influenza vaccination is recommended for all ESRD patients, due to a high risk of influenza-related complications. Through the CDC’s Outpatient Illness Surveillance, information on patient visits to health care providers for influenza-like illness (ILI) is collected. These data give estimates of the percent of all OP visits that are for presumed influenza, and give national information on timing and severity of each influenza season. We assessed the association between CDC ILI data and outcomes in ESRD patients.

Methods: We aggregated weekly ILI data from 2000-2012 to monthly, and calculated the monthly number of deaths and hospitalizations among US ESRD patients during the same time period. Using time series decomposition, we subtracted out seasonal and trend components from both series, and computed correlations between the ILI and mortality/hospitalization data.

Results:

The figure displays deaths and ILI data after removing seasonal and trend components. There were 2 influenza seasons (2003-2004 and 2009-2010) during this time period where the peak was at the end of the calendar year (early in the influenza season) instead of at the beginning of the next calendar year. Similar “early” peaks are seen in deaths among ESRD patients. There is also correlation between other peaks and valleys of the ILI data and ESRD deaths; correlation coefficient = 0.63. Correlations were also calculated with cause-specific hospitalizations: 0.69 for ILI-influenza/pneumonia; 0.42 for ILI-any infection; 0.16 for ILI-MI; and 0.02 for ILI-stroke.

Conclusions: The association between ILI and outcomes in ESRD patients is strong. While influenza vaccination rates among ESRD patients have improved over the last decade, the overall rate is still below 70%, suggesting room for further improvement.

Funding: Pharmaceutical Company Support - Amgen

FR-PO782
The Burden of Pneumonia in Patients Receiving Dialysis: Incidence, Case Fatality, and Costs to Medicare Scott Sibbel,1 Reiko Sato,2 Abigail Hunt,1 Wendy Tureume,1 Steven M. Brunelli,1 David V. Kshirsagar,1 Diane Reams, Magdalene M. Assimon, Anne Mobley Butler, Jennifer E. Flythe, M. Alan Brookhart. Univ of North Carolina at Chapel Hill.

Background: End-stage renal disease patients receiving dialysis are at particular risk for infection. We assessed the clinical and economic burden of pneumonia in a population of Medicare-enrolled ESRD patients with respect to incidence and case fatality rates, rates of all-cause hospitalization, and costs.

Methods: Patients included in the analysis received dialysis between 01 Jan 2009 and 31 Dec 2011, and were enrolled in Medicare Parts A and B. Pneumonia episodes were identified from institutional and supplier claims. Patients were considered at-risk from the first date of Medicare coverage and were censored from the analysis upon transplant, withdrawal from dialysis, recovery of renal function or death. Linear mixed effects models were used to assess hospitalization rates and costs over the 3 months prior to and 12 months following a pneumonia diagnosis.

Results: The pneumonia incidence rate for the study period was 21.4 events/100 patient-years with the majority of episodes (90.1%) requiring inpatient treatment. The 30-day case fatality rate was 10.7%; case fatality rates were higher for older patients and for pneumonia requiring inpatient treatment (11.2%). All-cause hospitalization rates were greater in the month of the pneumonia episode vs month -3 prior to diagnosis (IRR, 4.61; 95%CI: 4.46, 4.76) and remained higher than baseline over the 1-year follow-up period. Mean per patient per month costs were $10,976 (95% CI: $10,717, $11,275) higher in the month of the index episode compared to month -3, largely driven by increased inpatient costs, and remained elevated through end of follow-up.

Conclusions: Pneumonia episodes are frequent among ESRD patients and result in hospital admissions and greater overall costs to Medicare (~$20,000 incremental) over the following year.

Funding: Pharmaceutical Company Support - Pfizer Inc

FR-PO783
Opioid Use Associates with Infection Related Morbidity and Mortality in Hemodialysis Patients Abhijit V. Kshirsagar, Diane Reams, Magdalene M. Assimon, Anne Mobley Butler, Jennifer E. Flythe, M. Alan Brookhart. Univ of North Carolina at Chapel Hill.

Background: Opiates are frequently prescribed for pain in the US hemodialysis (HD) population but have intrinsic properties that increase risk of infection, a common cause of morbidity and mortality for patients. Data regarding the association of opioids with infection are lacking.

Methods: We conducted a retrospective cohort study using data from a large national dialysis provider linked with the United States Renal Data System and Medicare Part D (2006-2010). We used a new user design – comparing only new users of opioids to new users of prescription non-steroidal anti-inflammatory drugs (NSAIDS) to address confounding, as well as excluding patients with cancer, use of hospice services, or use of > 1 opiate. We assessed treatment effects on infection-related morbidity and mortality using inverse probability of treatment weighted Kaplan-Meier methods, adjusting for many comorbidity, lab, and clinical variables.

Results: 5,113 patients met entry requirements, of which 3,439 (67.3%) received an opioid. Relative to new NSAID users, new opioid users had similar baseline laboratory values, but were slightly younger, and had a higher prevalence of comorbidities, including recent infections (8.7% vs 6.8%), diabetes (52.3% vs 49.3%), and chronic obstructive pulmonary disease (COPD), 17% vs 12.2%. After multivariable adjustment, we observed an elevated risk of 90-day infection-related hospitalization, (Risk Difference (RD) 2.5/100 patient-years) for recent infections (8.7% vs 6.8%), diabetes (52.3% vs 49.3%), and chronic obstructive pulmonary disease (COPD), 17% vs 12.2%. After multivariable adjustment, we observed an elevated risk of 90-day infection-related hospitalization, (Risk Difference (RD) 2.5/100 patient-years) for recent infections (8.7% vs 6.8%), diabetes (52.3% vs 49.3%), and chronic obstructive pulmonary disease (COPD), 17% vs 12.2%.

Conclusions: We found that opioids were associated with increased risk of infection-related outcomes in the dialysis population.
Conclusions: Our results suggest that opioid initiation increases the short-term risk of infection-related morbidity and mortality among HD patients.

Funding: Clinical Revenue Support

FR-PO784

A Retrospective Review of the Two-Step Tuberculin Skin Test in Manitoba’s Dialysis Population

Rukhsana A. Foster,1,2 Thomas W. Ferguson,1 Claudio Rigatto,1 Navdeep Tangri,1 Blake R. Lerner,1 Reid Whitlock,3 Paul Komenda,3
Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; 3Medicine, Univ of Manitoba, Winnipeg, MB, Canada.

Background: Reactivation of latent Mycobacterium Tuberculosis (LTB) is a health concern in patients on dialysis due to their immunosuppressed state. The most frequently used test for LTBI screening in this population is the Tuberculin Skin Test (TST). The diagnostic accuracy (sensitivity and specificity) and clinical utility of the TST in a contemporary North American dialysis population is unknown.

Methods: We performed a retrospective cohort study of 483 hemodialysis and peritoneal dialysis patients across 4 dialysis units. All patients received a two-step TST and subsequent treatment if positive. We then linked the cohort with the Manitoba Health TB Registry to ascertain if treatment was received for LTBI.

Results: Of 483 patients, 406 were two-step TST positive (84%). Patients with a BCG vaccination were more likely to test positive (50 vs. 34%, p = 0.07). Using a diagnostic gold standard of an abnormal chest X-ray as a proxy for LTBI, the TST has limited diagnostic and clinical utility for LTBI screening in this population.

Conclusions: The TST is limited and diagnostic utility for LTBI screening in patients on dialysis. Further research into the diagnostic accuracy of interferon-gamma release assays, and a revision of TST screening guidelines in patients on dialysis should be considered.

FR-PO785

Reliability and Construct Validity of the Coping Strategy Inventory-Short Form in Hemodialysis (HD) Patients in 13 Countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Elodie Speyer,1 Hal Morgenstern,1 Yasuaki Hayashino,1 Peter G. Kerr,1 Hugh C. Rayner,1 Reid Whitlock,1
1Arbor Research Collaborative for Health; 2University of Michigan; 3Teurion Hospital; 4Monash Health & Monash Univ; 5Birmingham Heartlands Hospital.

Background: In international studies, questionnaires are often translated into several languages without consideration of cultural and linguistic differences that may compromise the reliability and validity of survey instruments, especially those measuring psychosocial factors. The Coping Strategies Inventory-Short Form (CSI-SF) is a 16-item questionnaire, developed in English, and previously validated in US cardiac failure patients. It is scored by calculating 4 scales (each with 4 items) to measure 4 different coping strategies. The aim was to assess and construct validity of the CSI-SF in HD patients across 13 countries.

Methods: The CSI-SF was self-administered to HD patients across 13 countries in 9 languages in DOPPS 4 (2009-11). Cronbach’s alpha was used to assess internal consistence. Exploratory and confirmatory factor analyses were used to assess the factor structure of the CSI-SF by country and language.

Results: 6,656 HD patients completed the CSI-SF and were included in this analysis (55% male; median age 63, range: 18-96 yrs). Using the English version in 4 countries and the Swedish version, we found good internal consistence (α=0.63-0.77) for 3 of the 4 scales; the 4th scale was internally consistent if two items were dropped. In these countries, both types of factor analyses indicated a factor structure perfectly consistent with these same 4 scales. In the 8 other non-English versions, results were very different: internal consistence was lower for the 4 scales; no country showed an exploratory factor structure similar to that found previously, nor was the 4-factor structure confirmed with factor analysis.

Conclusions: The CSI-SF is reliable for measuring coping in HD patients in English and other English versions, as tested in the DOPPS. The importance of coping for predicting outcomes in HD patients can now be described in these countries. More research is needed for measuring coping strategies in other countries and languages.

Funding: Pharmaceutical Company Support - Aorgen, Kyowa Hakko Kirin, AbbVie, Sanofi, Amgen, Baxter Healthcare, and Vifor Fresenius Medical Care R&D, Ltd; BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hexal AG, DGN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), DOPPS Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

FR-PO786

Associations Among Psychosocial/Medical Factors and Quality of Life in Hemodialysis Patients with End-Stage Renal Disease

Gumwoo Kang, Internal Medicine, Catholic Univ of Daegu School of Medicine, Daegu, Korea.

Background: Patients with end-stage renal disease (ESRD) have a significant impairment in quality of life (QoL). Most previous studies have focused on medical factors mainly. However, quality of life can also be affected by psychosocial problems in the circumstances of chronic illness. The aim of this study was to identify the associations among psychosocial factors, medical factors and QoL in hemodialysis (HD) patients.

Methods: The study included 101 patients with ESRD who were undergoing HD (mean age 57.1 ± 2.1 years). Psychosocial factors were evaluated using the Hospital Anxiety and Depression Scale (HADS), Multidimensional Scale of Perceived Social Support, Montreal Cognitive Assessment and Pittsburgh Sleep Quality Index. In addition, for evaluating caregivers’ burden in part of psychosocial factors, HADS and Zarit Burden Interview of main caregivers were administered. We also accessed medical factors (Kt/V and urea reduction ratio, etc.) with laboratory results (body mass index, albumin, hemoglobin, etc.). The QoL was evaluated using WHO Quality of Life-BREF (WHOQOL-BREF). Canonical correlation analysis was used to investigate the patterns of associations.

Results: The canonical correlation between psychosocial factor and QoL was 0.49. The first canonical correlation was 0.67 (p = 0.001) and the second was 0.519 (p = 0.006). However, the canonical correlation between medical factor and QoL was not significant (p = 0.586). The second canonical correlation was 0.713.

Conclusions: The QoL of patients with ESRD was not associated with medical factor, but psychosocial factor in canonical correlation analysis. This finding may suggest that medical workers should recognize and treat psychosocial problems as well as clinical problems. We also would like to emphasize the comprehensive approach with cooperation between psychiatrists and nephrologists for improvement of QoL in ESRD patients.

FR-PO787

Longitudinal Associations of Dietary Protein and Energy Intake with Protein-Energy Wasting Syndrome in Hemodialysis Patients

Chiara Regazzoni,1,2 Xin Tian,1,2 Xiaorui Chen,1,2 Xiaowei Sun,1,2 Dan Zhu,1,2 Tomir Gur,3 Yvonne de Zwaan,2,4
1University of Glasgow; 2Robert Gordon University, UK; 3University of Utah; 4VA SLC, VA Denver.

Background: The associations of baseline dietary protein intake (DIPI) (<0.6 g/kg/d) and low dietary energy intake (DEI) (<25 kcal/kg/day) are included in the definition of protein-energy wasting (PEW) syndrome. Therefore, we aimed to examine the longitudinal associations of baseline DIPI and DEI with PEW syndrome (defined by modified criteria that excludes dietary variables) at 1 year of follow-up in 1480 MHD pts in the HEMO Study.

Methods: DIPI and DEI were obtained by 24-h dietary recall. PEW syndrome at month 12 was defined as the presence of 2 out of the 3 criteria: serum chemistry (albumin by BCP method < 3.5 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 23 kg/m² or wt loss > 10% over 1 yr), and muscle mass (mid-arm muscle circumference 10% or more than the 50th percentile of reference population). PEW syndrome at month 12 was related to baseline DIPI and DEI in logistic regression models.

Results: 17.4% had PEW at month 12. The prevalence of PEW syndrome at month 12 by baseline DIPI and DEI quartiles are summarized in the figure.

The associations of baseline DIPI and DEI with PEW syndrome at month 12 in logistic regression models are summarized in table.
Associations of baseline DPI or DEI with the presence of PEW syndrome at month 12*  

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Model 1*</td>
<td></td>
</tr>
<tr>
<td>DPI=0.6 g/kg/d</td>
<td>0.39 (0.25, 0.62)</td>
</tr>
<tr>
<td>DEI=25 kcal/kg/day</td>
<td>0.29 (0.21, 0.39)</td>
</tr>
<tr>
<td>Model 2*</td>
<td></td>
</tr>
<tr>
<td>DPI=0.6 g/kg/d</td>
<td>0.40 (0.26, 0.63)</td>
</tr>
<tr>
<td>DEI=25 kcal/kg/day</td>
<td>0.30 (0.22, 0.41)</td>
</tr>
</tbody>
</table>

*Each cell represents a separate logistic regression model, 1 Adjusted for demographics, ESRD duration, Kt/V group, race group, smoking and alcohol use, 2Adjusted for above plus diabetes, CAD, CVD, PVD, CHF and arrhythmia.

Conclusions: The contrarian finding of lower risk of PEW in those with low DEI and DPI could reflect mathematical coupling (as both DEI and DPI include body wt in the denominator and those with PEW have lower body wt).

Funding: NIDDK Support

FR-PO788

PEW Syndrome, Inflammation and Mortality in Hemodialysis Patients  
Sri Sri Beddu, Xiaoxiu Chen, Wei, E. Boucher, Dominique Ferrari, Kalani L. Raphael, Tom Greene, Michel Chonchol.

Background: The term ‘malnutrition-inflammation complex syndrome’ implies that malnutrition and inflammation are tightly interlinked. Therefore, we examined whether the mortality associations of markers of inflammation and protein-energy wasting syndrome (PEW) are attenuated by each other in 906 maintenance hemodialysis (MHD) patients in the HEMO Study, a multi-center RCT that examined the effects of dialysis dose and dialyzer flux on mortality.

Methods: High sensitivity Creative Protein (hsCRP), tumor necrosis factor (TNF)-a and interleukin (IL)-6 were measured in the month 12 stored samples. Weight loss was estimated from baseline and month 12 post-dialysis weights and hence, PEW syndrome at month 12 was defined as the presence of 2 out of 3 criteria: serum chemistry (albumin by nephelometry < 3.5 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 23 kg/m^2 or wt loss > 10% from baseline), and muscle mass (mid-arm muscle circumference 10% or more than the 50th percentile of reference population). Cox models were used to relate month 12 PEW syndrome and hsCRP, TNF-a and IL-6 with subsequent mortality.

Results: Mean age was 57 ± 14 yrs, 45% were women. 67% were black. PEW syndrome was present in 17.4% at month 12. Median (IQR) serum hsCRP was 6.3 (2.6-16.4) mg/L, IL-6 3.3 (2.0-7.6) pg/ml, and TNF-a 31.2 (21.3-46.1) pg/ml. There were 388 deaths over 2189 years of follow-up. PEW syndrome had 2 fold higher risk of mortality which was only marginally attenuated by adjustment for markers of inflammation (table). CRP and IL-6 were associated with higher mortality risk independent of PEW. TNF-a was not associated with mortality.

<table>
<thead>
<tr>
<th></th>
<th>Model 1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEW syndrome</td>
<td>2.22 (1.78, 2.76)</td>
</tr>
<tr>
<td>Each doubling of CRP -</td>
<td>1.04 (1.00, 1.17)</td>
</tr>
<tr>
<td>Each doubling of TNF-a -</td>
<td>1.03 (0.90, 1.17)</td>
</tr>
<tr>
<td>Each doubling of IL-6 -</td>
<td>1.13 (1.00, 1.18)</td>
</tr>
</tbody>
</table>

Conclusions: PEW and inflammation are independent predictors of mortality. These results suggest PEW and inflammation might not be tightly interlinked.

Funding: NIDDK Support

FR-PO790

Association of Pre-Transplant Dialysis Modality and Post-Transplant Outcomes: A Meta-Analysis  
Emily Joachim, Ali I. Gardezi, Suddheer Mudugunti, Sana Waheed, Jung-Im Shin, Brad C. Astor, Micaiah R. Chau.

Background: Patients who undergo dialysis prior to renal transplant have overall worse outcomes than patients who receive a preemptive transplant. However, individual studies give conflicting results regarding whether post-transplant outcomes differ based on pre-transplant dialysis modality (peritoneal dialysis (PD) versus hemodialysis (HD)).

Methods: We searched English-language literature from January 1, 1980 through August 31, 2014, national conference proceedings and reference lists of all included studies. We used combinations of terms related to dialysis (hemodialysis, peritoneal dialysis, or renal replacement therapy), kidney transplant and outcomes. Studies were included if they measured post-transplant patient mortality for both pre-transplant HD and PD. Studies were excluded if they were not in English or if they included pediatric patients.

Results: A total of 15 studies reported five-year patient mortality. These included 166,531 patients on HD and 51,980 patients on PD pre-transplant. The pooled hazard ratio for five-year patient mortality after renal transplant was 0.91 (CI 0.85-0.97) in favor of pre-transplant PD over HD (p<0.006).

Conclusions: Distance is an important factor in patient decision-making when initiating PD, particularly for those living farther away from commonly offered HD services. Analyses of treatment selection must appropriately model distance to reflect logistics of treatment options and service availability to patients.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO790

Impacts of Geographic Distance on Peritoneal Dialysis (PD) Utilization: Refining Models of Treatment Selection  

Background: Proximity to dialysis services may ease patient travel burden. Different frequency of visits to dialysis facilities and resulting differences in travel distance may affect patients’ selection of hemodialysis (HD) versus PD. PD has historically been less commonly available in dialysis facilities and less commonly used than HD. We refine methods of prior research to reassess the relationship between patients’ distance to dialysis care and modality choice to better reflect the conditions of patients’ choice set of providers’ location (absolute distance) and available services (relative distance).

Methods: Retrospective cohort of 70,131 patients initiating dialysis and 4,795 dialysis facilities in 2006 using USRDS data. The primary outcome was patient PD use. Independent variables included absolute distance from patients’ home to nearest HD facility, relative distance dichotomized as the nearest PD facility closer or same distance as nearest HD facility, and their interaction. Logistic regression was used to model distance on PD use, controlling for patient and market factors.

Results: 9% of new dialysis patients used PD in 2006. There was a positive, non-linear relationship between absolute distance to closest HD services and PD use (p=0.006). In terms of relative distance, odds of PD increased if a PD facility was closer or the same distance as the nearest HD facility (p=0.006). The interaction of absolute and relative distance was not significant.

There was moderate heterogeneity among these studies (I^2=41.4%, p=0.05). Six studies included an adjusted risk ratio (RR); the pooled RR for these studies was 0.89 (CI 0.82-0.97) in favor of PD (p=0.006). There was significant heterogeneity among these six studies (I^2=72.7%, p=0.003).

Conclusions: Based on these results, pre-transplant peritoneal dialysis is associated with better post-transplant survival at five years compared to hemodialysis. Further work should explore potential reasons for this difference and compare additional outcomes such as graft survival, delayed graft function and rejection.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Impact of Poverty and Health Care Insurance on Pre-End Stage Renal Disease Care in Dialysis Patients

Robert Nee,1 Lawrence Agodoa,2 Kevin C. Abbott,1 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 1NIDDK, National Insts of Health, Bethesda, MD.

Background: Access to nephrology care prior to end-stage renal disease (ESRD) is significantly associated with lower rates of morbidity and mortality. We assessed the association of area and individual-level indicators of poverty and types of health care insurance on pre-ESRD care provided by nephrologists.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 739,537 patients initiated on maintenance dialysis from January 1, 2007 through December 31, 2012. We assessed the Medicare-Medicaid dual eligibility status as an indicator of individual-level poverty and ZIP code-level median household income (MHI) data obtained from the 2010 United States Census. We conducted multivariable logistic regression of pre-ESRD care as the outcome variable, as reported on the Centers for Medicare and Medicaid Services Form 2728.

Results: The proportions of dual-eligible and non-dual eligible patients who had pre-ESRD care were 53.06% and 61.82%, respectively (p<0.001). Dual-eligibility was associated with significantly lower likelihood of pre-ESRD care (adjusted odds ratio [aOR] 0.83, 95% confidence interval [CI] 0.82-0.84). Patients in the lowest area-level MHI quintile had an aOR 0.89 (95% CI 0.88-0.90) compared to those in higher quintile levels. Both African American (AA) and Hispanic patients were significantly less likely to have pre-ESRD care (aOR 0.85, 95% CI 0.84-0.86 and aOR 0.71, 95% CI 0.70-0.72, respectively). Interaction terms for dual eligibility and AA race and Hispanic ethnicity were significant (p<0.001 and p=0.002, respectively).

Conclusions: Individual and area level measures of poverty were independently associated with lower likelihood of pre-ESRD care. Efforts to improve pre-ESRD nephrology care may require focusing on the poor and minority groups. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, Department of the Navy, Department of Defense, or the United States government.]

Prevalence and Development of the Charlson Comorbidity Scoring System for Korean Incident Peritoneal Dialysis Patients

Hyunjoeon Cho,1 Myoung-Hee Kim,1 Seung Seok Han,1 Jae Yoon Park,1 Hyunjoo Ryu,1 Hye Jin Kim,1 Dong-Ryeol Ryu,1 Haejong Lee,1 Jung Pyo Lee,1 Chun Soo Lim,4 Kook-Hwan Oh,1 Kwon Wook Joo,1 Won Su Kim,1 Dong Ki Kim.1 Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; 2Dental Hygiene, College of Health Science, Eulji Univ, Gyeonggi-do, Korea; 3Internal Medicine and Ewha Medical Research Inst, School of Medicine, Ewha Womans Univ, Seoul, Korea; 4Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea.

Background: The Charlson Comorbidity Index (CCI) has widely used for predicting mortality and adjusting as a confounder in statistical analyses. However, the CCI remains disputed as an index to be applied to ESRD populations because the CCI was developed for general population. In this study, we modified the CCI and developed a modified Charlson comorbidity index in incident peritoneal dialysis patients (mCCI-IPD) to improve risk stratification for mortality.

Methods: The mCCI-IPD was developed based on 7,606 Koreans who received their first peritoneal dialysis treatment between 2005 and 2008. Data were obtained from the Korean Health Insurance dataset. The mCCI-IPD score was the sum of the weights which were assigned to individual comorbidities according to their relative prognostic significance determined by multivariate Cox proportional hazards model. The modified index was validated in an independent prospective cohort (n=664).

Results: The Cox proportional hazards model showed that the CCI comorbidities except ulcers, peripheral vascular disease, dementia and connective tissue disease significantly predicted mortality. Thus, the mCCI-IPD included 11 comorbidities with re-assigned severity weights. In the validation cohort, the CCI and the mCCI-IPD were correlated with mortality. However, the analyses using continuous net reclassification improvement revealed that the mCCI-IPD improved net mortality risk reclassification by 30.8% (95% CI, 7.6-54.1; P<0.009) relative to the CCI.

Conclusions: The mCCI-IPD performed the better risk stratification for mortality in incident peritoneal dialysis patients than the CCI. It suggests that the mCCI-IPD may be a preferred tool for clinical study of peritoneal dialysis patients.

Diabetes, Black Race, Female: Risk Factors for Hospitalization After Dialysis Start in a Nationwide Cohort Sample

LaTonya J. Hickson,1-2 Bjorg Thorsteinsdottir,3-4 Priya Ramar,1 Jordan K. Rosedahl,1 Cynthia S. Crowson,2 Robert C. Albright,1 Nana-Hawa Yayeh Jones,1 Rozalina G. McCoy,2 Suzanne M. Norby,1 Andrew D. Rule,1 Amy W. Williams,1 Nilay D. Shah,1 Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Mayo Clinic Kern Center for the Science of Health Care Delivery, Mayo Clinic; 3Primary Care IM, Mayo Clinic; 4Pediatrics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Young dialysis patients have a high frequency of hospitalizations and readmissions. Multiple factors likely contribute to this occurrence, but have not been fully elucidated.

Methods: Young, incident dialysis patients aged 20-44 years included in the US Renal Data System with first dialysis service in 2005-2011. Multivariable multinomial logistic regression models examined associations and interactions between baseline predictors and hospitalizations through claims in the first 3-15 months; all p-values <0.05.

Results: For 46,895 patients (mean age: 36; 58% male; 46% black, 48% white, 4% Asian, 2% other race, 41% with diabetes, 23% with Charlson score ≥4) mean hospitalization rate was 2.3 per year. Subgroups for low to high utilizers included: 0 (46%), >0-4 (25%), >4-10 (20%) and >10 (10%) per year. Compared to the 0 hospitalization group, the >10 group had more females (48% vs 39%), more blacks (51% vs 45%), fewer Asians (2% vs 5%), more diabetics (52% vs 34%), more with Charlson score ≥4 (41% vs 14%). Diabetes were more likely to be high utilizers (odds ratio [OR]: 1.98 (1.84, 2.14) adjusting for age (OR:1.30(1.23,1.37) per 10 year decrease; sex (OR:1.23 (1.15,1.32) females vs males), black race (OR:1.24(1.16,1.34) blacks vs whites). Charlson ≥4 were also more likely to be high utilizers (OR: 7.00(6.75, 7.84) vs Charlson score 0-1), with higher comorbid females having nearly twice the risk as highly comorbid males (OR: 12.62 x 6.23, interaction p<0.001) when compared to low comorbid males.

Conclusions: Hospitalizations are frequent among young incident dialysis patients, particularly among diabetics, blacks, females, and those with multiple comorbidities. Further investigation into socioeconomic factors and causes of hospitalizations is needed to clarify these findings for targeted interventions.

Does Race Affect the Cause of Mortality in End Stage Kidney Disease?


Background: Cardiovascular disease accounts for 50% of mortality in end-stage kidney disease (ESKD). Caucasians (C) are more likely to die from cardiovascular disease, infection and withdrawal compared to Afro-Caribbean’s (AC). Little is known about the causes of mortality for Indo-Asian (IA) patients; with the rise in diabetes mellitus (DM) it is inevitable that more patients from IA backgrounds will get ESKD. We aim to investigate whether there are any differences in causes of mortality based on race.

Methods: We performed a single center, prospective, observational study. Electronic case notes were used to extract data to include cause of death, age of initiation of RRT, age of death, dialysis vintage (DV), gender and presence of DM. Patients were excluded if RRT was less than 90 days, or if they were transplanted.

Results: In total 3431 patients commenced RRT during the study period, 802 patients died, 364 were C, 259 IA and 178 were AC. There were no significant differences between the groups for age at initiation, DV, and age of death. Significantly fewer IA died during the follow up period compared to C (p<0.0001) and AC (p<0.0001). More IA and AC were diabetic (p<0.0001). Cardiovascular deaths were more common in C and AC patients compared to those of IA race (p<0.0001). IA had higher sepsis related deaths when compared C or AC (p<0.0001).

Conclusions: Despite the increased prevalence in DM, IA patients do not have worse survival outcomes or cardiovascular deaths compared to C and AC. We believe that the elevated sepsis related mortality in IA patients is secondary to the higher prevalence of diabetes. This data enables stratifying management therapies dependent on race and may help in designing cardiovascular end points trials in racially diverse group of patients.

Funding: Other NIH Support - William Harvey Research Institute

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO795

Association of Dialysis Provider Assignment with Early Dialysis Mortality in U.S. Veterans: A Transition of Care in CKD Study

Eleni Strege, Melissa Soochoi, Connie Rhee, Vanessa A. Ravel, Joline L.T. Chen, Jenny Jing, Csaba P. Kovesdy, Kamary Kalantar-Zadeh, UC Irvine; UTHSC.

Background: Mortality is high during the first months after initiating kidney replacement therapy including in U.S. veterans. Only 10% of veterans receive dialysis therapy in a Veterans Administration (VA) based dialysis clinic and the majority of veterans are assigned to non-VA centers and dialysis chains.

Methods: We examined all-cause mortality during the 3, 6, 12 and 24 month period after transition in a cohort of 52,158 US veterans who transitioned to ESRD over 4 years (10/2007-9/2011) and the association of dialysis provider assignment. Baseline provider was determined by facility information and divided into 5 categories: DaVita(DV), Fresenius(NR), Other Chain(OC), Non-Chain(NC), and VA. Associations were examined in Cox proportional hazard models and adjusted for age, gender, race, ethnicity, initial vascular access and primary cause of ESRD.

Results: Upon dialysis transition, patients were 70+12 yrs old, 6% female, 25% African-American, 19% initially used AV fistula and 42% had diabetes as the cause of ESRD. At baseline, 24%, 28%, 13%, 21%, and 10% of veterans received treatment at DV, FR, OC, NC, and VA facilities, respectively. Over the first 3, 6, 12 and 24 mos after transition, 5489(11%), 9283(18%), 14339(27%) and 21697(42%) veterans died, respectively (Figure left). Compared to patients initiating treatment at the VA, all patients receiving treatment at other facilities had higher risk of mortality through all periods of follow-up, after adjusting for case mix covariates (Figure right).

Conclusions: Veterans transitioning to dialysis treatment in a VA based hospital dialysis center have the best survival over the first 2 years of follow up. Whether the better survival of VA dialysis care is from selection bias versus true superior care in the VA system warrants additional studies.

Funding: NIDDK Support

FR-PO796

Time-Varying Racial/Ethnic Differences in Mortality After Initiation of Dialysis in U.S. Dialysis Patients

Guofen Yan, Keith C. Norris, Alison J. Yu, Tom Greene, Jenny Z. Ma, Wei Yu, Alfred K. Cheung, Univ of Virginia; UCLA; Univ of Southern California; Univ of Utah.

Background: While survival advantage for African Americans (AAs) and Hispanics, compared to Whites, has been observed for decades, our understanding of the mechanism is still incomplete. Using national dialysis patients, we examined whether this survival advantage exists across the entire course of ESRD or just within a certain time interval after initiation of dialysis.

Methods: The study included 1,255,640 adult incident dialysis patients between 1995 and 2010 in the USRDS. We calculated age-specific hazard ratios (HRs) of death for AAs and Hispanics vs. Whites, adjusted for covariates, for every 6-month interval in the first 4 years of dialysis and for the period thereafter.

Results: For each age group above 40 years (Table), lower risk of death for AAs than Whites (HR<1) did not vary greatly across these time intervals. In contrast, in each age group under 40 years, the HR for AAs vs. Whites evolved over time, which was highest in the first year, declined in the second year, and reached stable over time. Hispanics exhibited lower mortality risks in all age groups that remained relatively constant over time (not shown).

Table. Adjusted HRs for AAs vs. Whites

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Months after Initiation of Dialysis</th>
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<tbody>
<tr>
<td>18-30</td>
<td>1.72</td>
</tr>
<tr>
<td>31-40</td>
<td>1.34</td>
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<tr>
<td>41-50</td>
<td>0.89</td>
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<tr>
<td>51-60</td>
<td>0.76</td>
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<tr>
<td>61-70</td>
<td>0.72</td>
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<tr>
<td>71-80</td>
<td>0.76</td>
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<tr>
<td>&gt;80</td>
<td>0.84</td>
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</tbody>
</table>

Note: most of these HRs were significant at p<0.05

Conclusions: AAs over 40 years old and Hispanics of all ages have uniformly lower risks of death than Whites across the course of ESRD. For younger AAs, conversely, their higher-mortality risk period is limited to the first two years of dialysis. Further studies to delineate the factors responsible for excessive mortality associated with racial subgroups will improve care for all dialysis patients.

Funding: NIDDK Support

FR-PO797

Real Threat of ESRD in China: A Ten-Year Experience from Nanjing 3 Million Insurance Covered Population

Yun-Chen Han, Ling Sun, Han-Ming Huang, Kun Ling Ma, Bei Wang, Bi-Cheng Liu, Zhongda Hospital, Southeast University; Nanjing, Jiangsu, China; Nanjing Municipal Human Resources and Social Security Bureau, Nanjing, Jiangsu, China; Southeast Univ School of Public Health, Nanjing, Jiangsu, China.

Background: In the past decade, Chinese government has made great efforts to provide an affordable and equitable access to renal replacement therapy (RRT) for most of ESRD patients. Here we analyzed the ten years registry data of 3 million Nanjing Urban Employee Basic Medical Insurance (UEBMI) covered population and firstly provided the epidemiological data about ESRD in this developing country.

Methods: Using the electric registry system of UEBMI, we included all subjects insured by UEBMI in Nanjing from 2005 to 2014, and identified subjects who developed ESRD in this cohort. The prevalence and incidence of ESRD was analyzed based on this unique data system.

Results: During the 10-year period, the incidence rate of ESRD in UEBMI cohort in Nanjing gradually declined from 289.3ppm in 2005 to 218.8ppm in 2014. However, the prevalence rate increased steadily from 891.7ppm in 2005 to 1228.6ppm in 2014. The annual mortality rate declined from 138 per 1000 patient-years in 2005 to 97.8 per 1000 patient-years in 2014. Long-term survival rate of ESRD fluctuated during the past decade, with 1-year survival rate ranging from 85.1% to 91.7%, 3-year survival rate from 69.9% to 78.3% and 5-year survival rate from 58% to 65.4%.

Conclusions: This study firstly provided an epidemiological data about ESRD based on the complete electric registry data system in large population in China. Due to the lack of a national complete registry data system, the real burden of ESRD in China is still unclear. Nanjing is one of the biggest cities in China. Our present study based on the ten years complete electric registry data system provided a convincing data about the real threat of ESRD in China. According to this study, we estimated that China will probably have over 1.5 million ESRD patients in the near future with the establishment of improved healthcare system. It is therefore utmost important for both medical communities and government to take active measures to control this coming disaster.

Funding: Government Support - Non-U.S.

FR-PO798

An Evaluation of Completeness of Monthly Clinical Data in CROWNWeb, a New Data Source for the United States Renal Data System

Valarie B. Ashby, Lingqun Liu, Xizhao Li, Tempie H. Shearon, Bruce M. Robinson, Douglas E. Schaubel, Yi Li, Rajiv Saras, Univ of Michigan, Ann Arbor; Mi; Arbor Research Collaborative for Health, Ann Arbor, Mi.

Background: CROWNWeb (CW) is a web-based system which collects administrative and clinical data from all Medicare-certified dialysis facilities in the US. It includes patient admission, tracking, and discharge information, CMS forms, and clinical data elements, and is not limited to Medicare patients. Monthly clinical data submission began in May 2012.

Methods: Monthly clinical data were only available to the USRDS through administrative claims for Medicare patients.

Results: The percentages of patients with CW data (any, high) are shown below. All measures had an increase in reporting from 2013 to 2014. High-level reporting in 2014 ranged from 75% (Hemodialysis (HD) Kt/V) to 90% (vascular access type). For all measures, reporting was higher for HD than PD patients, for adults than children, and for peritoneal dialysis (versus without) diabetes as cause of ESRD. 72% of HD patients had high-level reporting for all 5 HD measures. 70% of PD patients had high-level reporting for all 5 PD measures.

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

Underline represents only recommends presenting author.

547A
Conclusions: CW is now an integral part of the USRDS. Our study suggests a generally high and increasing proportion of completeness of clinical components in CW. These data will enhance the value of the USRDS database for researchers in coming years.

Funding: NIDDK Support

FR-PO799

Facility Size and Impact of Extreme Measure Values on DFC Star Ratings

Christopher J. Harvey,1 Claudia Dahlerus,1 Zezhi (zac) Zhang,1 Joseph M. Messana,1 Ji Zhu,1 Cindy Liao,1 Natalie Scholz,1 K. A. Wisniewski,1 Richard Hirth,1 Elena K. Balovenkov,2 Joel S. Andrassy,3 Yi Li.1 Biostatistics, Kidney Epidemiology and Cost Center, Univ of Michigan, Ann Arbor, MI;2 Centers for Medicare and Medicaid Services.

Background: In 2015 CMS implemented star ratings for dialysis facilities to make it easier for consumers to compare dialysis facilities by providing a summary of each facility’s performance on a set of 9 DFC quality measures. Our study compares two scoring approaches to the star rating to assess the impact of each on controlling outlying measure values with regard to facility size.

Methods: Fixed percentiles are applied to assign 10% of facilities 1-star or 5-stars based on performance. 2013 data were extracted from the 2015 January DFC file. Probit ranking and z-score transformation were applied to the DFC measures to develop an overall score and final star rating. We compared the final distribution of star ratings for each approach and assessed impact on smaller facilities. We represent the rating by number of patients in each facility contributing to the hospitalization measure, and split ~6000 facilities into groups of ~100 and calculated percentage of each star rating in each group.

Results: Use of original measure values and z-scores allowed skewed measures to highly influence the ratings, but preserved original measure distributions. Probit ranking resulted in giving more 5-star ratings to smaller facilities and z-scored approach resulted in assigning more 1-star and 5-star ratings to smaller facilities (Figure 1).

Figure 1: Distribution of Star Ratings by Facility Size

FR-PO800

P11 as Marker and Vitamin D as Treatment Option in Depression in Maintenance Dialysis Patients


Background: Depression is a disabling condition impairing all aspects of human functions. The serotonin system has been implicated in the pathophysiology of depression. Recently, as a member of the S100 family of proteins, P11 is known to have relation to functions. The serotonin system has been implicated in the pathophysiology of depression.

Methods: As a single center cross-sectional study, we examined the peripheral blood mononuclear cells P11 mRNA, IL-6, TNF-α, 25-hydroxycholecalciferol (25-(OH)D3) of patients with hemodialysis (HD, N=27), peritoneal dialysis (PD, N=39) and healthy group (N=7). Groups were divided by presence of depressive mood and categorized by severity of depressed mood via Beck Depression Inventory (BDI).

Results: In non-depressive group (BDI<10), the mean means of P11 were high in HD group (5.51 ± 7.0 (HD, N=15) vs. 1.39 ± 0.33 (PD, N=11) and 2.29 ± 0.37 (control, N=7), p < 0.05). The mean IL-6 levels were low in control group (4.31 ± 1.34 pg/mL (HD) and 7.53 ± 1.39 pg/mL (PD) vs. 2.23 ± 0.49 pg/mL (control), p < 0.05). The mean TNF-α levels were low in control group (4.31 ± 0.26 pg/mL (HD) and 4.15 ± 0.25 pg/mL (PD) vs. 1.85 ± 0.53 pg/mL (control), p < 0.05) respectively. In depressive group (BDI>10), P11 levels showed relationships with depression severity in peritoneal dialysis group ( spearman rho=0.2, p <0.09).

In hemodialysis group, 25-(OH)D3 level was lower in depressive group (11.98 ± 3.8 vs. 7.5 ± 2.7, p < 0.05), but there was no difference in peritoneal dialysis group (6.3 ± 3.3 vs. 7.4 ± 7.1, p =0.55).

Conclusions: By diagnostic tool, P11 can be used in peritoneal dialysis group as a depression marker despite taking the effect of inflammation into consideration, but not in hemodialysis group. As other treatment option, 25-(OH)D3 can be used in hemodialysis group for depression management, but not in peritoneal dialysis group.
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<table>
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<td>Hb</td>
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<td>10.7</td>
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<td>Average anticoagulation dose</td>
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% change t0: t3
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FR-PO803
Anti-Platelet Factor 4 Antibodies: A One HIT Wonder
Suzanne H. Forbes, Sean Platton, Michael K. Almond, Neil Ashman, Laura Green, Nephrology, Royal London Hospital; Haematology, Royal London Hospital; Nephrology, Southend Hospital.

Background: Hemodialysis (HD) patients are exposed to regular anticoagulation, usually unfractionated heparin (UFH) or low-molecular weight heparin (LMWH). For standard HD (4 hrs, 3 days/week) this equates 26 full days exposure/y. Recently there was interest in the presence of heparin induced thrombocytopenia (HIT) in HD, and the causative anti-platelet factor 4 (PF4) antibody. There are several publications suggesting the presence of the antibody, without the clinical syndrome of HIT, is present in up to 25% HD patients, and may be an independent risk factor for cardiovascular and vascular access morbidity.

Methods: We looked for HIT antibodies in 2 prevalent HD cohorts, one with UFH, one LMWH (i.e. line lock sodium citrate). We tested serum for anti-PF4 antibodies using several established tests; STic Expert® (IgG-specific exclusion test), Diamed (particle gel immuno-assay), polyclonal IgG/A/M ELISA, IgG-specific ELISA.

Results: We included 127 patients: 60 receiving tinzaparin, 61 receiving UFH and 6 heparin-free. Serum samples were taken at the start of a standard HD session. The average duration on dialysis was 3.4 years. Results of the various tests are shown.

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>LMWH</th>
<th>Heparin-free</th>
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<tbody>
<tr>
<td>Platelet Count</td>
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<tr>
<td>STic Expert</td>
<td>positive - 52% negative - 48%</td>
<td>positive - 40% negative - 60%</td>
<td>positive - 0% negative - 100%</td>
</tr>
<tr>
<td>Diamed</td>
<td>positive - 1% negative - 99%</td>
<td>positive - 1% negative - 99%</td>
<td>negative - 0% positive - 100%</td>
</tr>
<tr>
<td>Poly-specific ELISA</td>
<td>median OD - 0.2 (positive - 0.4)</td>
<td>median OD - 0.15 (positive - 0.4)</td>
<td>median OD - 0.09 (positive - 0.4)</td>
</tr>
<tr>
<td>IgG specific ELISA</td>
<td>median OD - 0.13 (positive - 0.4)</td>
<td>median OD - 0.07 (positive - 0.4)</td>
<td>median OD - 0.05 (positive - 0.4)</td>
</tr>
</tbody>
</table>

Only 1 patient tested antibody positive (OD 0.5) in the LMWH group. Platelet count and reactivity (as measured by TEG) in the UFH and LMWH group did not differ but the STic Expert positive/negative groups, the UFH LMWH groups, or those with higher or lower tertiles of ELISA OD.

Conclusions: Despite the previously reported concern over the presence of HIT antibodies in HD patients, we comprehensively show here no evidence of antibody positivity in HD patients. Exclusion tests such as STic Expert are not useful in these patients.

FR-PO804
Upper Gastrointestinal Bleeding Among Dialysis Patients in an Endemic Area for Chronic Liver Disease: Taiwan National Cohort Study
Chih-Chiang Chien, Chien-Ya Hung, Chih Hwa Univ of Medical Technology, Tainan, Taiwan; Chi Mei Medical Center, Tainan, Taiwan.

Background: End-stage renal disease (ESRD) and chronic liver disease (CLD) both increase the risk for upper gastrointestinal (UGI) bleeding. The prevalence of ESRD and CLD are high in Taiwan. The aim of this study was to evaluate the incidence, risk factors, and categories of UGI bleeding in ESRD dialysis patients.

Methods: Using Taiwan’s National Health Insurance research database, we enrolled 42,457 incident ESRD dialysis patients who began dialysis between 1999 and 2004. The patients were followed until death, dialysis cessation, or 31 December 2008. Cumulative incidence of UGI bleeding after initiation of dialysis was calculated using Kaplan-Meier methods. Predictors for UGI bleeding were determined using Cox models.

Results: During the follow-up period, 5,528 patients had a UGI bleeding. Male, elderly, receiving hemodialysis (HD) and patient with comorbidities had a higher rate of UGI bleeding. The 1-, 3-, 5- and 7-year cumulative incidence rate of UGI bleeding were 9.8%, 21%, 25.3% and 28% in patients with liver cirrhosis (LC) on HD, 5.8%, 16.2%, 22.2% and 24.4% in patients with LC on PD, 3.7%, 9.2%, 13.2% and 16.4% in patients without LC on HD, and 2.1%, 5.5%, 8.2% and 10.4% in patients without LC on PD (log-rank: p < 0.001). After multivariate adjustment, prior gastrointestinal bleeding (HR 1.731, 95% CI, 1.651-1.834), LC (1.682, 95% CI, 1.524-1.856), alcoholism liver disease (1.536, 95% CI, 1.635-1.834), and receiving HD (1.316, 95% CI, 1.153-1.502) were independently risks for UGI bleeding in ESRD dialysis patient. Gastric ulcers were found to be the most common source of bleeding (50.3%), while bleeding resulting from a gastroduodenal ulcer was least frequent.

Conclusions: ESRD dialysis patients had a higher risk for UGI bleeding, especially those with prior gastrointestinal bleeding, LC, and alcoholism liver disease. In addition, receiving HD is a strong predictor for UGI bleeding. More attention should be paid to select dialysis modality, especially in high risk patients.

FR-PO805
Palmitoylethanolamide Is a Promising Potential Therapeutic Target for Increasing High Density Lipoprotein Cholesterol Levels
Hamid Moradi, Miki Igarashi, Melissa Soooho, Elani Streja, Hamid M. Said, Moti L. Kashyap, Daniele Piomelli, Kamyar Kalantar-Zadeh, UC Irvine; VA Long Beach.

Background: End stage renal disease (ESRD) is associated with significant increased risk of cardiovascular (CV) mortality. High density lipoprotein (HDL) deficiency and dysfunction is a major contributor to CV disease in ESRD. Strategies aimed at improving HDL level and function are crucial in improving CV outcomes. Palmitoylethanolamide (PEA) is an anti-inflammatory lipid derived mediator that activates PPARalpha nuclear transcription factor. We hypothesized that serum PEA will correlate with HDL and PEA can increase HDL via activation of apoA1/Apo(Al-Apo) expression.

Methods: Serum PEA concentration was determined in 50 patients on maintenance hemodialysis (MHD) using LC/MS technology and correlated with clinical laboratory indices including a lipid panel. Liver cells (Hepatoma cell line HepG2) were exposed to various concentrations of PEA in vitro for 24 hours and subsequently mRNA expression of ApoA1, the major protein component of HDL, was measured using real-time PCR.

Results: Serum PEA concentrations strongly correlated with serum HDL levels in MHD patients (r=0.57, p <0.0001). PEA also correlates with total cholesterol (r=0.36, p<0.009) however not with LDL or triglycerides. In the in-vitro studies, PEA at a concentration of 60 micromolar and 120 micromolar was increased ApoA1 expression significantly in HepG2 cells after 24 hours.

Conclusions: For the first time we report that serum PEA concentrations strongly correlate with serum HDL concentrations in MHD patients. Involvement of PEA in HDL production is confirmed in in-vitro studies where incubation of liver cell in PEA resulted in increased ApoA1 expression. These novel findings indicate that PEA may be a promising therapeutic target in HDL deficiency treatment associated with not just ESRD but any proatherosclerotic condition.

Funding: NIDDK Support

FR-PO806
Arachidonoylglycerol, a Major Activator of the Endocannabinoid System, Is Significantly Increased in Patients with Kidney Disease
Hamid Moradi, Miki Igarashi, Melissa Soooho, Elani Streja, Connie Rhee, Hamid M. Said, Moti L. Kashyap, Norstatola D. Vaziri, Daniele Piomelli, Kamyar Kalantar-Zadeh, UC Irvine; VA Long Beach.

Background: Chronic kidney disease (CKD) is associated with oxidative stress and inflammation. There is evidence that cannabinoid 1 receptor activation leads to increased oxidative stress and inflammation. We previously showed that 2-arachidonoylglycerol (2-AG), one of the main activators of the endocannabinoid system, is significantly increased in the kidney of animals with ischemia-reperfusion (IR) injury. We hypothesized that serum 2-AG levels will be significantly elevated in CKD patients.

Methods: Serum concentrations of AG were determined in 21 healthy controls, 50 randomly assigned age and gender matched patients on maintenance hemodialysis (MHD), 13 patients on peritoneal dialysis (PD) and 6 patients with CKD stage IV using LC/MS technology. In MHD patients, serum levels of AG were correlated with various laboratory indices.

Results: Serum levels of 1-AG and 2-AG were significantly and incrementally increased with 2-AG compared to healthy controls. MHD patients had the highest AG levels which positively and significantly correlated with number of treatments per week (r=0.47, p=0.008), AST/ALT (r=0.5, p=0.001), platelet count (r=0.40, p=0.010), ferritin (r=0.36, p=0.016) and negatively with HDL cholesterol (r=-0.43, p=0.04).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: For the first time we report that serum AG concentrations are significantly increased in CKD patients. These novel findings are in line with our report on IR acute kidney injury and with a recent study which showed that in an oxidative stress setting, monoacylglycerol lipase, an enzyme responsible for AG breakdown is inhibited leading to increased levels. Moreover, the substantial increase in MHD patients is intriguing given association of MHD with increased oxidative stress, inflammation and platelet activation.

Funding: NIDDK Support

FR-PO807
Newly Launched Cellulose Tri-Acetate Membrane with Asymmetric Structure Dramatically Improves Peripheral Circulation and Hemodynamic Stability During Hemodialysis
Ikuto Masakane, Tabuki Hospital, Nephrology, Yamagata, Japan.

Background: The most important concern about the biocompatibility of dialysis membrane is the activation of platelets and it would lead hemodynamic instability during dialysis session. The newly launched CTA with asymmetric thick structure (ATA) was produced in order to reduce stimulant property to platelets and the rapid reduction of the serum levels of small urmic solutes by thickening the membrane. We evaluated the solute removal performance and biocompatibility of ATA.

Methods: Seven chronic hemodialysis patients were enrolled to the current study. The conventional CTA was used for the first 4 months and ATA was used for the next 4 months. We evaluated the solute removal property by the clearance of urea, beta2 microglobulin (B2MG) and removed amount of alpha1 microglobulin (a1mG) and albumin loss in spent dialysate. The biocompatibility was evaluated by changes in WBC and platelet count, IL-6, Pentorexine-3 (PTX-3) and high sensitive CRP (hsCRP). The peripheral circulation was estimated by the Skin Perfusion Pressure (SPP) by PAD-3000® (Kaneka Medix, Osaka, Japan). Intra-dialytic hemodynamic stability was evaluated by arterial blood pressure and subjective feelings of the patients.

Results: The clearance of Urea was significantly reduced through dialysis session in both groups but the B2MG clearance was maintained only in ATA. The total removed amount of A1mG was significantly higher in ATA than CTA. The platelet count didn’t change in ATA during dialysis session but significantly decreased in CTA. WBC counts, IL-6, PTX-3, hs CRP in both groups didn’t change. The systolic blood pressure and frequency of intra-dialytic hypotension were not different in both groups whereas some of the patients felt post-dialytic fatigue improved in ATA. SPP was maintained during dialysis session in ATA but deteriorated in CTA.

Conclusions: The new ATA membrane could reduce the activation of platelets and maintain the peripheral circulation during a dialysis sessions and the time-dependent deterioration of solute removal. The new ATA membrane may improve the QOL and prognosis of chronic dialysis patients.

FR-PO808
Mathematical Modeling of Fluid Transport in Peritoneal Cavity
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Background: The current standard method (peritoneal equilibration test (PET)) is used to obtain transport characteristics of the peritoneal membrane for creatinine, urea and electrolytes, but not for fluid volume. Consequently, ultrafiltration profiles are difficult to obtain because the weight difference between the inlet and outlet dialysate show only net removal during PD. The aim of this study was to investigate whether the rate of change in fluid (Vf) in peritoneal cavity and body tissue fluid volume (Vb) can be simulated with a two compartment model.

Methods: Segmental bioposmance was continuously monitored in ten PD patients to provide Vf during standard PET in the clinical unit (Zhu, et al. Am J Kidney Dis, 2003). Vf was measured with whole body bioposmance technique (Hydra 4200). A two compartment model of Vf and Vb (Fig. 1(a)) was established (Eq.1-Eq.4). Two transport coefficients: k1 and k2 represent the rate of fluid shift from Vf to Vb by reabsorption and from Vb to Vf , driven by the glucose gradient. k1 and k2 were estimated by best fitting with the actual measurements based on the Marquardt-Levenberg algorithm.

Results: Parameter estimation was successful (residuals=0.01) in all but one patient, who experienced technical problems during the measurements. Fig. 1 (b) shows change in Vf and Vb, during standard PET simulation in a patient. K2 correlated inversely with the initial tissue fluid volume Vb (k2=-0.0002* Vb +0.0024, R2=0.46, p<0.05).

Conclusions: This model describes dynamics of fluid transport during PD treatment. K1 and k2 reflect the characteristics of peritoneal membrane in individual patient. The relationship of K2 and Vb suggests that fluid status could be a factor in ultrafiltration,which could be helpful in clinical practice.

Funding: Private Foundation Support

FR-PO809
Linagliptin Ameliorated Methyglyoxal-Induced Peritoneal Fibrosis in Mice
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Background: Recent studies have reported that methyglyoxal (MGO) was increased in peritoneal dialysis patients, playing an important role in the development of peritoneal fibrosis. On the other hand, linagliptin, a dipeptidyl peptiase-4 (DPP-4) inhibitor, exhibits beneficial effects in diabetes patients independent of blood glucose concentration. In this study, we examined whether linagliptin suppressed MGO-induced peritoneal fibrosis in mice.

Methods: Male C57BL/6 mice were divided into three groups: a vehicle group, an MGO injection group, or an MGO injection plus linagliptin group (n=6 per group). Peritoneal fibrosis was induced by a daily intraperitoneal injection of saline containing 40 mmol/L MGO for 21 days. Saline was given in the vehicle group. Linagliptin was administered at a dose of 10 mg/kg by oral gavage once a day.

Results: Immunohistochemical staining revealed that linagliptin suppressed the expression of α-smooth muscle actin and fibroblast-specific protein-1, the deposition of collagen 1 and collagen 3 and infiltration of macrophages (F4/80). In addition, linagliptin reduced TGF-β1 concentration in peritoneal fluid of MGO-treated mice. Peritoneal equilibration tests showed improvement of peritoneal function in mice receiving linagliptin treatment.

Conclusions: These results suggest that oral administration of linagliptin ameliorated MGO-induced peritoneal fibrosis.

Funding: Private Foundation Support

FR-PO810
Addition of Alanyl-Glutamine to Dialysis Fluid Restores Peritoneal Cellular Stress Responses – A Randomized Controlled First-in-Man Trial
Andreas Vychytil,1 Klaus Kratochwill,2,1 Michael Boehm,2 Rebecca Herzog,2 Katharina Gruber,1 Anton Lichtenauer,2 Lilian Kuster,3 Dagmar Csacsiuch,1 Andreas Gleiss,1 Martin Bilban,3 Seth L. Alper,1 Christoph Aufricht.1 1Medical Univ of Vienna, Vienna, Austria; 2Zytoprotec GmbH, Vienna, Austria; 3Beth Israel Deaconess Med. Cit, Harvard Medical School, MA.

Background: Peritoneal dialysis (PD) fluid cytotoxicity and intermittent bacterial infection contribute to membrane failure and peritonitis in PD patients. Recent meta-analyses revealed no significant influence of newer biocompatible PD fluids on peritonitis rate or peritoneal membrane function, but glutamine addition to standard PD fluids has shown cytoprotective effects both in vitro and in vivo.

Methods: In this open-label randomized controlled cross-over phase I/II trial (NCT01353638), 20 stable PD patients each underwent two 4 h peritoneal equilibration tests with glucose-based PD fluids supplemented with or lacking 8 mM alananyl-glutamine ( Ala(αGl)n), and separated by a 4 week washout phase. Effects of AlaGln on peritoneal inflammation and stimulated cytokine release were also tested in a mouse model of PD-associated peritonitis.

Results: Intraperitoneal (IP) exposure to Ala(αGl)n-supplemented PD fluid increased dialysate [glutamine] more rapidly (at 2 h mean 0.55-0.71 mM, p<0.05) and increased heat shock protein expression in peritoneal effluent cells (median 2.12-3.20, p<0.05), but did not alter peritoneal ultrafiltration, small solute transport, cell counts, or biomarkers. AlaGln increased ex vivo LPS-stimulated TNF-α release (effect C1 60-100 pg/mL, p<0.001) and, in patients with previous peritonitis, decreased dialysate [IL-8] (effect C1 0.1-4.3, p<0.05).

IP A/G also reduced inflammation and enhanced cytokine release in the mouse model. No adverse effects of AlaGln were noted.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

550A
Conclusions: Ala-Gln addition to standard PDF acutely attenuated PD-related parietal thickening in humans and in mice. These data encourage our ongoing phase II testing IP Ala-Gln supplementation as a routine therapeutic intervention in clinical PD.

**Funding:** Pharmaceutical Company Support - Zyprotec GmbH

**FR-PO811**

Dipeptide Alanyl-Glutamine Protects from Peritoneal Fibrosis and Attenuates IL-17 Dependent Pathways During Peritoneal Dialysis

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Georgios Liappas,
Marc Vila cuenca,
Robert H.j. Beelen,
Manuel Lopez-Cabrera.

**Background:** Peritoneal dialysis (PD) is complicated by chronic inflammation and progressive parietal membrane damage. Alanyl-Glutamine (Ala-Gln), a stable dipeptide commonly used in parenteral nutrition, has immunomodulatory effects and improved resistance of mesothelial cells to PD fluids. Recently, IL-17 was identified as novel player in PD induced peritoneal damage. In this study we investigated if intraperitoneal Ala-Gln administration confers protection against peritoneal damage by modulating IL-17 expression in uremic rodent PD models.

**Methods:** Uremic Peritoneal Dialysis Rat Model

**Results:** Supplementation of PD fluid with Ala-Gln resulted in reduced peritoneal thickness (70.90 ± 13.45 vs 16.23 ± 0.70, P < 0.001), ASMA expression and angiogenesis. Addition of Ala-Gln also showed attenuation of PD induced IL-17 mediated pathways, reflected by substantial reduction normalisation of peritoneal levels of IL-17 (32.35 ± 13.32 vs 7.99 ± 1.59, P < 0.001), TGfβ, IL-6 and ROR(γ). Moreover, repeated exposure of the Ala-Gln treated group to recombined IL-17 increased peritoneal fibrosis which was however restored upon IL-17 neutralization.

**Conclusions:** These results suggest that intraperitoneal administration of Ala-Gln ameliorates PD induced peritoneal damage at least in part by modulating IL-17 expression. Therefore, this evidence paves into investigations whether Ala-Gln could be a potential strategy to ameliorate peritoneal deterioration during PD.

**Funding:**

**FR-PO813**

MicroRNA Expression Profiling in Peritoneal Fibrosis

Yoshiyuki Morishita,
Daisuke Nagata.

**Background:** Peritoneal fibrosis (PF) is an intractable complication leading to peritoneal membrane failure in peritoneal dialysis (PD). The aim of this study was to identify the microRNAs (miRNAs) involved in PF.

**Methods:** miRNA screen was performed using microarray analysis in peritoneal tissue of PF patients. miRNA expression was induced by intraperitoneally injection of PD fluid containing methylglyoxal (MGO). The expression level of identified miRNAs of serum and drained dialysate were evaluated using qRT-PCR.

**Results:** The initial profiling study identified 6 miRNAs (miRNA-21-5p, miRNA-221-3p, miRNA-223-3p, miRNA-142-3p, miRNA-327 and miRNA-34a-5p) increased more than two fold and no miRNA decreased less than half in peritoneum tissue of PF patients compared with control rats. Among them, serum level of miRNA-21-5p (D/P Cr –r=0.44, p<0.01; D/D0 glucose –r=0.43, p<0.01), miRNA-327 (D/P Cr –r=0.48, p<0.01; D/D0 glucose –r=0.50, p<0.01) and miRNA-221-3p (D/P Cr –r=0.50, p<0.01; D/D0 glucose –r=0.50, p<0.01) and drained dialysate level of miRNA-221-3p (D/P Cr –r=0.52, p<0.01; D/D0 glucose –r=0.46, p<0.01) and miRNA-34a-5p (D/P Cr –r=0.44, p<0.01; D/D0 glucose –r=0.48, p<0.01) were significantly correlated with peritoneal membrane functions in PD patients. Anti-miRNA-21-LNA significantly inhibited miRNA-21-5p expression in peritoneum of PF mice. It also inhibited peritoneal fibrosis thickening and maintained better peritoneal membrane functions. It significantly increased PPAR-α expression in peritoneum of PF mice.

**Conclusions:** The results of present study suggested several miRNAs involved in PF, and they may be used as the novel diagnosis biomarkers and therapeutic targets for PF.

**Funding:** Government Support - Non-U.S.

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**FR-PO814**

Nanoparticles of Lipids Associated with Paclitaxel as an Alternative Strategy to Block Peritoneal Fibrosis

Filipe M. Silva,
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Elerson Costalonga,
Irene L. Noronha.

**Background:** PF is a progressive peritoneal membrane damage and is the main limitation for the long term use of PD. 3-4% of PD patients develop PF, which is a major complication leading to hospitalization, increased costs, and loss of mediated peritoneal dialysis (PD) treatment. Advances in nanotechnology enabled drug release systems that can provide the release of an active drug in the target tissue. Nanoparticles similar to LDL were developed, linked to Paclitaxel (NanoPACL), an antiproliferative drug. NanoPACL have the ability to bind to LDL receptors present on the cell surface, particularly in immune-inflammatory sites. The aim of this study was to analyze the effect of NanoPACL administration in an experimental model of PF.

**Methods:** PF was induced in Wistar rats by daily IP injections of chlorhexidine gluconate (CG) at 0.1% during 15 days. Animals (n=20) were divided into 4 groups: Control, NanoPACL, Paclitaxel and NanoPACL+Paclitaxel. Nanoparticles without Paclitaxel, via IP; NanoPACL, PF rats treated with NanoPACL (4mg/kg every 3 days, via IP). Euthanasia was performed on day 30. Peritoneal thickness and function, immunohistochemistry and qPCR were analyzed.

**Results:** NanoPACL significantly reduced peritoneal thickness, α-SMA expression and cell proliferation compared with control groups. Treatment with NanoPACL decreased TGF-β and Smad 3 mRNA expression and preserved peritoneal membrane function characterized by preservation of UF and reduced mass transfer of glucose (MTG).

**Funding:** Government Support - Non-U.S.
Vitamin D Receptor Activator (VDRA) Attenuates Epithelial-to-Mesenchymal Transition (EMT) via Modulation of NADPH Oxidase (NOX) Activity and Mitochondrial Dysfunction in Human Peritoneal Mesothelial Cells (HPMC)  

Duk-Hee Kang, Juyeon Ko, Eun sun Ryu, Hyun-yon Jung, Shina Lee, Dong-Ryeol Ryu, Seung-Jung Kim, Kyu Bok Choi. Dept of Internal Medicine, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea.

Background: EMT is known as a key mechanism of peritoneal fibrosis in peritoneal dialysis. Oxidative stress induced by NOX and mitochondrial dysfunction is one of the mechanisms responsible for EMT. Paricalcitol, a selective VDRA, is known to exert anti-fibrotic effect organ fibrosis, however there are no studies about the role of paricalcitol on peritoneal fibrosis. We investigated whether paricalcitol imposed any effect on TGFβ1-induced EMT of HPMC with an exploration of mechanism of anti-fibrotic effect of paricalcitol in terms of modulation of oxidative stress.

Methods: EMT was evaluated by morphological changes of HPMCs and the expressions of E-cadherin and α-smooth muscle actin. Intracellular ROS was analyzed by measuring NOX activity, NOX mRNA expressions with DCF-DA and MitoSox stained. Activation of Erk1/2, p38 MAPK, nuclear translocation of β-catenin and snail expression were assessed by western blotting and immunocytochemistry. Effect of paricalcitol on ROS generation and EMT was analyzed in HPMC exposed to TGFβ1.

Results: TGFβ1 (1mg/ml) induced EMT of HPMCs with an increase in ROS generation and NOX activity from 30 minutes, and mitochondrial ROS production from 6 hours. TGFβ1 also increased the phosphorylation of Erk and p38 MAPK from 1 hour, which was followed by nuclear translocation of β-catenin and snail up-regulation in HPMC. Paricalcitol (50nM) ameliorated TGFβ1-induced EMT in HPMC, which was associated with a decrease in both NOX- and mitochondria-mediated ROS production. TGFβ1-induced EMT was partially alleviated by N-acetyl cysteine (5mM) or apocynin (100μM), which was further inhibited by an addition of rotenone (1μM) or paricalcitol.

Conclusions: One of the VDRAs, paricalcitol, ameliorated TGFβ1-induced EMT of HPMCs by a decrease in ROS generation in HPMCs. Anti-oxidant effect of paricalcitol seems to be related to the direct inhibition of NOX and mitochondria-mediated ROS production.

Funding: Government Support - Non-U.S.

FR-PO816

Adenosine Monophosphate-Activated Protein Kinase Inhibitor (AMPAK) Agonist Attenuated Epithelial-to-Mesenchymal Transition (EMT) of Mesothelium and Peritoneal Fibrosis via an Amelioration of Oxidative Stress  

Duk-Hee Kang, Juyeon Ko, Eun sun Ryu, Hyun-yon Jung, Shina Lee, Dong-Ryeol Ryu, Seung-Jung Kim, Kyu Bok Choi, Sun-Hee Park, Yong-Lim Kim. Dept of Internal Medicine, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; Kyungpook National Univ School of Medicine, Daegu, Republic of Korea.

Background: Phenotype transition of peritoneum has been regarded as an early mechanism of peritoneal fibrosis. Meformin, one of the AMPK agonists, has recently received a new attention due to an inhibitory effect on EMT of cancer cells. We investigated whether meformin imposed any effect on EMT of HPMC with an exploration of cellular mechanism for anti-fibrotic effect of meformin.

Methods: EMT was evaluated by morphological changes and the expressions of E-cadherin and α-SMA after stimulation of TGFβ1 (1ng/ml). ROS generation was analyzed by measuring NOX activity, NOX mRNA expressions, and MitoSox stained. Activation of Smad2/3, MAPK, nuclear translocation of β-catenin and snail expression were also assessed. Animal model of peritoneal dialysis (PD) was established by daily infusion of HGP-induced PD animal model, Twist and YB-1 were also up-regulated and a transformed fibroblastic phenotype of HPMCs was found stimulated by high glucose (HG, 60mmol/L).

Results: TGFβ1-induced EMT of HPMC was ameliorated by meformin. TGFβ1 increased ROS generation and NOX activity from 30 min, and mitochondrial ROS production from 6 hrs. TGFβ1 increased the phosphorylation of Smad2/3 and MAPK, which was followed by nuclear translocation of β-catenin and snail up-regulation. Meformin ameliorated ROS production, the activation of Smad2/3 and MAPK, and snail expression. In PD model, meformin decreased peritoneal thickness and EMT with an increase in ratio of E-cadherin to oxidized glutathione and superoxide dismutase activity. Meformin also decreased the expression of nitrosyrrine in peritoneum and 8-OhdG in dialysate.

Conclusions: AMPK may play a role in preservation of peritoneal function by protecting the peritoneum from phenotype transition and fibrosis via an amelioration of oxidative stress.

Funding: Government Support - Non-U.S.

FR-PO817

Twist Accelerates Human Peritoneal Mesothelial Cells Proliferation and Fibrosis by Regulating YB-1  

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Background: We have previously shown that E-box–binding transcription factor Twist is overexpressed in high glucose damage of human peritoneal mesothelial cells (HPMCs) and is involved in peritoneal membrane (PM) fibrosis in vitro. Here, we further identify its precise function related to peritoneal membranes (PM) fibrosis.

Methods: We have previously shown that E-box–binding transcription factor Twist is overexpressed in high glucose damage of human peritoneal mesothelial cells (HPMCs) and is involved in peritoneal membrane (PM) fibrosis in vitro. Here, we further identify its precise function related to peritoneal membranes (PM) fibrosis.

Results: Here, up-regulated expression and activation of Twist and YB-1 were found in HPMCs under extensive periods of PM fibrosis ex vivo. In immortal HPMCs and in HG-induced PD animal model, Twist and YB-1 were also up-regulated and a transformed fibroblastic phenotype of HPMCs was found stimulated by high glucose (HG, 60mmol/L).

Conclusions: One of the VDRAs, paricalcitol, ameliorated TGFβ1-induced EMT of HPMC, which was associated with a decrease in both NOX- and mitochondria-mediated ROS production. TGFβ1-induced EMT was partially alleviated by N-acetyl cysteine (5mM) or apocynin (100μM), which was further inhibited by an addition of rotenone (1μM) or paricalcitol.

Conclusions: Our data suggested that activation of Twist/YB-1 pathway might contribute to the growth retardation of HPMCs and the progressive PM fibrosis during PD.

Funding: Government Support - Non-U.S.

FR-PO818

The Expression of miRNA200a in Peritoneal Dialysis Associated Peritoneal Fibrosis  

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Background: Peritoneal fibrosis (PF) is an almost invariable consequence of peritoneal dialysis (PD), which is an established alternative for the replacement therapy of end-stage renal disease. We know that miR-200a belong to miR-200 family, which is closely related to a variety of fibrotic diseases.However, the role of miR-200a in peritoneal fibrosis is largely unknown.

Methods: The peritoneal fibrosis mouse model associated with PD was established by intraperitoneal injection of lipopolysaccharide + 4.25% peritoneal dialysate. The expression of miRNA was detected by microarray. The expression of miRNA profiles between fibrotic and normal peritoneal tissues was compared (n=3 in each group). The differentially expressed miRNA (miR-200a) was validated by real-time PCR in larger sample size cohorts (n=15). The expressions of miR-200a were also detected in the epithelial-mesenchymal transition (EMT) process of peritoneal mesothelium cells.

Results: In mice model of PD, peritoneal tissue was markedly thickened and with a massive extracellular matrix accumulation. By miRNA microarray analysis, miR-200a was significantly down regulated (3.31 folds change, P<0.05) in fibrotic peritoneal tissue. The down-regulated expression level of miR-200a was also validated by real-time PCR in larger cohorts (P<0.05). Then, the expression level of miR-200a was detected in the EMT process of human peritoneal mesothelium cells. During the process of TGFβ-1 induced EMT, miR-200a was significantly down-regulated compared with the control (P<0.05)

Funding: Government Support - Non-U.S.

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Underline represents presenting author.

552A
FR-PO820
Effects of Astragaloside IV against the TGF-β-Induced Epithelial-to-Mesenchymal Transition in Peritoneal Mesothelial Cells by Promoting Smad7 Expression

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Background: To investigate the effect of Astragaloside IV (AS-IV) on the regulation of the TGF-β1 Smad signaling pathway in mesothelial cells with an epithelial-to-mesenchymal transition (EMT).

Methods: EMT of human peritoneal mesothelial cells (HMrSV5) was induced using 2 ng/ml TGF-β1. Cells were randomly divided into a vehicle group, a vehicle group with AS-IV, a TGF-β1-treated group, and a TGF-β1-treated group receiving varied doses of AS-IV or NAC. Real-time quantitative PCR and western blot were used to detect the expression of genes and proteins associated with the TGF-β1/Smad signaling pathway and EMT. DCFH-DA was used to detect the generation of ROS in HMrSV5 cells, and a transwell migration assay was used to verify the capacity of AS-IV to inhibit EMT in HMrSV5 cells. Lentivirus were used as carriers for the overexpression or knockdown of the Smad7 gene.

Results: Expression levels of E-cadherin (epithelial marker) were decreased and vimentin, α-SMA (EMT markers) and collagen I (extracellular matrix protein) phospho-Smad2/3, Smad1 and Smad2 were increased significantly in the TGF-β1-treated HMrSV5 cells. AS-IV was associated with downregulated expression of vimentin and phospho-Smad2/3 in a dose-dependent manner, while the expression of Smad7 increased. Silenced or forced expression of Smad7 verified its role in the inhibitory effect of AS-IV on TGF-β1-induced EMT in HMrSV5 cells.

Conclusions: AS-IV effectively promotes the upregulation of Smad7 in the TGF-β1/Smad signaling pathway during the EMT of HMrSV5 cells, indicating its potential therapeutic effect for the control of PF.

Funding: Government Support - Non-U.S.

FR-PO821
Extracellular Vesicles in Peritoneal Effluent

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Background: Continuous and long-term exposure to peritoneal dialysis (PD) solutions induces constant low-grade inflammation and remodeling of peritoneal membrane morphology. Although the biochemical composition of peritoneal effluent offers the opportunity to explore the peritoneal membrane status in a simple and non-invasive manner, to date no clinically useful effluent biomarker has been identified that reflects the peritoneal membrane integrity sufficiently. As human body fluids contain extracellular vesicles (EVs), which are now believed to provide novel biomarkers for diseases, we investigated the presence of EVs in peritoneal effluent.

Methods: Peritoneal effluent of a short-term PD patient was collected from a regular dialysis dwell. After centrifugation, aliquots of cell-free effluent were frozen in liquid nitrogen and stored at -80°C until analysis. EVs were isolated by size exclusion chromatography. Thereafter, transmission electron microscopy (TEM) and flow cytometry (comprising markers for epithelial and mesothelial cells, leucocytes, platelets and erythrocytes) were used to detect the presence of single EVs.

Results: EVs and liposomes were identified by TEM and flow cytometry. EVs exhibited their characteristic cup shape. The majority of EVs had a mean diameter <100nm, and were present in similar amounts as in human plasma. Most EVs originate from epithelial and mesothelial cells. Moreover, EVs stained positive for leucocyte antigens, mesothelin and cancer antigen 125.

Conclusions: This is the first study to demonstrate the presence of EVs in human peritoneal effluent. Furthermore, the cellular origin of most peritoneal EVs is established.

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FR-PO822

miR-200a Negatively Regulates TGF-β1-Induced Peritoneal Mesothelial Cell Epithelial-Mesenchymal Transition by Targeting ZEB1 and ZEB2 Expression

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Background: Peritoneal fibrosis (PF) is an almost invariable consequence of peritoneal dialysis (PD), which is an established alternative for the replacement therapy of end-stage renal disease. In our previous study, we found that the expression level of miR-200a were down-regulated in fibrotic peritoneum and the epithelial-mesenchymal transition (EMT) process of peritoneal mesothelial cell. However, the role of miR-200a in EMT of peritoneal mesothelial cell and peritoneal fibrosis is largely unknown.

Methods: Human peritoneal mesothelial cell line (HMVSV5) was cultured in the presence or absence of TGF-β1. The protein expression levels of EMT index and E-box-binding homeobox (ZEB) 1/2 were determined by western blot. The level of miR-200a was determined by real-time PCR. miR-200a mimic or inhibitor and it negative control RNA were transfected into HMVSV5 cells using Lipofectamine 2000.

Results: We found that miR-200a mimic can attenuated TGF-β1 induced peritoneal mesothelial cell EMT and synthesis of extracellular matrix. It was also demonstrated that the miR-200a was responsible for protecting peritoneal mesothelial cells from mesenchymal transition by targeting suppression of ZEB1/2.

Conclusions: The results suggested that miR-200a may not only be a useful biomarker of EMT in ovarian cancer, but also of potential therapeutic value in peritoneal fibrosis.

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FR-PO823

Identification and Functional Characterization of Human Peritoneal Fibroblast Subsets According to the Expression of CD90/Thy-1

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Background: The exact origin of myofibroblasts in PD-associated peritoneal fibrosis is unknown. Lineage tracing studies suggest that resident submesothelial fibroblasts may be their major precursors. Here, we set out to identify HPFB subsets in human peritoneum and examined co-expression of CD90/Thy-1 with markers of the myofibroblastic phenotype.

Methods: HPFB were isolated from omentum, purified and then separated (MACS) into CD90/Thy-1+ and CD90/Thy-1- populations for assessment of myofibroblastic markers:

- qPCR, immunofluorescence, and ELISAs. Moreover, the presence of FSP-1+ and CD90/Thy-1+ fibroblasts was studied by immunofluorescence in peritoneal biopsies of 12 PD, 5 uremic patients, and 8 healthy controls.

Results: Cells positive for FSP-1+ and CD90/Thy-1- were absent in healthy controls, but were detectable in uremic and PD patients. In those, the majority (>95%) of FSP-1+ HPFB were also CD90/Thy-1+. In vitro studies showed that CD90/Thy-1+ HPFB had a 1.2-fold higher proliferation rate (MTT assay; n=12, p<0.05) than CD90/Thy-1-. Expression of myofibroblastic markers in CD90/Thy-1- cells was significantly higher with α-SMA, collagen-1 and TGF-β1 being increased (2.5-, 1.6- and 1.8-fold, respectively; n=13, p<0.05).

Conclusions: The vast majority of FSP-1+ HPFB detected in the peritoneum of uremic and PD patients expressed CD90/Thy-1+. In contrast, this phenotype was not detected in normal peritoneum. In vitro studies demonstrated increased expression of myofibroblastic markers in CD90/Thy-1+ HPFB. These cells may thus contribute to peritoneal fibrosis which often develops in patients during chronic PD.

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

Underline represents presenting author.

FR-PO824

Innovative Index to Follow the Peritoneal Infections and for Monitoring the Recovery Process After Peritonitis

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Background: Cell-free DNA is present in the peritoneal effluent of stable PD patients, but there is no data on cDNA in case of peritonitis. We investigated the variation of peritoneal cDNA (pcDNA) levels in PD-related peritonitis.

Methods: We enrolled 53 PD patients: 30 without any history of systemic inflammation and peritonitis in the last 3 months (groupA) and 23 with acute peritonitis (groupB). PcdNA were quantified by Real-Time PCR. Peritoneal samples on day 1-3-10-30 and until the 120th from the start of peritonitis were collected for WBC counts and pcdNA evaluation in group B.

Results: Quantitative analysis of pcdNA showed significantly higher levels in groupB compared with groupA (p<0.01), similarly as WBC. PcdNA showed significantly higher levels in groupB on day 1-3-10 and 30 compared with groupA (p<0.05). A significant correlation was observed between pcdNA level and WBC on day1 (rho=0.89) and day3 (rho=0.5) both p<0.05. No statistically significant correlation was observed on day10 and 30. In groupB, pcdNA tends to progressively decrease. From this decreasing curve, we estimated that 49 days are necessary to reach the value of 31 GE/ml (75percetile in groupA) and 63 days to reach 31 GE/ml (median). We observed a new rapid increase of cDNA level (consistent with WBC) in 5 relapsing patients, at the first day of relapsing peritonitis.

Conclusions: pcDNA increased in peritoneal effluent in PD-relatetd peritonitis and tended to progressively decrease in relation with membrane repair process. Peritoneal cDNA could be a new method to determine acute damage and an inverse index of repair process. PcdNA could help to evaluate functional and structural integrity of peritoneal membrane and to follow the evolution of infections during peritonitis.

FR-PO825

The Role of Cell-Free DNA for Management in PD-Related Peritonitis

Grazia Maria Virzi, Sabrina Milan manani, Alessandra Brocca, Massimo de Cal, Ilaria Tantillo, Carlo Crepaldi, Claudio Ronco. Nephrology, San Bortolo Hospital-IRRI.

Background: Peritonitis and exit site infections are the major complications of PD, and remains the major cause of switch from HD. In this study, we investigated the role of peritoneal cell-free DNA (cDNA) and its association with peritonitis.

Methods: We enrolled 23 PD patients with peritonitis and without any history of systemic inflammation (14 male, mean age: 68±16yrs). cDNA were extracted and quantified in peritoneal effluent by Real Time PCR for β-globin gene.

Results: All patients were treated and clinically recovered from peritonitis in 13 5.5 days. 18/23 patients had a first episode of peritonitis and responded to first-line antibiotics (65% Gram+, 22% Gram- and 13% sterile), whereas 5/23 had a relapsing episode of peritonitis (responded to other course of intra-peritoneal antibiotics). There...
There was no difference in cDNA levels between Gram^+^ (Gram-positives) patients with single episode and relapsing peritonitis, but there was a significantly difference in cDNA between PD patients with positive and negative outcomes (n=4), defined as death (p=0.05). cDNA showed significantly higher levels in 3 patients required catheter removal (p=0.05). There was no difference in cDNA levels between PD patients with a negative history of previous peritonitis (n=3) and PD patients with a positive history (n=20) (p=0.48). There was no statistically significant correlation between cDNA and number of previous peritonitis (r=0.13, p=0.55).

Conclusions: This pilot study provided substantial basis for further investigations of molecular mechanisms of peritoneal injury and potential clinical application of cDNA. cDNA could provide some additional information about patient’s outcome and management. These results can be considered hypothesis generating, and stimulate further exploration of a prognostic and predictive role of cDNA in PD-related peritonitis.

FR-PO826
Epimorphin Expressions in Mice Model of Peritoneal Fibrosis
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Background: Long-term peritoneal dialysis induces peritoneal fibrosis in submesothelial area. Epimorphin is a mesenchymal protein that regulates epithelial morphogenesis through epithelial-mesenchymal interactions, has recently attracted attention as an important modulator of tissue repair. We previously reported that epimorphin was involved in the repair of fibrosis in mice (Lab Invest 2010). In this study, we evaluated the epimorphin expressions in the peritoneal fibrosis mice model.

Methods: Peritoneal fibrosis was induced by the injection of 0.1% chlorhexidine gluconate in 15% ethanol and 85% normal saline (CG-injected mice) into peritoneal cavity of 10-week-old male C57Bl6 mice every other day. Control mice received glucose lactate-based NPDS (PD) and the same NPDS with dissolved H+ (HPD). Peritoneal tissues were subjected to morphological analysis including Masson’s Trichrome staining. Epimorphin expressions were assessed by IF staining for epimorphin. PMCs were assessed by Masson’s Trichrome staining and IF staining for epimorphin.

Results: In CG-injected mice, the marked thickening of the submesothelial compact zone was shown in Masson’s trichrome staining. IF staining for epimorphin was positive in the submesothelial area corresponding to the fibrotic area. Epimorphin staining was significantly stronger than that in control mice. Such an increase in epimorphin expression was confirmed by and real-time RT-PCR (n=5, p<0.05 vs control).

Conclusions: Our results showed that L-PDF induced apoptosis by importing lactate via MCT-1 in HPMCs, and suggest that B-PDF improved biocompatibility by inhibiting mesothelial cell apoptosis.

FR-PO827
Peritoneal Mesothelial Cells (PMCs) Injury Induced by Neutral Peritoneal Dialysis Solution (NPDS) and Its Amelioration by Molecular Hydrogen (H+), Lijie He, Shiren Sun, Dept of Nephrology, Xijing Hospital, Xi’an, Shaanxi, China.

Background: PMCs play pivotal roles in suppression of peritoneal fibrosis, adhesion, and bacterial infection in PD therapy. It is reported that histological changes of peritoneum and incidence of encapsulating peritoneal sclerosis, have been decreased by NPDS introduction. However, meta-analysis did not show superiority of NPDS in incidence of bacterial peritonitis, suggesting bio-incompatibility of current NPDS. H+ has anti-oxidative effects in biological way, and its clinical application has been studied. The present study aims to examine PMC injury by NPDS, and its ameliorating effect of H+.

Methods: Male SD rats (n=24) were divided into three groups: control (Con), 2.5% glucose lactate-based NPDS (PD), and the same NPDS with dissolved H+ (400 ppm) (HPD). The latter two groups were given NPDS or H2-NPDS intraperitoneally for 10-day 20 mL once a day. Peritoneal tissues were subjected to morphological analysis including immunohistochecmistry (cytokeratin, vimentin, proliferation, Ki67 and apoptosis, M30 cytodeath), and PMCs obtained to gene analysis by real time PCR, and microarray assay.

Results: The collagen thickness increased in PD and HPD, however, there were significant changes in stainings of vimentin, M30 cytodeath, and Ki67 in PD as compared to Con. There was no change in PD. In gene cluster analysis, there were changes by 8.7% in whole gene expression between PD and Con, and 3.7% changes between PD and HPD. In PCR, no difference was found in Epithelial-Mesenchymal Transition (Snail, TGF-β, ASMA) among the groups, while wound healing (MMP9, CTGF, Fibronectin, FAK), cytokines (IL1b, TNFα, IL6) were decreased in PD as compared to Con, but no changes in HPD.

Conclusions: This pilot study provided substantial basis for further investigations of molecular mechanisms of peritoneal injury and potential clinical application of cDNA. cDNA could provide some additional information about patient’s outcome and management. These results can be considered hypothesis generating, and stimulate further exploration of a prognostic and predictive role of cDNA in PD-related peritonitis.

FR-PO828
Bicarbonate-Buffered Peritoneal Dialysis Solution Suppresses Lactate-Induced Apoptosis via Monocarboxylate Transporter-1 in Human Peritoneal Mesothelial Cells
Akiko Kuma, Tetsu Miyamoto, Ryota Serino, Yumi Furuno, Yoko Fujimoto, Hiromichi Ueno, Yutaka Otsuji, Masahito Tamura. Dept of Nephrology, Univ of Occupational and Environmental Health, Kitakyushu, Japan.

Background: Long-term peritoneal dialysis is associated with functional and structural alterations of the peritoneal membrane. Lactate-buffered peritoneal dialysis fluid (L-PDF) has impaired biocompatibility due to the presence of supra-physiological levels of lactate. Although bicarbonate-buffered PDF (B-PDF) has been developed, its biocompatibility remains unclear. Here, we investigated the effects of L- or B-PDF on cell viability and apoptosis in cultured human peritoneal mesothelial cells (HPMCs), focusing on monocarboxylate transporters (MCT).

Methods: HPMCs were cultured in media containing 10% fetal bovine serum and L-PDF with 1.5% glucose (L1), 2.5% glucose (L2), B-PDF with 1.5% glucose (B1) or 2.5% glucose (B2), or no PD (control). Cell viability and apoptosis were determined using the WST-1 and TUNEL assays, respectively. The percentage of MCT-1 and -4 on lactate-induced apoptosis were evaluated by siRNA transfection for MCT-1 and -4.

Results: Cell viability was significantly decreased in cells incubated with L1 (12±2.2%, control–100%) and L2 (2±1.1%), compared with B1 (74±2.5%) and B2 (72±2.5%) after 72 h incubation. Apoptotic cells were also increased in L1 (69±1.6%), L2 (73±8.5%) when compared with B1 (3±0%) and B2 (4±1%). MCT-1 and -4 protein and mRNA expression levels, examined by Western blotting and real-time PCR, were similar in all cells. Protein expression levels of MCT-1 and -4 were almost completely diminished after transfection of siRNA for MCT-1 and -4, respectively. MCT-1 siRNA increased the levels of cell viability by 3.2–3.7-fold and decreased the amount of apoptotic cells from 64±8% to 47±4% in cells treated with L1 for 72 h. Interestingly, MCT-4 siRNA had no effect on cell viability and apoptosis.

Conclusions: Our results showed that L-PDF induced apoptosis by importing lactate via MCT-1 in HPMCs, and suggest that B-PDF improved biocompatibility by inhibiting mesothelial cell apoptosis.

FR-PO829
MiRNA-143/145 Gene Cluster Enhances Cell Deformation and Fibrosis of Human Peritoneal Mesothelial Cells via Modulating TPA4
Bicarbonate-Buffered Peritoneal Dialysis Solution Suppresses Lactate-Induced Apoptosis via Monocarboxylate Transporter-1 in Human Peritoneal Mesothelial Cells
Lijie He, Shiren Sun. Dept of Nephrology, Xijing Hospital, Xi’an, Shaanxi, China.

Background: In this study, we work for the function and mechanism of miR-143/145 gene cluster in human peritoneal mesothelial cells (HPMCs), which were used as possible triggers for peritoneal membrane fibrosis.

Methods: To investigate if miR-143/145 gene cluster could promote PM fibrosis, all these immortal HPMCs were characterized by fibrosis related markers and tested the expression of miRNA-143/145 cluster and tropomyosin4 (TPM4) by real-time PCR or Western blot. We also used PD dialysis rat model to observe the response of PM to miR-143/145 gene cluster and their possible target.

Results: Here, we found that miR-143/145 gene cluster, which are examined to be highly expressed in HG-induced HPMCs (HG, 60 mmol/L) and in PD animal model. TPM4 were found significantly lower expression in HG-induced HPMCs. So our study showed that HG-induced HPMCs expressed miR-143/145 gene cluster and their possible target. 

Conclusions: Our data suggested that miR-143/145 gene cluster pathway might contribute to the cell deformation of HPMCs and the progressive PM fibrosis during PD.

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Mitochondrial DNA Copy Number Is Associated with Peritoneal Dialysis Failure in Younger and Metabolically Healthier Peritoneal Dialysis Patients

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Background: Insulin resistance and inflammation are known to be closely related to adverse outcomes in peritoneal dialysis (PD) patients. Recently, mitochondrial function has been reported to play a key role in glucose metabolism as well as systemic inflammation in various populations. However, the clinical consequences of mitochondrial function in PD patients are not well known. Therefore, this study was aimed to investigate the relationship of mitochondrial DNA (mtDNA) copy number and clinical outcome in PD patients.

Methods: A total of 120 prevalent PD patients were recruited. mtDNA copy number was counted by a PCR based method. Primary outcome was PD catheter removal due to ultrafiltration failure. Metabolic syndrome was defined using the Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria. Cox proportional hazard analysis was performed to determine the independent association of mtDNA copy number with primary outcome.

Results: The mean age was 52.3 years and 52 patients (42.5%) were male. The mean mtDNA copy number was 29.1±14.9. During a mean follow-up duration of 59.4±39.3 months, primary outcome was observed in 54 patients (45.0%). There were no significant differences in baseline characteristics between non-PD and PD failure group except for serum adiponection levels (20.5±7.3 vs. 17.5±7.3 mg/mL, P=0.028). mtDNA copy number was significantly associated with PD failure in multivariate Cox analysis (hazard ratio (HR)=0.995, 95% confidence interval (CI)=0.976-1.015, P=0.634). However, a subgroup analysis revealed that mtDNA copy number was an independent predictor of PD failure in patients younger than 55 years without metabolic syndrome (HR=0.819, 95% CI=0.692-0.970, P=0.020) after adjustment for confounding factors.

Conclusions: mtDNA copy number may be associated with ultrafiltration failure in younger and metabolically healthier patients treated with PD.

IL-6 Induces VEGF Production by Human Peritoneal Mesothelial Cells During Peritonitis Through SP4-Mediated Trans-Signaling with sIL-6R

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Background: Vascular endothelial growth factor (VEGF) has been implicated in peritoneal angiogenesis and membrane remodelling in peritoneal dialysis (PD). Human peritoneal mesothelial cells (HPMC) have been identified as a major source of VEGF in the peritoneum. However, the exact mechanism of VEGF induction in HPMC is unclear. Since IL-6 concentrations in the drained dialysate correlate with VEGF levels, the link between the two has been suggested. While HPMC do not bear classical IL-6 receptor, they can respond to IL-6 trans-signalling that involves soluble IL-6 receptor (sIL-6R).

Methods: HPMC were isolated from normal omentum. Dialysate effluent was obtained from stable PD patients and during peritonitis. VEGF mRNA and protein levels were measured by RT-qPCR and ELISA, respectively. The involvement of transcriptional factors was assessed by EMSA, transient transfections with VEGF promoter constructs, and siRNA silencing.

Results: IL-6 and sIL-6R alone had no effect on VEGF release by HPMC. However, the exposure to IL-6+sIL-6R resulted in a time- and dose-dependent induction of VEGF mRNA and protein. The combination of IL-6+sIL-6R activated the VEGF promoter region that contained high affinity binding sites for the transcription factor SP4. Specific mutation of the SP4 binding site eliminated VEGF promoter activation. In turn, the induction of SP4 was controlled by ST2. Exposure of HPMC to dexamethasone efficiently obtained during acute peritonitis and containing increased levels of IL-6 and sIL-6R resulted in a dose-dependent VEGF induction. This effect was significantly attenuated in cells treated with siRNAs for either SP4 or ST2.

Conclusions: Dialysate IL-6 and sIL-6R act through the trans-signalling pathway controlled by the STAT3-SP4 axis to up-regulate mesothelial VEGF production during peritonitis.

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IF NMR Based Metabolome Can Predict Relapsing Peritonitis and Differentiate Bacterial and Fungal Peritonitis as Well

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Background: Conventional culture methods for microbes are inherently slow and inefficient. Treatment of bacterial (BP) and fungal peritonitis (FP) are different and quick differentiation is needed. Presently, there is no biomarker to predict relapsing peritonitis (RP). Bacteria and fungi may have different metabolome as one is prokaryotic and other eukaryotic.

Methods: Five unused PD fluid, 13 effluent from normal PD and 45 effluents from 15 patients (at baseline, 1 week and 2 weeks of therapy) with BP including 3 who relapsed and 3 FP were included. Half of each was subjected to total and differential WBC count and culture; and half was frozen at -80°C for NMR analysis. BP and FP was diagnosed based on identification of organism. RP was defined as per standard definition. High Resolution NMR spectra were recorded at 291 K on a Bruker Avance III 800 MHz spectrometer. Standard 1D 1H NMR spectra were acquired using the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence. To confirm the assignment of marker peak, two-dimensional (2D) 1H-1H COSY and HH-13C HSQC spectra were also acquired.

Results: Five unused and 13 normal PD effluents after 6 hours of dwell did not show any marker peak at NMR spectra at 0.67 ppm while 15 cases of BP showed marker peak; however marker peak disappeared after resolution of peritonitis at 1 week and 2 weeks of antibacterial therapy except for 3 cases who relapsed in whom marker peak was persisting despite absence of clinical peritonitis. The 3 cases of FP did not show any such marker peak differentiating it from BP. Marker signal represent trans-methylene protons of cyclopropene ring moiety as reported earlier and depicted in Figure 1.

Conclusions: The cyclopropane signal at 0.67 ppm can be marker signal to differentiate BP and FP and persistence of this signal at 2 weeks after clinical resolution of peritonitis predicts RP.
CVD. Increased intact parathyroid hormone and FGF-23 levels are associated with the progression of parenchymal fibrosis in peritoneal dialysis (PD) patient. N-acetylcysteine (NAC) acts on atherosclerosis and also improves the endothelial functions. This study was designed to evaluate the correlation between FGF-23, endothelial dysfunction and markers of inflammation in chronic PD patients and to evaluate the effect of three months of treatment with NAC in these parameters.

Methods: All patients underwent Doppler studies to assess endothelial function by the flow mediated dilatation (FMD) of the brachial artery and carotid arterial intima media thickness (CIMT). Brachial artery was imaged during reactive hyperemia (endothelium-dependent) and during a glyceryl trinitrate dilatation (nitrergic-mediated dilatation, NMD, endothelium-independent) in all PD patients. NAC was given in the dose of 1200 mg in two divided doses for a period of three months. The associations between different parameter were analyzed using Spearman correlation. All patients were repeated after three months of therapy with NAC.

Results: A total of 73 chronic PD patients were enrolled in this study. FGF-23 showed strong positive correlation with serum homocysteine level ($r=0.90, P<0.001$), hsCRP ($R=0.977, P<0.001$), Endothelium Dependent Dilatation (EEDD) ($r=0.968, P<0.001$) and CIMT ($r=0.994, P<0.001$), but negatively correlated with Endothelium Independent Dilatation and Vitamin D level. All these parameters including FGF-23, hsCRP, homocysteine, CIMT and EDD were significantly reduced after three months of therapy with NAC.

Conclusions: FGF-23 correlated well with inflammatory markers and endothelial function. With three months of therapy, NAC significantly reduces the CIMT, inflammatory markers and improves the endothelial function in chronic PD patients.

FR-PO835
SRF Enhances Cell Adhesion, Migration and Peritoneal Fibrosis via Modulating miRNA-199a/214 Cluster in Human Peritoneal Mesothelial Cells Li Jie He, Shiren Sun. Dept of Nephrology, Xijing Hospital, Xi’an, Shaanxi, China.

Background: Our previous work showed that serum response factor (SRF) was involved in fibrosis of peritoneal membrane, but the exact underlying mechanism were still unclear. Here we further study the role of miR-199a/214 cluster and the relationship of SRF in peritoneal fibrosis.

Methods: We isolated HPMCs from the effluents of end-stage renal disease (ESRD) patients with peritoneal dialysis (PD), and also used PD dialysis rats model to observe the response of PM to miR-199a/214 cluster and the predicted target CDH1 and CLDN2.

Results: In this study, we found that miR-199a-5p/214 cluster, which was examined to be highly expressed in HG-induced HPMCs by real time PCR, was directly regulated by SRF after HG stimulation. All these HG induced immortal HPMCs became scatter, have the migration ability, lost cell-cell adhesion, and characterized by phenotype markers. The overexpression of SRF in peritoneal fibrosis. Gefitinib treatment abrogated increased phosphorylation of EGFR, inhibited overproduction of transforming growth factor-$\beta 1$ and multiple proinflammatory cytokines and the accumulation of macrophages to the injured peritoneum. Moreover, gefitinib significantly reduced peritoneal increase of CD31 (+) blood vessels and vascular endothelial growth factor (+) cells after injury.

Conclusions: These results demonstrate that EGFR contributes to peritoneal fibrosis, inflammation and angiogenesis and suggest that EGFR inhibitors may have therapeutic potential in peritoneal fibrosis.

FR-PO837
Effects of Alanyl-Glutamine Addition in Peritoneal Dialysis Fluid on Peritoneal Immune Modulation – A Pilot Clinical Trial Klaus Khorntschull, 1,2 Rebecca Herzog, 1,2 Manoj K. Bhasin, 1 Seth L. Alper, 3 Andreas Vychytil, 4 Christoph Aufricht. 1 Medical Univ of Vienna, Vienna, Austria; 2 Zytoprotec GmbH, Vienna, Austria; 3 Beth Israel Deaconess Med. Ctr., Harvard Medical School, Boston, MA.

Background: Low peritoneal glutamine levels may contribute to reduced immune defense and increased inflammation in the peritoneal cavity. As a pilot clinical trial, PD patients were treated with PD fluid supplemented with 8 mM alanyl-glutamine (AlaGlN) and the effect on peritoneal cell immuno-competence was studied by functional assays and transcriptomics using RNA-sequencing (RNAseq) and microRNA (miRNA) profiling of cells derived from PD effluents.

Methods: In an open-label, randomized, crossover clinical trial at the Medical University of Vienna (EudraCT-2012-00404-36), 6 stable PD patients received either standard PD fluid (Physionol-40 3.86%, Baxter) or AlaGlN-supplemented PD fluid for an overnight dwell followed by a 4 h peritoneal equilibration test. Cytokine release from effluents of treated effluent was assessed as a measure of immuno-competence. Cells were also analyzed by RNAseq (TruSeq Single-end miRNA, Illumina) and miRNA microarray analysis (Affymetrix) using an integrated bioinformatics workflow developed in the Bhasin Lab.

Results: AlaGlN treatment significantly increased cytokine release following ex-vivo stimulation, consistent with restoration of previously suppressed peritoneal immunocompetence. Peritoneal effluent cell transcripts of 9,797 genes were identified. Unsupervised clustering and principal component analysis revealed partial separation between patients. Supervised analysis using the paired approach identified 13 differentially expressed miRNAs and 41 differentially expressed genes with $>1.5$-fold change ($P<0.01$). Functional enrichment analysis of these genes indicated pathways linked to immune response and modulation.

Conclusions: In summary, AlaGlN-mediated improvement in peritoneal leukocyte immuno-competence was correlated with changes in peritoneal leukocyte transcriptome status in well-documented clinical samples. To strengthen these promising data, larger numbers of patients will be treated with AlaGlN for a prolonged period in an international multi-center RCT.

Funding: Pharmaceutical Company Support - Zytoprotec GmbH

FR-PO838
Choice of Dialysis Modality for Children with End Stage Renal Disease Julien Hospes, 1,2 Cecile Couderc. 1,2 Pediatric Nephrology, Robert Debre Hospital, Paris, France; 3REIN Registry, Agence de la Biomédecine, La Plaine Saint Denis, France.

Background: Despite many studies that aim to assess the best modality of dialysis, results remain conflicting both in adults and in children. This lack of medical evidence leads commentators to emphasize the importance of patients’ choice in the decision process. Thus, we try to assess factors that impact the choice of the dialysis modality in children and to determine which from medical factors, center practices or patients’ wishes plays the major role.

Methods: All incident patients <20 years old at start of dialysis, recorded in the French ESRD registry between 2002 and 2013 were included. We used multivariate hierarchical logistic regression models to study patients and centers characteristics associated with the probability of starting with peritoneal dialysis (PD). The effect of centers was assessed by including centers as a random effect.

Results: Among 806 patients treated in 177 centers, 601 (74.6%) started with hemodialysis (HD) and 205 (25.4%) with PD. A higher probability of PD was found in younger children while starting HD was associated with a low use of PD. Low and high educational level of the town of residence were both associated with less probability of PD when compared with average educational level. There was a significant variability between centers, that was not explained by patients’ case-mix. Being treated in specialized pediatric centers was associated with less probability of PD, while the probability of PD was proportional to the rate of PD in the center.

Conclusions: Although little evidence exists to favor a dialysis modality over the other in children, HD remains the predominant modality in France. PD is still mostly offered to the ‘old’ patient or to ‘uncooperative’ children while it remains understudied in patients starting RRT in emergency. However, we found that besides medical factors, centers practices play a major role in the choice of dialysis modality. This raise concerns about the place left to patients’ and families’ choices and to what extend doctors may influence the final decision. Further pediatric studies focusing on children and parent’s wishes are needed in order to provide cares as close as possible to there expectations.
FR-PO839
Clinical Course of Children Born with Chronic Kidney Disease – A Single Centre Experience
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Background: The number of babies born alive suffering from chronic kidney disease (CKD) is constantly increasing.

Methods: We analyzed the outcome of infants with CKD and renal replacement therapy (RRT) treated within their first year of life. Between 2007 and 2013 17 infants (11 male; 6 female) developed end-stage renal disease resulting in RRT in our department.

Results: All of them received peritoneal dialysis (PD) initially at a median age of 34 [1-334] d. During follow-up 10 children underwent renal transplantation (RTx), 1 child was still on PD at last follow-up, 1 child had to go back to hemodialysis after graft loss and 2 had a recovery of renal function. 3 out of 17 children died during the PD period. Causes of death were severe sepsis twice and one cerebral bleeding. The mean GFR at last follow-up (22.6±7.3 years) of patients who underwent RTx was 105±28 ml/min/1.73 m². The mean age at transplantation was 29.2±14.3 months. Mental development was measured by Mental Developmental Index T1 (Bayley Scales of infant development BSID-II) at an average age of 12 [9-16] months and showed developmental delay at the motor, mental and behaviour rating scale. At time of transplantation 6/10 infants had tube feeding, 9/10 were <3. percentiles of height, 3/10 were <3. percentile of body weight.

Conclusions: RRT started in the first year of life was associated with reasonable outcome and should be offered to all infants with end stage renal disease. It is, however, associated with a high risk of developmental delay. This work emphasizes the great demands made on an interdisciplinary team of pediatric nephrologists, psychologists and social workers.

FR-PO840
Altered Myogenesis and Oxidative Stress in a Rat Model of Chronic Kidney Disease
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Background: Skeletal muscle atrophy and impaired muscle function are associated with lower quality of life, and greater disability and mortality risk in those with chronic kidney disease (CKD). However, the pathogenesis of atrophy is unknown.

Methods: We used a slowly, progressively, naturally occurring, CKD rat model (Cy-rat) and its normal littermate (NL). At 35 weeks, we tested muscle strength, sacrificed and collected tissues and blood. RNA and protein were isolated from skeletal muscle and real time PCR and western blot performed.

Results: CKD rats developed sarcopenia evident by reduced cross sectional area (p<0.05), increased connective tissue deposition on histology (p<0.05), and impaired strength (p<0.05). Strength was defined as the maximal amount of force produced during maximal, electrically stimulated dorsiflexion. These findings of atrophy can be explained by reduced regeneration, increased catabolism, or differentiation of muscle stem cells toward myofibroblasts. By PCR, there was increased activation and differentiation of muscle stem cells (reduced Pax-7, increased MyoD and myogenin (p<0.05)) and increased proteolytic markers (Atrogin-1 and MuRF-1 (p<0.05)). Fibrosis may be enhanced via decreased miR-29b (p<0.05) and increased Wnt5a (p<0.01). Finally myostatin was increased in blood (p<0.05). Strength was defined as the maximal amount of force produced during maximum, electrically stimulated dorsiflexion. Time PCR and western blot performed.

Conclusions: It is possible that the deregulation of TLR2 and TLR4 expression on leukocytes may be caused by uremic toxins in CKD population. Besides, the high workers may be related to inflammatory mechanisms in uremic patients.

FR-PO841
Can Calcitriol and Calcidiol to Regulate Toll Like Receptors 7, 9 Expression and IL-6 and IFN-γ Expression on Lymphocytes Incubated with Uremic Serum? Maria Dalboni,1,2,3 Danilo Takashi Aoike,4,5 1,2Nephrology, Univ Fed of Sao Paulo, Sao Paulo, Brazil; 3Medicine, Tufts-New England Medical Center, Boston; 4Medicine, Univ Nove de Julho, Sao Paulo, Brazil.

Background: VD deficiency is highly prevalent among patients in all stages of CKD. Studies have reported that the Vitamin D deficiency is associated with mortality and morbidity in CKD patients and may modulate TLRs that are involved in inflammatory responses. Thus, the purpose was evaluate the effect of cholecalciferol on IL-6, IFN-γ expression on lymphocytes B and T in patients on dialysis with vitamin D hypovitaminosis.

Methods: In a randomized, placebo-controlled, double-blind study, we investigated the effect of cholecalciferol (100,000 UI once per week or placebo) for 3 months, in patients on chronic dialysis, who had nutritional vitamin D deficiency. The 25(OH)D detection was performed by immunoenzyme and 25(OH)D, IFN-γ, TNF-α, IL-10, VDR, CYP27 and CYP24 expression by flow cytometry on lymphocytes B and T.

Results: After 3 months of treatment, Cholecalciferol increased 25(OH)D levels (16.0±5.4 vs 42.8±13.06 p<0.01) and reduced IFN-γ levels (525.3 (128-1775) vs 484.8 (262-7250) p<0.001), but have no effect on TLR7 and TLR9 expression. However, 25(OH)D increased expression of TLR7 (305±78 vs 252±45 p<0.01) and TLR9 (1864±700 vs 548±370 p<0.001 and CYP24 (264±136 vs 200±86 p<0.01) and increased of VDR (730±360 vs 965±440 p=0.006) and CYP27 (245±38 vs 442±380 p=0.04) expression.

Conclusions: Cholecalciferol treatment in CKD patients showed to be efficient to correct hipovitaminosis D. In addition, we observed impact of 25(OH)D, repletion on expression of the TLR7, TLR9, IFN-γ and improve of regulatory mechanisms.
associated with intracellular production of vitamin D on lymphocytes from CKD patients. These results suggest that novel treatment play an important role on TLRs expression as an anti-inflammatory and that this may contributed to a better systemic inflammation response in CKD patients.

FR-PO844
The Effect of Selenium Deficiency on Thyroid Hormone and Cardiovascular Diseases in Hemodialysis Patients  So Mi Kim,1 Eun Kyong Lee,2 Yun Jung Oh,3 Ja Soon Kim,4 1Div of Nephrology, Dept of Internal Medicine, Jeju National Univ Hospital, Jeju National Univ School of Medicine, Jeju, Jejudo, Republic of Korea; 2Div of Nephrology, Dept of Internal Medicine, Dankook Univ Hospital, Cheonan, Chungnam, Republic of Korea; 3Div of Nephrology, Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Jejudo; 4Div of Nephrology, Dept of Internal Medicine, Incheon sarung Hospital, Incheon, Kyongkido, Republic of Korea.

Background: Selenium deficiency is known to associate with impairment of thyroid hormone and cardiovascular diseases such as ischemic heart disease (IHD), cardiomyopathy or sudden death. In hemodialysis (HD) patients, various causes may contribute to selenium deficiency, including malabsorption, alteration of metabolism, and removal through dialysis itself. Therefore, we tried to investigate the effect of selenium deficiency on thyroid hormone and cardiovascular diseases in HD patients.

Methods: This cross-sectional study enrolled 83 HD patients. They were divided into two groups based on serum selenium levels: 62 patients were normal level and 22 patients were low level. Then, thyroid hormones such as TSH, free T4 were measured. And cardiovascular diseases, including IHD, heart failure or cardiomyopathy, were evaluated.

Results: Thyroid hormone impairment, including hypothyroidism and subclinical hypothyroidism, showed higher tendency in selenium deficient group than that in non-selenium deficient group. (27.5% vs 10% P=0.06) The prevalence of IHD was significantly higher in selenium deficient group than that in the non-selenium deficient group. (59% vs 21%, P=0.04) But there was no difference in heart failure and cardiomyopathy. The patients with thyroid hormone impairment showed high prevalence of IHD, and the coincidence of thyroid hormone impairment and IHD was also significantly higher than that in selenium deficient group than that in non-selenium deficient group. (18% vs 4%, P=0.014).

Conclusions: This study showed the significant high prevalence of thyroid hormone impairment and IHD in HD patients with selenium deficiency. Selenium deficiency may be affect heart disease, associating with thyroid hormone impairment.

FR-PO845
Associations of Prelude (Pre-ESRD) BMI and Weight Change with Early Dialysis Mortality Among U.S. Veterans: A Transition of Care in CKD Study Flani Strega,1 Melissa Soodoo,1 Joline L.T. Chen,2 Amanda R. Torторici,1 Jennie Jing,1 Danh V. Nguyen,1 Csaba P. Kovessy,1 Kamyar Kalantar-Zadeh,3 1UC Irvine; 2UTHSC.

Background: In end stage renal disease (ESRD) lower body mass index (BMI) portends a higher risk of mortality while obesity is protective, the so-called obesity paradox. However, the association of BMI and change in BMI over time in the pre-ESRD period and early post-ESRD mortality is unknown. We hypothesized that lower and decreasing BMI prior to transition to ESRD may be associated with higher early dialysis death.

Methods: In a cohort of 22,716 US veterans who transitioned to dialysis between 10/2007 and 9/2011 with available BMI values within the last 2 year prelude period (prior to transition to ESRD), we adjusted for age, sex, race, ethnicity, cause of ESRD, and region. In the models of BMI slope, we also adjusted for BMI level at the time of transition.

Results: The mean±SD age was 69±11 yrs, 27% were African-American, 7% Hispanic, and 49% diabetic. There was a reverse I-shaped association between BMI and mortality, where patients with BMI <27 kg/m² were at higher risk of death (Figure A). When examining changes in weight over the 2-year prelude there was a U-shaped association where patients with little to no change in BMI (-1 to +1 kg/m² per year) exhibited the best survival (Figure B).

Conclusions: Among veterans transitioning to dialysis, obese patients and those patients with little to no weight change in the last 2 years prior to ESRD have the greatest survival in the first 3 months post transition. Weight change in late stages of pre-dialysis CKD, possibly due to uremic wasting and fluid gain, portend poor outcomes, and could be used to identify at-risk patients.

Funding: NIDDK Support

FR-PO846
Nutritional Assessment for Incident Dialysis Patients Kurt Masakane,1 Yuya Sakai,1 Miho Suzuki,1 Yubaki Hospital, Nephrology, Yamagata, Japan; 2Yubaki Hospital, Dept of Health and Nutrition.

Background: Nutritional status is one of the most powerful predictors of patient survival in chronic dialysis patients especially in elderly. It is generally accepted that aging itself is one of the risk factors of malnutrition. Recently the patients who started dialysis have become older and older as the average age of incident dialysis patients in Japan is nearly 70 years old. It is very meaningful to evaluate the status of malnutrition in new elderly dialysis patients, its time-course and to establish strategies for preventing progression of malnutrition.

Methods: The nutritional status of 257 incident dialysis patients in YHG was retrospectively evaluated by MIS. The nutritional status on 37 patients out of the 257 patients has been followed for 3 years. The “malnutrition” was diagnosed as “moderate-severe” in MIS and fullfill of the diagnosis of PEW. Patients greater than 75 years old were categorized as Elder and patients under 75 years old as Non-elder. The statistical significane of time-dependent changes in nutritional status was evaluated by paired-T test.

Results: The prevalence of malnutrition at the point of dialysis initiation by MIS in average was 7%, 12% in Elder and 5% in Non-elder. The nutritional status had been improved in the non-elder but not in the elderly. The lean body mass had decreased in the first year of dialysis vintages in both groups and had remained the same in the following 2 years. Body mass fat had increased consistently for 3 years in non-elderly. It had increased for the first 2 years but had began to decrease in the third year in the elderly. Protein and energy intake per ideal body weight were lower in elderly dialysis patients.

Conclusions: Malnutrition in elderly dialysis patients was often accompanied by the initiation of chronic dialysis therapy and would gradually develop in the maintenance period. In order to protect the progression of malnutrition several proposals were addressed as the proper timing of the initiation of dialysis before the deterioration of daily activities; nutritional education for sufficient energy and protein intake, exercise education and sufficient dialysis prescription with biocompatible dialysis membranes.

FR-PO847
Uric Acid Is a Determinant of Glomerular Filtration Rate in Inflammatory Conditions Suad Ma Hannawi, Issa AL Salmi, Medicine, The Ministry of Health, Dubai, United Arab Emirates; The Renal Medicine Dept, The Royal Hospital, Muscat, Oman.

Background: The presence of gout or a baseline serum uric acid in the upper range are possibly stronger predictors of first CV events than some traditional CV risk factors or parameters of inflammation. Presence study analysis UA determinants in relation to GFR.

Methods: Patients attending the only centre of MOH in Dubai were studied during their OPD and Laboratory visit from Jan 2014 till Dec 2014. Many laboratory tests including UA were performed. MDRD formula was used to get eGFR. Simple statistical and regression models were performed. Variables that normally distributed being log transformed.

Results: 79 (88.6%,11.4%) were recruited with mean age46.14(3.4) years. Mean UA was 249.8 (84.4, eGFR137.1(50.5)(59.6,306.1).

Regression analysis found a negative relationship between UA and GFR (P<0.001,-0.004,-0.002) and positive relationship between uric acid and age (p=0.032, 0.001-0.011), urea (p=0.001,0.041-0.137), microalbuminuria (p=0.046,0.000-0.001), microalbumin/cr (p=0.001,0.031-0.013), SBP(P=0.025,0.001-0.014), age at DX RA (p=0.028,0.001-0.010), monocyte% (p=0.009,0.013-0.088), monocyte count (p=0.003,0.015-0.776) TG (p=0.034,0.009-0.231), but also negative with cholesterol (p=0.033,-0.148,-0.007).

Uric acid multiple model has maintained a strong correlation with eGFR (p<0.005), monocyte count (0.009), cholesterol (p=0.007),microalbuminuria(0.01), after adjustment for all the above mentioned variables.

Conclusions: UA is determined by eGFR and other renal parameters in inflammatory condition. On the other hand, uric acid increase the risk of renal impairment and CVD in inflammatory condition. Thus, uric acid level might be an elemental key factor that result in high renal and CV associated morbidity and mortality in the inflammatory diseases. UA is a powerful independent predictor of prevalent renal dysfunction but was also a significant predictor of progression of renal disease. UA may not be just an innocent bystander but may be an active player in the pathogenesis of renal disease by causing endothelial dysfunction, intravascular renal disease and renal impairment in inflammatory conditions.

FR-PO848
Does Nutritional Status and Serum Electrolytes Change when Dialysis Patients Reduce Their Fluid Overload? Penny Faith Sheppard,1 Suzette Thompson,2 Laura Rosales,1 Nathan W. Levin,1 Peter Kotanko,1 Fansan Zhu,1 1Renal Research Inst, New York, NY; 2Fresenius Vascular Care, New York, NY.

Background: Electrolyte balance between the intracellular (ICV) and extracellular (ECV) fluid compartment is essential in the control of normal physiological functions. Nutritional status is mainly reflected by ICV. In hemodialysis (HD) patients the relationship between control and management of fluid balance is not completely understood. We aimed to evaluated whether the degree of reduction of fluid overload affects the measurement of ICV, and concentrations of serum albumin (Alb), sodium, potassium, and calcium.

Methods: Fifty six HD patients were studied. At baseline (BL), the fluid status was evaluated by calf bioimpedance spectroscopy (cBiS). If patient’s dry weight (DW) was not reached by criteria of cBiS DW, the post target weight was gradually reduced (Zhu et al, 2015/ JASN). Then, Patients were divided into two group: one group reduced fluid overload (POD) and the other group didn’t (NONPOD). The analysis were performed with paired T test and ANOVA test with post hoc, respectively. The paired T test was used to compare the pre and post treatment as well as different groups.

Results: The between group of two groups are statistically significant for all variables. After treatment, the ICV level, sodium, potassium, calcium concentration increased significantly, respectively P<0.05. The ECV level increased in both groups, respectively P<0.05.

Conclusions: The reduction of fluid overload is associated with increase of ICV and decreased in ECV, which may affect heart disease, associating with thyroid hormone impairment. Selenium deficiency may be affect heart disease, associating with thyroid hormone impairment.
Physiol Meas, 29:S530-S516, 2008). At six months follow up, the patients either reached DW or did not (NDW) due to difficulty in prolonging treatment time. ECV and ICV, weight, and systolic blood pressure (SBP) were measured pre and post HD. Comparison of all parameters between BL and follow up were made using student t test.

Results: Thirty one patients reached DW and 25 did not. Weight and ECV were significantly reduced during follow up. However, ICV, electrolytes and Alb concentrations did not change between different fluid statuses. Post HD SBP significantly decreased from BL to the end of the study in DW but not in NDW groups.

Conclusions: Although extracellular fluid (ECV) was largely reduced, the ICV and serum concentrations of sodium, potassium, and calcium did not differ significantly. This implies that there is no fluid or mass shift from ICV to ECV, suggesting over all isotonic removal of sodium and that nutritional status is not changed by attainment of dry weight.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BL (n=31)</th>
<th>DW</th>
<th>BL (n=25)</th>
<th>NDW</th>
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<tr>
<td>Na+ (mEq/l)</td>
<td>138±2.38</td>
<td>47.0±8.9</td>
<td>91±10.6</td>
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<tr>
<td>K+ (mEq/l)</td>
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<td>16.3±0.3</td>
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<td>Ca++ (mEq/l)</td>
<td>18.5±5.4</td>
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<td>Alb (g/l)</td>
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<tr>
<td>k/v</td>
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<td>Pre HD ECV (%)</td>
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<td>Pre HD ICV (%)</td>
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FR-PO849

Trends in Weight Change During the First Two Years of Transition to Hemodialysis Treatment

Vivian Ngo,1 Elani Strejfa,1 Anna Mathew,2 Tae Hee Kim,1 Yoshitsugu Obi,1 Connie Rhe1,3 Csaba P. Kovedy,2 Kamyar Kalantar-Zadeh,1 UC Irvine; Hofstra North Shore LIJ Health System; UTBSC.

Background: Some hemodialysis patients may undergo rapid weight loss in the first few months of starting dialysis, but the nature of this trend has not yet been characterized in large nationally representative studies. We hypothesized the trajectory of weight change during the first 24 months of hemodialysis therapy may differ by baseline body mass index (BMI).

Methods: We examined percent post-dialysis weight (kg) change from baseline in 37,759 incident hemodialysis patients who initiated dialysis in a large US dialysis organization in calendar years 2007-2011 and who survived the first 2 years of hemodialysis. Trends of percent weight change over time were analyzed using crude and case-mix adjusted mixed effects models. Baseline BMI was categorized into 8 categories (<18.5, 18.5-20, 20-23, 23-25, 25-30, 30-35, 35-40, >40) kg/m2).

Results: Patients were 60±14 years old, 64% diabetics, 44% female, and had an average starting weight of 82±22 kilograms. Patients reached a nadir of weight at the 5th month of dialysis with an average 2% weight loss from baseline. At 14 months, patients' weight had not reached a nadir and lost approximately 6% of their weight by the 24th month. Obese patients (BMI >40) did not reach a nadir and lost approximately 6% of their weight by the 24th month.

Conclusions: Baseline BMI can affect the trajectory of weight change over the first two years in hemodialysis patients. Further studies are needed to better understand the cause of these differences and their impact on clinical outcomes.

Funding: NIDDK Support

FR-PO850

Significance of Renal Autonomic Nerves in the Reduction of Body Weight by SGLT2 Inhibitors

Aika Hagiwara, Kazutoshi Miyashita, Masaaki Sato, Hiroyuki Inoue, Kentaro Fujii, Masanori Tamaki, Hiroshi Itoh. Nephrology, Endocrinology and Metabolism, School of Medicine, Keio Univ, Shinjuku, Tokyo, Japan.

Background: Sodium-glucose co-transporter (SGLT) 2 inhibitors decrease not only serum glucose level but also body weight significantly. Similarly, it is reported that renal denervation (RDN) decreases body weight, in addition to blood pressure. The urinary glucose might have a relationship with sympathetic activation that controls body weight, however, the relationship has not been elucidated.

Methods: The present study examined the roles for renal autonomic nerves in the weight reduction by SGLT2 inhibitors through performing RDN on mice fed on a high-fat diet. The C57BL/6 mice fed on a high-fat diet were divided into 4 groups; control group, RDN group, SGLT2 inhibitor group and SGLT2 inhibitor with RDN group. The body weight, glucose tolerance, tissue weights, tissue hormone sensitive lipase (HSL) activity and noradrenaline concentration were examined. The SGLT2 inhibitor (tobiglitazin 50 mg/ kg pellet) was administered to mice from 8 weeks old mixing it in the high-fat diet (60 Kcal% fat). RDN was performed at 7 weeks old by surgically stripping the renal arteries and coating the vessels with a solution of 10% phenol in ethanol.

Results: The body weight at 16 weeks old significantly decreased in the SGLT2 inhibitor group. In that group, the catecholamine levels in subcutaneousfat and the activity of HSL which was measured by the phosphorylation level were increased. On the other hand, RDN with SGLT2 inhibitor group significantly weakened the degree of the reduction of body weight by the SGLT2 inhibitor associated with suppression of the catecholamine levels and the activity of HSL in the adipose tissue. In RDN without SGLT2 inhibitor group, the body weight significantly decreased; however, HSL in the adipose tissue was not activated.

Conclusions: These results indicate that HSL activation in the adipose tissue mediated by the renal autonomic nerves was involved in the mechanism of weight reduction by SGLT2 inhibitors. The renal autonomic nerves were suggested to have a role in the control of tissue HSL activity and body weight.

Funding: Government Support - Non-U.S.

FR-PO851

The Combination of Walking Exercise and Branched Chain Amino Acid Recovered Response of Protein Synthesis in Low Protein Diet Fed Chronic Kidney Disease Model Rats


Background: Low protein diet (LPD) protects progression of renal injury in patients with chronic kidney disease (CKD). However, LPD may accelerate muscle wasting in these patients. The exercise and branched chain amino acid (BCAA) are known to increase the muscle synthesis by activating mTOR signaling pathway. The aim of this study is to investigate whether walking exercise and BCAA would increase muscle protein synthesis in LPD fed CKD (5/6 nephrectomized) rats.

Methods: CKD rats were fed LPD or LPD fortified with BCAA diet (BD), and about half of the each group were loaded with the walking exercise (7 weeks of treadmill, 15 min/m, 1 hour/day, 5 days/week). After 7 weeks, the kidney and the soleus muscle were collected to evaluate the renal fibrosis and the muscle protein synthesis, respectively.

Results: The renal fibrosis and fibrosis were not different between LPD and BD fed CKD rats, and the walking exercise did not accelerate renal damage in both LPD and BD fed CKD groups. The walking exercise increased the phosphorylation of p70S6kinase, a biomarker of mammalian target of rapamycin complex 1 activity, in soleus muscle of LPD and BD fed CKD rats. However, the phosphorylation of p70S6kinase was lower in LPD fed CKD rats when compared with sham-operated groups and BD fed CKD group.

Conclusions: CKD reduces activation of muscle protein synthesis. Combination of walking exercise and BCAA recovered the muscle protein synthesis in CKD rats. These results suggest combination of walking exercise and BCAA may be beneficial to improve the muscle protein synthesis in CKD.

Funding: Government Support - Non-U.S.

FR-PO852

Unacyl-Ghrelin: A Key Molecule in Uraemic Cachexia in Children and Adult Patients

Alice Monzani,1 Michela Perrone,2 Sara Testa,1 Fabio Paulliolonga,2 Silvia Consolo,2 Gianlugi Ardissoni,2 Francesca Tel,2 Marta Lepore,2 Stefani Rotondo,2 Antonietta Biasuzzi,2 Luciana Ghio,2 Gianni Bona,2 Alberto Edefonti,2 Div of Pediatrics, Univ del Piemonte Orientale, Novara, Italy; 2Pediatric Nephrology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy.

Background: Cachexia and poor growth are common in children with chronic kidney disease (CKD). Several mechanisms are involved, including loss of appetite and poor food intake. Unacyl-ghrelin (UAG) is known to produce an inhibitory effect on feeding. We measured UAG levels in children and adolescents with CKD stage II-IV on conservator treatment (CKD-CT), on haemodialysis (CKD-HD) and after transplantation (Tx), compared with children and adolescents without CKD (CK). We measured also plasma ghrelin (Ghrl) levels in the same subjects and GFR was calculated by Schwartz formula. Weight, height and bicipital, tricipital, subcapacular and suprailliac folds were measured, and BMI z-score, fat-mass and fat-free mass pro body weight (FM/BW and FFM/BW, respectively) were calculated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underlines represents presenting author.
FR-PO853

Visceral Fat Area Is Associated with Renal and Cardiac Function in a Population with Normal or Mildly Impaired Renal Function
Sung Jin Kim,1 Yunju Nam,1 Hyeon Seok Hwang,1 Seok Joon Shin.1,2 Hye Eun Yoon.1,2 1Internal Medicine, The Catholic Univ of Korea, Seoul, Korea; 2Internal Medicine, Incheon St. Mary’s Hospital, Incheon, Korea.

Background: Visceral fat is involved in the development of metabolic and cardiovascular diseases. This study was to evaluate the association between visceral fat area (VFA) and renal and cardiac function and arterial stiffness in a population with normal or mildly impaired renal function.

Methods: This cross-sectional study included 719 middle-aged adults who underwent a voluntary health check-up program. Participants with estimated glomerular filtration rate or mildly impaired renal function. A Pearson correlation coefficient was determined between VFA and uric acid, HOMA-IR, total body fat, and visceral fat. Results: Across the tertiles of VFA, there was a significant trend for decline in eGFR (P=0.001), increase in baPWV (P=0.001) and left ventricular mass index (P<0.001), and decrease in the ratio of early mitral inflow velocity to peak mitral annulus velocity (E/E’; P<0.001), increase in baPWV (P<0.001) and left ventricular mass index (LVMi, P<0.001), and E/E’ (P=0.01, 95% confidence interval [CI] -0.11 – -0.01, P=0.02), LVMi (β = 0.08, 95% CI 0.06 – 0.10, P<0.001), and baPWV (r = 0.28, P<0.001), LVMi (r = 0.31, P<0.001), and E/E’ (r = 0.21, P<0.001). In multivariate analysis, VFA was linearly associated with eGFR (β = -0.06, 95% confidence interval [CI] -0.11 – -0.01, P=0.02), LVMi (β = 0.08, 95% CI 0.06 – 0.10, P=0.001), and E/E’ (β = 0.01, 95% CI 0.006 – 0.19, P=0.001), after adjustments for cardiovascular risk factors. In contrast, total body fat was not associated with eGFR.

Conclusions: VFA is associated with renal and cardiac function in middle-aged adults with normal or mildly impaired renal function. Measuring VFA may predict risks of renal and cardiac diseases.

Funding: Government Support - Non-U.S.

FR-PO854

Serum Ferritin <70 µg/L Predicts Functional Iron Deficiency in Patients with Chronic Kidney Disease Neha Garg, Miralalini Kotru, Om Prakash Kalra, Meera Sikka. Pathology, UCMS and GTBH, Delhi, New Delhi, India.

Background: Chronic Kidney Disease (CKD) is a major public health problem with anemia occurring early in the course of disease. Its most common cause is erythropoietin deficiency which can be effectively treated with erythropoietin stimulating agents. However most of the patients do not respond adequately due to development of Functional Iron Deficiency (FID). The current diagnostic criteria for FID as recommended by KDOQI 2006 tend to miss the diagnosis of FID. The study was conducted to explore the role of hsCRP and Interleukin-6 (IL-6) along with Serum Ferritin (SF) in improving the efficacy of this criteria.

Methods: 77 clinically diagnosed patients of CKD (Stage 3, 4 and 5) of either sex, age >18 years with Hb <11 g/dL were included in the study. Complete clinical history and physical examination was done. Complete hemogram with peripheral smear, serum iron, total iron binding capacity, Transferrin Saturation (TSAT), SF, transferrin receptors (TfR), hsCRP, IL-6, ESR were estimated.

Results: stIB/log ferritin (taken as gold standard) detected 31/77 patients as having iron deficient erythropoiesis. Out of these 31 patients, 12 patients had SF <12 µg/L indicating absent iron stores. Remaining 19 patients had SF in these. TSAT <20% and SF <100 µg/L detected FID in only 2 patients with a sensitivity of 6.45%. SF at a cut-off <70 µg/L showed the best sensitivity (83.87%) and specificity (73.91%) in detecting FID in these patients. Another 2 patients were missed in this group as who were missed FID cases who were missed by hsCRP. In the absence of raised hsCRP, SF <70 µg/L had very good sensitivity (100%). However, in the presence of raised hsCRP sensitivity was reduced (79.16%).

Conclusions: TSAT <20% and SF <100 µg/L had a sensitivity of only 6.45%. However, SF <70 µg/L emerged as the most sensitive and specific in identification of iron deficient erythropoiesis. SF <12 µg/L - SF <70 µg/L was able to identify 14/19 cases of FID. Also hsCRP could be used to stratify the CKD group in which FID could be detected with high sensitivity and specificity.

Funding: Government Support - Non-U.S.

FR-PO855

Chronic Inflammation Is Associated with Poor Clinical Outcomes Independent of Mineral Metabolism Abnormalities in the HEMO Study
Anna Jeanette Jovanovich,1,2 Eugene J. Nuccio,2 Alfred K. Cheung,3 Tom Greene,1 Michel Chonchol,2 Kristen L. Nowak,2 1Denver VA Medical Center; 2University of Colorado Denver; 3VA Salt Lake City, Utah.

Background: Epidemiological studies show a high prevalence of chronic inflammation, vitamin D deficiency, and fibroblast growth factor 23 (FGF23) excess in hemodialysis patients. Whether the relationships of high circulating C-reactive protein (CRP) and interleukin-6 (IL-6) with all-cause mortality and cardiac and infectious events are attenuated in the presence of circulating markers of mineral metabolism is unknown.

Methods: We studied the association of inflammatory markers (CRP and IL-6) with all-cause mortality, and cardiac and infectious hospitalizations and deaths among 1340 subjects from the Effect of Dialysis and Membrane Flux in Maintenance Hemodialysis (HEMO) trial. Cox regression models adjusted for important confounding variables: demographics, comorbidities, Kt/V, dialyzer, smoking, albumin, and mineral metabolism markers including serum calcium, phosphorus, intact parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and FGF23.

Results: Mean age was 58±14 years, 56% were female, and 63% were black. Median (IQR) CRP and IL-6 levels were 6.1 (2.6-15.2) µg/mL and 3.2 (1.7-6.9) pg/mL, respectively. Over mean 2.8 years follow-up, there were 582 deaths, 514 cardiovascular events, and 499 infectious events. Among subjects with levels in the highest quartile compared to the lowest quartile, both CRP and IL-6 were significantly associated with all-cause mortality in adjusted analyses, odds ratio (OR) 1.96 (95% CI, 1.27-3.02) and 1.51 (95% CI, 1.02-2.33), respectively. However, only CRP, was associated with cardiovascular disease events (OR 1.90, 95% CI, 1.04-3.44) and infectious events (OR 3.84; 95% CI, 1.37-10.74) among subjects with levels in the highest quartile compared to the lowest quartile.

Conclusions: CRP and IL-6, were significantly associated with all-cause mortality independent of mineral metabolism abnormalities. Only CRP was significantly associated with cardiovascular disease and infectious disease events independent of mineral metabolism abnormalities among subjects in the HEMO trial.

Funding: NIDDK Support, Veterans Administration Support

FR-PO856

Assessment of Protein-Energy Wasting: Comparing a New PEW Score and the MIS in Chronic HD Patients
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Background: the assessment of protein-energy wasting, a syndrome of decreased body protein and energy fuels, remains debated. Recently, a French group introduced a new PEW score, encompassing BMI, serum creatinine, pNPA and serum albumin. In a cohort of chronic hemodialysis patients, we compared the predictive value of this score with the Malnutrition Inflammation Score (MIS) using all-cause mortality as end point. Furthermore, we investigated which of these scores correlates best with quality of life (QOL).

Methods: from data of the CONvective TRAnsport STudy (CONTRAST), the new PEW score and the MIS were determined at baseline. QOL was measured with the Kidney Disease QOL-Short Form 36, which results in 2 general and 12 kidney-disease specific domains of QOL. Discrimination and calibration for mortality were tested by Cox regression models adjusted for important confounding variables: demographics, comorbidities, Kt/V, dialyzer, smoking, albumin, mineral metabolism markers including serum calcium, phosphorus, intact parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and FGF23.

Results: 489 out of 714 patients were analyzed. 183 died during follow-up (mean 3.7±1.7 years). Discrimination for mortality was higher for MIS than the new PEW score (Harrell’s C statistic 68.0 (95% CI 65.7-69.8) and 61.0 (95%CI 59.0-63.3), respectively). Furthermore, mortality calibration was adequate for MIS (p=0.65), but not for the new PEW score (p<0.05). Lastly, MIS correlated with 13 domains of QOL (p<0.12), whereas the new PEW score only correlated with the physical component score (p=0.18).

Conclusions: both the MIS and the new PEW discriminate for mortality, but the MIS performs better. Furthermore, only the MIS is properly calibrated. Third, the MIS correlates with more QOL domains with higher correlation coefficients. Therefore, we conclude that MIS is preferred over the new PEW score in assessing PEW.

FR-PO857

Change in MIS Over 1 Year Is Not Associated with Mortality in Chronic Hemodialysis Patients
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Background: protein-energy wasting, a state of decreased body protein and energy fuels, has been associated with increased mortality as measured by the Malnutrition Inflammation Score (MIS), a composite, clinical, nutrition-related score. Longitudinal data on this score, however, are limited. We checked whether a change in MIS over 1 year of follow-up is associated with mortality.

Methods: data from CONTRAST were used, a well-defined cohort of end-stage kidney disease patients. Patients were selected for analysis if MIS was available at baseline (M0) and at 12 months (M12). Delta (Δ) MIS was calculated as MIS (M12) – MIS (M0). As the
association between ΔMIS and mortality was not linear; patients were divided into quartiles of ΔMIS. Cox proportional hazards models, crude and adjusted for potential confounders, were used to calculate hazard ratios (HRs) of patients with severe deteriorating MIS (increase >2 points), mild deteriorating MIS (increase of 1 or 2 points), stable MIS versus patients with an improving MIS.

Results: 404 patients were available for analysis. Mean age was 63.0±13.5 and 62.4% were male. During follow-up (median 3.1 years), 135 patients died. Median ΔMIS was 1.0 (IQR -1.0 to 3.0). Survival curves are shown in fig. 1. HR of patients with a mild deteriorating or stable MIS versus patients with an improving MIS was 0.85 (95%CI 0.53-1.39) and 0.97 (95%CI 0.56-1.67), respectively; for patients with a severe deteriorating MIS, HR was 1.63 (95%CI 1.02-2.51). After correction for age, sex, dialysis vintage and dialysis modality, this association did not remain significant (p=0.1).

Conclusions: a change in MIS over 1 year is not associated with mortality in a multivariable survival analysis.

FR-PO858
Soluble CD14, a Marker of Endotoxemia, Associates with Survival and Cardiovascular Disease in CKD Patients
Ruben Poesen,1 Ian Barrows,1 Ali Ramezani,2 Pieter Evenepoel,3 Kathi Claessens,4 Bjorn Meijers,5 Dominic S. Raj,2 *Nephrology, Univ Hospitals Leuven, Belgium; 1Renal Diseases and Hypertension, George Washington Univ.

Background: CKD goes along with gut microbial dysbiosis and gut barrier dysfunction, possibly contributing to endotoxin translocation. Subsequent binding of endotoxin to toll-like receptor-4 and its co-receptor CD14 activates the innate immune system. As half-life of systemic endotoxin is very short, soluble CD14 (sCD14) has been proposed as better marker of endotoxin exposure. Whether sCD14 relates to adverse outcome in CKD patients not yet on dialysis is unknown.

Methods: We performed a prospective study in CKD patients stage 1-5. Plasma sCD14 was determined with ELISA. Determinants of sCD14 were examined with regression analysis. The relationship between sCD14, survival and cardiovascular disease was determined using Cox proportional hazard analysis.

Results: 495 CKD patients were followed from 2005 until 2010. Median plasma level of sCD14 was 11.6 μM (IQR 5.7–21.8). We observed a highly significant inverse correlation between sCD14 and serum TMAO (rho -0.71, P < 0.0001). During follow-up, we noted a total of 51 deaths and 75 cardiovascular events. In univariate Cox proportional hazard analysis, sCD14 was a significant predictor of mortality (HR 1.521 (1.183 – 1.956), P < 0.0001) and cardiovascular disease (HR 1.570 (1.283 – 1.921), P < 0.0001). However, significance was lost after adjustment for eGFR for overall mortality (HR 1.126 (0.795–1.647), P=0.10).

Conclusions: Serum levels of TMAO rise in parallel to a declining renal function and further analysis of 24h urine samples is ongoing to elucidate its renal handling. In this European cohort of CKD patients, we were not able to find an association between TMAO and adverse outcome that is beyond renal function, which is in contrast to previous observations in US populations, both general and CKD. This may question the validity of TMAO as a universal biomarker for cardiovascular disease, possibly due to population-specific differences in diet and/or microbial metabolism.

FR-PO860
Microbiota Derived Phenylacetylglutamine Associates with Survival and Cardiovascular Disease in CKD Patients
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Background: Lately, there is increasing interest in gut microbiota derived uremic retention solutes as driving force behind adverse outcome in CKD. Both p-cresyl sulfate and indoxyl sulfate are considered representatives of this group, also commonly referred as to protein-bound solutes due to their high protein binding and dependence on active tubular secretion for renal clearance. Phenylacetylglutamine is another microbial metabolite subjected to high tubular secretion, although protein binding is rather low. We questioned whether this solute also relates to adverse outcome in CKD patients not yet on dialysis.

Methods: We performed a prospective study in CKD patients stage 1-5. Serum levels of phenylacetylglutamine were determined using LC-MS. Correlation between eGFR and serum phenylacetylglutamine was explored using Spearman’s rank correlation analysis. The relationship between phenylacetylglutamine, survival and cardiovascular disease was examined using Cox proportional hazard analysis.

Results: 488 CKD patients were followed from November 2005 until December 2010. Median serum level of TMAO was 11.6 μM (IQR 5.7–21.8). We observed a highly significant inverse correlation between eGFR and serum TMAO (rho -0.71, P < 0.0001). During follow-up, we noted a total of 51 deaths and 75 cardiovascular events. In univariate Cox proportional hazard analysis, TMAO was a significant predictor of mortality (HR 1.521 (1.183 – 1.956), P < 0.0001) and cardiovascular disease (HR 1.570 (1.283 – 1.921), P < 0.0001). However, significance was lost after adjustment for eGFR for overall mortality (HR 1.126 (0.795 – 1.647), P=0.10).

Conclusions: Serum levels of TMAO rise in parallel to a declining renal function and further analysis of 24h urine samples is ongoing to elucidate its renal handling. In this European cohort of CKD patients, we were not able to find an association between TMAO and adverse outcome that is beyond renal function, which is in contrast to previous observations in US populations, both general and CKD. This may question the validity of TMAO as a universal biomarker for cardiovascular disease, possibly due to population-specific differences in diet and/or microbial metabolism.
FR-PO861
Sarcopenia Among Prevalent Hemodialysis Patients: Weighing the Evidence

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Background: There is no consensus on the best way to define sarcopenia in ESRD. Use of muscle/height (H) is suggested by geriatric societies but may underestimate sarcopenia, particularly in the setting of excess adiposity. We compared three definitions of sarcopenia in a prevalent HD cohort.

Methods: ACTIVE/ADIPOSE enrolled HD patients from San Francisco and Atlanta from 6/09 to 8/11. Bioelectrical impedance spectroscopy was performed before a midweek dialysis session (n=645), and total-body muscle mass was estimated using an equation containing age, sex, body weight (BW), and intracranial water. We defined sarcopenia as muscle mass ≥2SD below sex-specific means for adults 18-49 y from NHANES data indexed to Ht, %BW, and body surface area (BSA) by DuBois formula. We compared the prevalence of low muscle mass among the three methods and assessed their correlation with handgrip strength.

Results: Mean age was 57±14 years, 41% were women, 61% black. The prevalence of sarcopenia was 8% by muscle/Ht, 25% by muscle/%BW and 32% by muscle/BSA. Most sarcopenic patients by muscle/BSA had normal muscle mass, while >50% of sarcopenic patients by %BW were obese. Almost none of the overweight or obese patients were identified as sarcopenic by muscle/Ht.

Conclusions: The imbalance in gut microbiota associated with alterations in colonic epithelium contributes to the accumulation of gut-derived uremic toxins in chronic kidney disease (CKD) patients. Therapeutic strategies like probiotic supplementation may modulate the gut microbiota and reduce the toxins levels. It is known that the effect of probiotics' supplementation on indoxyl sulfa levels in non-dialysis CKD patients.

Methods: This double-blind, placebo-controlled trial, 29 non-dialysis CKD patients were recruited. Patients were randomized to receive probiotic (1 capsule, containing 30 billion of colony forming units - S. thermophilus, L. acidophilus, and B. longum, n=17) or placebo (n=12) for 3 months. IS plasma levels were quantified by HPLC, calprotectin and protein C reactive were analyzed by immunoenzymatic assay. Five patients in probiotic group and three in placebo were lost to follow-up.

Results: Plasma IS increased significantly in patients who received probiotics whereas the other parameters did not change.

FR-PO862
Does a Probiotic Supplementation Alter the Indoxyl Sulfate Levels in Non-Dialysis Chronic Kidney Disease Patients? A Randomized Placebo-Controlled Clinical Trial

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Background: The imbalance in gut microbiota associated with alterations in colonic epithelium contributes to the accumulation of gut-derived uremic toxins in chronic kidney disease (CKD) patients. Therapeutic strategies like probiotic supplementation may modulate the gut microbiota and reduce the toxins levels. It is known that the effect of probiotics' supplementation on indoxyl sulfa levels in non-dialysis CKD patients.

Methods: In this double-blind, placebo-controlled trial, 29 non-dialysis CKD patients were recruited. Patients were randomized to receive probiotic (1 capsule, containing 30 billion of colony forming units - S. thermophilus, L. acidophilus, and B. longum, n=17) or placebo (n=12) for 3 months. IS plasma levels were quantified by HPLC, calprotectin and protein C reactive were analyzed by immunoenzymatic assay. Five patients in probiotic group and three in placebo were lost to follow-up.

Results: Plasma IS increased significantly in patients who received probiotics whereas the other parameters did not change.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
rats. The overall bacterial community composition was compared according to the UniFrac distance metric among control rats, CKD rats, and CKD + AST-120 rats. A principal coordinate analysis plot revealed clustering of each group. We identified the intestinal microbiome containing tryptophanase and/or tyrosine phenol-lyase gene in the genome sequences from NCBI bacterial genome. These enzymes metabolize tryptophan to indole and tyrosine to phenol, respectively.

Conclusions: Our data suggest that UT production is not only the cause of uremic symptoms but also correlated with a subset of indigenous gut microbes and affects the composition of gut microbiota.

FR-PO865

Association of Urine Volume at the Start of Dialysis and Subsequent Changes in Serum Albumin Level in Incident Hemodialysis Patients Rieko Furuichi,1 Yoshitsugu Obi,1 Connie Rhee,1 Steven M. Brunelli,2 Joline L.T. Chen,1 Anna Mathew,1 Tae Hee Kim,1 Elani Streja,4 Csaba P. Kovásvy,4 Kamyr Kalantar-Zadeh,1 1UC Irvine; 2Davita Clin Research; 3Hofstra North Shore-LIJ Health System; 4UTHSC.

Background: Previous studies have shown that low serum albumin (Alb) levels are associated with higher mortality in hemodialysis (HD) patients. While serum Alb is a critical inflammatory and nutritional marker, low Alb may also result from albuminuria. It is unknown if a change in serum Alb over time is due to the loss of residual kidney function. While data on urine Alb was unavailable, we hypothesized that higher urine volume (UV) correlated with a decrease in Alb.

Methods: Among 38,504 incident HD patients receiving care from a large dialysis organization from 2007-2011, we examined serum albumin level trajectory over 5 years (divided into 20 patient quarters) across five strata of baseline UV: <300, 300-<600, 600-<900, 900-<1200, >1200 mL. The association between baseline UV and serum albumin trend was examined using mixed effects models with adjustment for gender, age, race, kidney disease, and insurance type.

Results: Patients were 62±15 years old, 38% female, 28% black, and 46% diabetic. Higher baseline UV was incrementally associated with higher Alb levels across strata: 3.44±0.48g/dL, 3.50±0.46g/dL, 3.57±0.44g/dL, 3.59±0.45g/dL, and 3.65±0.46g/dL respectively. [Figure] Serum Alb increased over the first 6 patient quarters (18 months) on dialysis and then stabilized. Patients with higher UV not only had a higher baseline serum Alb level, but also maintained a higher serum Alb level over follow-up.

Conclusions: Higher baseline UV appears to be associated with sustained higher serum Alb levels over time. Improvement in hypoalbuminemia as a result of transition to dialysis therapy appears to be independent of residual kidney function and may suggest an inherent advantage of dialysis initiation.

Funding: NIDDK Support

FR-PO866

Individual Variation of Hippuric Acid and P-Cresyl Sulfate Plasma Levels Correlate with Variation of Intestinal Microbial Phyletypes in Hemodialysis Patients Greet Lrl Glorieux,1 Sara Vieira-Silva,2 Sunny Elloot,1 Eva Schepers,1 Annemieke Dhondt,1 Raymond C. Vanholder,1 Jeroen Raes,2 Geert Huys,2 Marie Joossens,2 Renal Div, Ghent Univ Hospital, Gent, Belgium; 3Microbiology and Immunology, KULeuven, Leuven, Belgium; 4Microbiology, Ghent Univ, Gent, Belgium.

Background: In chronic kidney disease (CKD), a myriad of metabolites accumulate in the circulation. A substantial part is generated by intestinal microbota. We hypothesize that there is a link between plasma levels of these uremic metabolites and the composition of the intestinal microbiota.

Methods: Over 4 months, up to 8 consecutive plasma and fecal samples from 16 hemodialysis patients (14M/2F, 74±10y; vintage 43±30mo) were collected. Uremic metabolites were quantified by UPLC. Fecal microbial DNA was amplified for 16S DNA (V4 hypervariable region) sequencing (Illumina MiSeq). After quality and chimera filtering (UCHIME) data was rarefied to 10,000 reads/sample and taxonomically annotated (RDP).

Conclusions: Gut microbiota in HD patients were significantly different compared to healthy controls (p<0.05). Many HD associated features were correlated with specific intestinal bacteria, such as bifidobacteria and eubacteria. The differences were neither in the microbial community detection nor in the microbial community composition.

Funding: NIDDK Support

FR-PO867

Decreased Vitamin K Intake in Italian Hemodialysis Patients Maria Fusaro,1 Claudia D’Alessandro,1 Marrianna Noale,1 Giovanni T rippi,1 Lucia Bonfante,2 Nicola Veronese,1 Irene Santinello,3 Sabina Zambon,1 Sandro Giannini,4 Maurizio Gallieni,2 Adarnasius Cupitoni.1 1CRN - Padua, Italy; 2Div of Nephrology Dept of Clinical and Experimental Medicine, Univ of Pisa, 3Nephrology Unit, Univ of Padua; 4CNR-IFC Clin. Epid. and Physiopathol. of Renal Dis. and Hypert. of Reggio Calabria; 5Clinica Medica 1, Univ of Padua, Italy; 6Univ of Padova; Dialysis Unit St Carlo, Milan, Italy.

Background: Vitamin K is involved in the production of Bone and Matrix GlA Proteins (BGP and MGP, respectively), regulating bone and vascular health. We carried out a pilot study to evaluate vitamin K intake in hemodialysis (HD) patients.

Methods: We measured vitamin K1 intake (7-day food record) in 78 Italian hemodialysis patients (48 M, 30 F) compared to intake in 39 healthy adults (28 M, 11 F).

Results: HD patients had a mean (± SD) age of 62.8±15.9 years, median dialytic age of 97 months, mean BMI of 25.4±4.5 Kg/m2. Mean serum levels of interest for CKD-MBD were: Ca 9 mg/dL, P 4.3 mg/dL, PTH 231.5 pg/mL, ALP 81.5 U/l. Control group mean age was 64.1±13.9 years. HD patients had a significantly lower intake of vitamin K1 compared to controls (see Table). We also evaluated and compared between HD patients and controls the intake of other fat soluble vitamins and of nutrients closely associated with bone and mineral disorders in CKD patients (see table). All were decreased in HD patients.

Conclusions: This vitamin K intake study is the first carried out on Italian diet. We found a decreased intake of Vitamin K1 in HD patients. This finding supports the hypothesis of supplementing vitamin K1 for the prevention of vascular calcifications and bone disorders in HD patients. Benefits of vitamin K1 supplementation should be proved by a randomized trial.

Funding: NIDDK Support

FR-PO868

Association of Geriatric Nutrition Risk Index with Body Fluid Composition, Renal Adverse Outcomes and Mortality in Patients with Chronic Kidney Disease Rekbin Tai, Yasushi Ohashli, Shbosuke Aoki, Shizuka Kobayashi, Osamu Akizawa, Ken Sakai. Dept of Nephrology, School of Medicine, Faculty of Medicine, Toho Univ, Tokyo, Japan.

Background: Decreased body stores of protein and energy fuels may express by the geriatric nutritional risk index (GNRI) consisting of body mass index (BMI) and serum albumin levels. We studied the association of the GNRI with body fluid composition, renal adverse outcomes and all-cause mortality in patients with chronic kidney disease (CKD).

Methods: Body fluid composition was measured in 306 patients with CKD from 2005 to 2014 and was separated into three components—(a) free water mass consisting of fluid, fat, and minerals, (b) intracellular water (ICW) content, and (c) extracellular water (ECW) content. Patients were categorized according to tertiles of GNRI levels. Of those, 275 patients were followed until March 2015. The adverse renal outcomes were defined by a decline of 50% or more from baseline glomerular filtration rate or initiation of renal replacement therapy.

Results: Patients with the lower tertiles of the GNRI levels were more likely to be higher age, have a lower BMI, diastolic blood pressure, serum albumin, hemoglobin, glomerular filtration rate, and proteinuria (P < 0.05). In the body fluid composition, those tended to have lower free water mass (r = 0.73, P < 0.001) and the ratio of extracellular water to
intracellular water (r = 0.37, P < 0.001). Compared with patients with the middle tertile of the GNRI levels during a median 2.5-year follow-up, the lowest tertile of the GNRI levels had higher mortality (6.8 vs. 1.7 per 100 patient-years, P < 0.001), but had no worse adverse renal outcomes (16.5 vs. 9.0 per 100 patient-years, P = 0.08). In multivariate analysis, the lower GNRI levels independently remained as a risk factor for all-cause mortality (hazard ratio, 3.16; 95% CI, 1.30–8.84; P < 0.001).

Conclusions: The GNRI may be a simple and useful tool for predicting the risk of mortality even in CKD population including patients with massive proteinuria. These findings emphasize the importance of adequate body stores of protein and energy fuels in patients with CKD.

FR-PO869
A Novel Index for Estimation of Sarcopenia Mass Using Biomarkers of Kidney Function: Sarcopenia Index
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Background: Sarcopenia is associated with poor patients’ outcomes in Intensive Care Unit (ICU). Tools to evaluate sarcopenia are DXA scan, CT and MRI, which may not be feasible for critically ill patients. We hypothesize a novel index which can be used as a surrogate for sarcopenia among ICU patients.

Methods: This is a secondary analysis of prospectively enrolled critically ill patients. Adult ICU patients (>18 years) with shock, sepsis, use of IV antibiotics and contrast media exposure, in 24 hours of enrollment, intra-abdominal hypertension or severe Trauma were included. We excluded patients with pre-existing acute kidney injury, pregnancy, and kidney transplant, or those who were on dialysis or were moribund. We measures paraspinal muscle surface area at L3 level, using Slice-O-Matic software (TomoVision®; Magog, Canada). Sarcopenia Index (SI) was calculated as [Serum Creatinine (Scr) X 100] / [Paraspinal Muscle Surface Area] X 100.

Results: A total of 226 patients met the inclusion criteria. Among these, 110 patients who had abdominal CT within ± 4 weeks of their index ICU admission were included in the final analysis. The median age (IQR) was 67 (57–77) years and 59 (54%) were male. SI and Paraspinal Muscle Surface Area were found to be statistically correlated (R² = 0.26, p < 0.0001).

Conclusions: SI has a fair correlation with gold standard in critically ill patients. This index would be a surrogate for sarcopenia for patients who cannot tolerate transfer to imaging testing.

FR-PO870
Association with Activities of Daily Living and Geriatric Nutritional Risk Index
Healthy Liver Foundation, Tokyo, Japan; 2. Dept. of Medical Informatics, Tokyo Medical and Dental University, Tokyo, Japan; 3. Dept. of Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan.

Background: Protein energy wasting (PEW) is a typical status of Malnutrition seems to be a prevalent complication in end-stage renal disease (ESRD), and is associated with poor prognosis. We previously reported that Geriatric Nutritional Risk Index (GNRI) is useful for a prevalent complication in end-stage renal disease (ESRD), and is associated with poor prognosis. We previously reported that Geriatric Nutritional Risk Index (GNRI) is useful for predicting the risk of mortality in HD patients.

Methods: This is a secondary analysis of prospectively enrolled critically ill patients. Adult ICU patients (>18 years) with shock, sepsis, use of IV antibiotics and contrast media exposure, in 24 hours of enrollment, intra-abdominal hypertension or severe Trauma were included. We excluded patients with pre-existing acute kidney injury, pregnancy, and kidney transplant, or those who were on dialysis or were moribund. We measures paraspinal muscle surface area at L3 level, using Slice-O-Matic software (TomoVision®; Magog, Canada). Sarcopenia Index (SI) was calculated as [Serum Creatinine (Scr) X 100] / [Paraspinal Muscle Surface Area] X 100.

Results: A total of 226 patients met the inclusion criteria. Among these, 110 patients who had abdominal CT within ± 4 weeks of their index ICU admission were included in the final analysis. The median age (IQR) was 67 (57–77) years and 59 (54%) were male. SI and Paraspinal Muscle Surface Area were found to be statistically correlated (R² = 0.26, p < 0.0001).

Conclusions: SI has a fair correlation with gold standard in critically ill patients. This index would be a surrogate for sarcopenia for patients who cannot tolerate transfer to imaging testing.
epithelial cytotoxicity. Note: MgT has significantly lower GI-effects (bleating and diarrhea) than other Mg formulations. These results warrant further in vivo and clinical studies to investigate the beneficial role of MgT in protecting against cisplatin-AKI.

**Funding:** Private Foundation Support

**FR-PO873**

**Impact of Uremic Serum on the Barrier Function and Inflammation in Human Colonocytes**  
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**Background:** In chronic kidney disease (CKD) it has been suggested that alterations of the gut are associated with inflammatory state and uremic toxicity. Studies suggest that uremia may impair the intestinal barrier function, by promoting increased intestinal permeability. In this study we aimed to evaluate the in vitro effect of uremic serum on the transepithelial electrical resistance (TER), inflammation and apoptosis in the intestinal epithelial cells.

**Methods:** Pools of serum were prepared from blood samples from patients maintained on hemodialysis (Pre-HD and Post-HD), and of patients with CKD stage 4 (NND-CKD). A pool of serum form healthy individuals served as control (CTL). When the TER exceeding 1,000 Ω cm² was reached, the T84 cells were incubated for 24 h in medium containing 10% pool of serum from each group. At the conclusion of the incubation period, the TER was measured again and the following parameters were determined by flow cytometry: expression of toll-like receptor (TLR), production of reactive oxygen species (ROS) and apoptosis. TNF-α and IL-6 in the culture supernatant was determined by ELISA. A total of nine experiments were performed.

**Results:** No differences among groups were found regarding TER (p=0.443), apoptosis (p=0.751), ROS (p=0.999), expression of TLR-2 (p=0.493), TLR-4 (p=0.418) and TLR-9 (p=0.937) and secretion of TNF-α (p=0.438). IL-6 secretion was higher (p<0.001) by cells incubated with post-HD pool (2.07±0.53 pg/ml) when compared with cells incubated with CTL pool (0.67±0.35), NND-CKD (0.61±0.53) and pre-HD (0.11±0.45).

**Conclusions:** The results obtained from this model suggest that uremic serum per se does not seem to impair the integrity of intestinal epithelial cells. The increased IL-6 secretion in post-HD condition may be a consequence of pro-inflammatory stimulus of the dialysis process.

**Funding:** Government Support - Non-U.S.

**FR-PO874**

**Prediction of One-Year Mortality and Hospitalization Risk Using Nutritional Indicators and Their Trajectories in a Large Prevalent Hemodialysis Cohort**  
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1 Renal Research Inst; 2 Univ of California - Santa Barbara; 3 Fresenius Medical Care North America.

**Background:** Existing nutritional scores developed in the hemodialysis (HD) population do not consider temporal trajectories of nutritional parameters. We aimed to develop predictive models for mortality and hospitalization using readily available nutritional indicators and their rates of change.

**Methods:** Using retrospective data from a large US HD provider, a cohort with HD vintage ≥1 year (N=21,082 and N=23,384 in mortality and hospitalization analyses, respectively) was randomly split 2:1:1 for model development, testing and validation. Parameters included demographics, nutritional/inflammation parameters, and slopes of all continuous variables over 6 months. Follow-up period was January-December 2012. Performance of generalized linear models and generalized additive models (GAM) was evaluated with area-under-the-curve (AUC), sensitivity and specificity.

**Results:** For both mortality and hospitalization prediction, GAM performed best. The best mortality model included neutrophil:lymphocyte ratio (NLR) slope, serum bicarbonate slope, albumin, creatinine, age, sex and vintage (AUC 0.85, 95% CI 0.83-0.86; sensitivity 0.70; specificity 0.83). The best hospitalization model included NLR slope, albumin, congestive heart failure, serum bicarbonate slope, creatinine, serum phosphate slope, vintage, diabetes, serum phosphate, volume of urea distribution, age and enPCR (AUC 0.70, 95% CI 0.62-0.79; sensitivity 0.41; specificity 0.88).

**Conclusions:** We developed novel and accurate predictive models for mortality and hospitalization using nutritional indicators and their slopes over time. Future studies are needed to assess if its application can improve nutritional intervention allocation and outcomes in HD patients.

**Funding:** Pharmaceutical Company Support - Renal Research Institute

**FR-PO875**

**Extracellular Fluid/Intracellular Fluid (ECF/ICF) Volume Ratio Is A Novel Risk Indicator of Death and Highly Related to Malnutrition-Inflammation-Arteriosclerosis (MIA) Complex in Hemodialysis (HD) Patients**  
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**Background:** Fluid overload and malnutrition are well recognized risk factors contributing to the high mortality in HD patients. Recent studies suggest pathophysiological link between fluid overload and malnutrition as a part of MIA complex. Because the ECF and ICF volume can represent fluid volume and nutritional status respectively, ECF/ICF ratio could be defined as a novel integrated marker reflecting both fluid overload and malnutrition. Accordingly we investigated the relationship of ECF/ICF ratio to survival in the context of MIA complex in chronic HD patients.

**Methods:** 77 HD patients (age 53±13 year, diabetes 38%) were prospectively enrolled. ECF/ICF volume was measured by multi-frequency bioimpedance analysis. Nutrition, inflammation, arteriosclerosis and volume status were measured by serum albumin, C-reactive protein (CRP), pulse wave velocity (PWV) and serum B-type natriuretic peptide (BNP) respectively.

**Results:** Mean ECF/ICF ratio was 0.56±0.06 and cut-off value for maximum discrimination of survival was 0.57 by ROC curve. As compared with low ECF/ICF group (ratio<0.57, 58%), high ECF/ICF group (ratio>0.57, 42%) had higher all-cause mortality, CRP, PWV, BNP and lower serum albumin level. During the 5-year follow-up, 24 all-cause death occurred (18 in high ECF/ICF group versus 6 in low ECF/ICF group, log rank P<0.001). In Cox analysis adjusted for age, diabetes, BP and cardiac function, the ECF/ICF ratio was an independent predictors of all-cause death (HR=1.25, 95% CI=1.01-1.54, per 0.01 in ECF/ICF ratio) and nullify the effect of MIA component and volume marker on survival. The degree of malnutrition (albumin), inflammation (CRP), arteriosclerosis (PWV) and fluid overload (BNP) were correlated well with ECF/ICF ratio.

**Conclusions:** Chronic HD patient with high ECF/ICF ratio is not only fluid overloaded but malnourished and have stiff artery with more inflammation. As a novel integrated marker of fluid overload and malnutrition, ECF/ICF ratio is highly related to MIA complex and a major risk indicator of death in chronic HD patients.

**FR-PO876**

**Weight Gain After Listing Independently Predicts Pre-Transplant Sensitization Status**  
Prithika Shrivastava,1 Krista L. Lentine,2 Ankit Sakhija,1 Fidel Barrantes,1 Diane M. Cibrik,1 Yihung Huang,1 Abhijit S. Naik,1  
1 Univ of Michigan; 2 Saint Louis Univ; 3 Renal Medical Associates, NM.

**Background:** Non-allodonnue stimuli such as infections, vaccinations and pro-inflammatory events cause sensitization to HLA antibodies and increased panel reactive antibodies. Obesity is recognized as an inflammatory state. Given relationship between obesity and inflammation we speculated that weight gain on the waitlist may increase sensitization status at the time of transplantation.

**Methods:** Using national data from the Organ Procurement and Transplantation Network we identified first time kidney only transplant recipients, aged 18-70, transplanted between January 1,2009 and June 30,2013. Previous non-renal transplants were excluded. A calculated panel reactive antibody of 20% or more at the time of transplant was considered to be “sensitized”. Using a priori chosen variables we performed a logistic regression model with sensitized status at time of transplantation as the dependent variable and change in BMI from listing to transplantation, BMI at transplant, recipient age, prior sensitization status, prior pregnancy, dialysis time and race as independent variables.
Results: Among 55,894 patients transplant recipients. 39.45 % were female of which 67.32% were previously pregnant. Overall 15.12% had received prior blood transfusions. Mean BMI at waiting list and transplantation was similar at 28.4± 5.5 kg/m². Greater than 50 % patients with BMI ≥ 30 kg/m² at listing had an increased their BMI by time of transplantation,while ≤50 % patients in BMI<30 kg/m² had lost weight. A 1-unit increase in BMI was associated with an increased risk of being sensitized.
aOR:1.01 (1.01-1.02). Other independent predictors included prior transplantation aOR:1.25 (1.18-1.33), AA race aOR:1.26 (1.19-1.32), pregnancy aOR:3.32 (3.04-3.63), dialysis time aOR:1.23 (1.11-1.14).

Conclusions: The majority of obese patients gain weight on the waitlist. We identified weight gain on the waiting list to be associated with a small but statistically significant increase in odds of being sensitized. Further studies are needed to determine the impact of malnutrition-inflammation complex on pretransplant sensitization.

FR-PO877
High Salt Diet Impairs the Immune Defense against Uropathogenic Escherichia coli in Murine Pyelonephritis
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Background: Recent studies demonstrated that NaCl stimulates immune responses, for example by promoting Th17 cells differentiation, macrophage recruitment into tissues and pro-inflammatory cytokine release from epithelial cell lines. Specifically, high salt diet (HSD) exacerbated experimental autoimmune encephalomyelitis and improved immune defense against L. major infection. Little is known about the influence of HSD on anti-microbial responses in the kidney – an organ with extremely high sodium chloride concentration.

Methods: Wild type female mice were given normal salt diet (NSD) or HSD one week prior to infection with uropathogenic E. coli into the bladder resulting in pyelonephritis development. 20 h after the infection, kidneys were harvested and analyzed for CFU and immune cell subsets by flow cytometry.

Results: HSD exacerbated pyelonephritis as measured by CFU. Additionally, in kidney medullas of mice fed HSD the number of PMNs, Ly6c^- macrophages and NK cells was significantly decreased in comparison with NSD fed mice. Although PMNs from mice given HSD produced more ROS than PMNs from mice on NSD, in vitro studies demonstrated that less mediatory PMNs from mice fed HSD than NSD were able to perform phagocytosis.

Conclusions: Contrary to the expectations, HSD worsened experimental pyelonephritis, possibly through affecting immune cell activation and/or migration into the kidney medulla. This finding may be of clinical significance and, if confirmed in human studies, decreasing salt intake during bladder infection or pyelonephritis could support antibiotic therapy. Further studies are needed to elucidate the immune mechanisms underlying the negative effect of HSD on pyelonephritis.

Funding: Government Support - Non-U.S.

FR-PO878
 Gut Microbiota Lactobacillus Protects against the Progression of Renal Impairment Through the Modulation of TLR2-Mediated Gut Barrier Stability in Rats
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Keio Univ, Japan.

Background: Gut microbiota has been shown to have some role in the pathogenesis of various diseases and previous study demonstrated that Lactobacillus(Lact) decreased in number in CKD. In this study, we elucidated the significance of Lact in the pathogenesis of CKD.

Methods: Six-week-old spontaneously hypertensive rats (SHR) were rendered CKD by 5/6th nephrectomy (Nx). The SHR were divided into three groups; sham-operated SHR (SHR), SHR with Nx (Nx) and Nx given Lact (Nx+Lact). After 12 weeks, biochemical parameters, urinary protein excretion, IL-6, histological changes in the kidney, and molecular changes of tight junctions and TLR2 expression were explored. Furthermore, the changes of total renal protein and tissue were evaluated. The expressions of colon tight junction proteins were examined by immunoblotting.

Results: The gut flora analysis revealed that the decrease in Lact in Nx, which was restored in Nx+Lact. However, fecal uromic toxins did not show significant changes. Both serum indoxylsulfate and IL-6 increased in Nx. These increases were ameliorated in Nx+Lact. The decreases in the tight junction proteins Occludin and ZO-1 as well as in TLR2 in Nx were mitigated by Lact. In the pseudourease-free condition, Lact decreased the urinary protein excretion. In caco-2 cells, the downregulations of Occludin and ZO-1 by indole were ameliorated by Lact. OxPAPC inhibited the Lact-induced restoration of these tight junctions.

Conclusions: The supplementation of Lact improves the gut environment through the activation of TLR2 pathway. This improvement would contribute to the decrease in systemic uromic toxin levels, systemic inflammation and urinary protein excretion. This probiotic therapy can provide novel therapeutic strategy against the progression of CKD.

Funding: Government Support - Non-U.S.
MHD patients.

The lack of correlation between GDR versus LDR in MHD subjects requires further investigation for understanding the effects of insulin signaling on protein metabolism in MHD patients.

Conclusions:
Leucine disposal rate reliably measures amino acid utilization in MHD patients. The lack of correlation between GDR versus LDR in MHD subjects requires further investigation for understanding the effects of insulin signaling on protein metabolism in MHD patients.

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FR-PO883

Nutrition Analysis Mobile Application in Patients with Chronic Kidney Disease

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Background: While mobile phone applications have become increasingly important in the last decade, few eating healthy mobile applications exist for patients. Yet in their daily lives, patients on a restricted diet often lack instant access to health information with regards to the food that is in front of them. It is there therefore an objective of this pilot project to introduce a device that patients can utilize to overcome such problems.

Methods: The nutrition analysis application is named “GoFoody Project” and primarily consists of two functions: a scanning system and a recommendation system.

Results: The first major component of this invention is the food scanning and recognition process, which is comprised of two sub-processes: a food recognition and a barcode scanning. In the photo recognition, the user can take a picture of food and send it to the cloud database for further processing, regardless of their location. Second, the recommendation system compares the patient’s medical profile with their consumptions records in order to make health and dietary suggestions.

Conclusions: Over the next few years, we anticipated that this invention will be popular in grocery stores such as Walmart, Target, etc. We plan to demonstrate our invention to the healthcare industry by using the example of computer vision technology and cloud database.

FR-PO884

Lipoxin A₄, Attenuates Obesity-Induced Adipose Inflammation and Associated Liver and Kidney Disease

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Background: Visceral obesity and adipose inflammation is considered a driving force of systemic disease, e.g. chronic kidney disease (CKD). Inflammatory resolution is actively regulated by specialized pro-resolving mediators (SPMs), including the lipid LXA₄. Impairment of SPMs may underlie development of obesity-related pathology. Here we explored the therapeutic potential of LXA₄ in experimental obesity-induced systemic disease, e.g. liver cirrhosis and CKD.

Methods: C57BL/6 or Adiponectin-/- mice were fed a standard (10% fat) or high fat (60% fat) diet for 12 weeks. LXA₄ (5ng/g) and benzo-LXA₄ analogue (1.7 ng/g) were given as intravenous therapeutics i.p. 3 times weekly, between wk 5-12. Furthermore, omental adipose tissue biopsies were isolated from obese (BMI 35-50) bariatric surgery patients (n=4). Adipose explants were incubated with vehicle or LXA₄ (1 nM) for 6h at 37°C, and leukocytes were characterized by flow cytometry.

Results: Obesity caused distinct pathologies, including impaired glucose-tolerance, adipose inflammation, fatty liver and CKD. Lipoxins attenuated obesity-induced CKD; reducing glomerular expansion, mesangial matrix and urinary H2O2. Furthermore, LXA₄ reduced liver weight, serum alanine-aminotransferase and hepatic triglycerides. LXA₄ decreased obesity-induced adipose inflammation, attenuating TNF-α and CD14+ M1 macrophages (MΦs), while restoring CD206+ M2-MΦs and increasing Annexin-A1. Lipoxins did not affect renal or hepatic MΦs, suggesting protection occurred via attenuation of adipose inflammation. Lipoxins restored adipose expression of autophagy markers LC3-II and p62. LX-mediated protection was demonstrable in adiponectin-/- mice, suggesting that the mechanism was adiponectin independent. The ongoing clinical studies are characterizing whether Lipoxins promote an M1-to-M2 MΦ phenotype shift in human omental adipose tissue.

Conclusions: In conclusion, Lipoxins protect against obesity-induced systemic disease and these data support a novel therapeutic paradigm for treating obesity and associated CKD.

 Funding: Other NIH Support - NIH DP3 award (DK094352-01), Veterans Administration Support, Government Support - Non-U.S.

FR-PO885

Prevalence of Protein-Energy Wasting Syndrome and Its Association with Anemia, Erythropoietin Resistance, Overhydration and Body Composition in Hemodialysis Patients

Carlos Adrián Chávez-Mendoza,1 José Luis Ortega Vargas, Jorge Osvaldo Montes Riveras, Ricardo Correa-Rotter, Olymka Vega-Vega.2 1. Nephrology and Mineral Metabolism, National Inst of Medical Science and Nutrition Salvador Zubirán, Mexico City, Mexico.

Background: The prevalence of protein-energy wasting syndrome (PEW) in Mexican hemodialysis (HD) patients is unknown. Accordingly, there is no information on which clinical, biochemical, quality of life (QL), and body composition (BC) variables are associated or predictive PEW in this population.

Methods: Observational comparative study that included 191 prevalent HD patients. BC was determined by BIS employing (BCM,Fresenius®), QL was measured with KDOQI and presence of PEW according to ISRN criteria.

Results: General characteristics are shown in Figure 1, prevalence of PEW was 22%(n=41). No differences between groups (with or without PEW) were present in age, Charlson index, number and type of drugs employed, time on dialysis, vascular access, history of PD or kidney transplant and hospitalization days in the last year. PEW patients had a higher prevalence of DM(p<0.04), lower Hb(p<0.006) and higher EPO requirement(p<0.04) despite similar iron reserves. In terms of BC, PEW patients had more overhydration (OH) and higher extracellular water (ECW), and lower lean and fat tissue indexes (TLT,FTI). Surprisingly, QL indicators were not different between groups. In a Cox multivariate logistic regression model analysis, predictors of PEW were: degree OH(OR 3.2,95% CI 1.2-8.3,p=0.001), and ECW(OR 0.51,95% CI 0.22-0.89,p<0.01).

FR-PO886

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Conclusions: In conclusion, Lipoxins protect against obesity-induced systemic disease and these data support a novel therapeutic paradigm for treating obesity and associated CKD.

 Funding: Other NIH Support - NIH DP3 award (DK094352-01), Veterans Administration Support, Government Support - Non-U.S.

FR-PO885

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Conclusions: In conclusion, Lipoxins protect against obesity-induced systemic disease and these data support a novel therapeutic paradigm for treating obesity and associated CKD.

 Funding: Other NIH Support - NIH DP3 award (DK094352-01), Veterans Administration Support, Government Support - Non-U.S.
Efficacy of Nutrition Counseling on Protein Intake Restriction in Chronic Kidney Disease Patients – Niigata Part of SOFT-J (Study on Regional Variation of FROM-J Intervention by JSN) 

**Background:** Low adherence is frequently observed in patients with chronic kidney disease (CKD) who are following a diet therapy. This study evaluated the efficacy of nutrition counseling focused on protein restriction for CKD patients in clinics by national registered dieticians using iPad and textbook used in FROM-J (Frontier of Renal Outcome Modification in Japan) study, aiming at promoting relationship between home doctor and nephrologist.

**Methods:** 47 patients with CKD stage 3 (eGFR 30-59 ml/min/1.73m²), age 40-85 were recruited. Nutrition counseling was conducted once for 30 min by national registered dieticians using iPad and textbooks in clinics without any dietician in the staff. Optimal protein and energy intake were prescribed as 0.9 g/kg/day and 25-30 kcal/kg/day, respectively. The amount of protein intake was estimated from dietary records and by 24 hours urine collection before and 2 months after counseling (pre/post, respectively).

**Results:** All patients recorded their daily diets, 24/7 provided 24 hours urine collections. Counseling significantly decreased protein intake (record pre 1.10 ±0.23 g/kg/day post 1.00 ±0.26 p<0.001, urine pre 1.02±0.29 post 0.91±0.22 p=0.04). Although energy intake slightly decreased (record pre 31.9±6.4 kcal/kg/day post 30.1±5.2 p=0.03), this was not below the prescribed optimal calories. Salt intake decreased in recorded data but not in urine data (record pre 8.4±2.8 g/day post 7.6±1.7 p<0.03, urine pre 9.0±4.2 post 9.1±4.4 p<0.86, respectively). There was no significant difference in body mass index, eGFR, HbA1c (diabetic patients), LDL cholesterol, uric acid and blood pressure.

**Conclusions:** iPad and textbook counseling by dieticians is effective in reducing protein intake without compromising necessary caloric requirements, even in clinics without regular nephrologist or dietary staff. Informational technology may be an effective method of delivering on-demand nutritional counseling that can directly benefit patient care.

**FR-P087**

**Activin B Has a Functional Role in Hepcidin Induction by Inflammation**

**Background:** Induction of the iron regulatory hormone hepcidin contributes to the anemia of chronic kidney disease by restricting iron availability. Bone morphoepoetic protein 6 (BMP6) signaling is a central transcriptional regulator of hepcidin. Recently, the transforming growth factor-β (TGF-β)/BMP superfamily member Activin B was implicated in hepcidin induction by inflammation via noncanonical SMAD1/5/8 signaling, but its mechanism of action and functional significance in vivo remain uncertain.

**Methods:** Hesp3 cells and primary hepatocytes were treated with Activin B, BMP6, or Activin A, without or with siRNA knockdown of Activin/BMP pathway components, and were tested for SMAD2/3 versus SMAD1/5/8 phosphorylation and hepcidin expression. Liver Activin B expression was measured and the effect of the Activin inhibitor follistatin-315 was examined in multiple rodent models of anemia of inflammation.

**Results:** Activin B, but not Activin A, stimulated SMAD1/5/8 signaling and hepcidin expression in liver cells to a similar degree ascanonical SMAD2/3 signaling, and with similar timecourse of peak and kinetics of induction. Activin B-induced hepcidin expression was blocked by the Activin type II receptors ACVR2A and ACVR2B, noncanonical BMP type 1 receptors ALK2 and ALK3, and SMAD5. The co-receptor homologulin (HV) bound directly to Activin B and facilitated Activin B-SMAD1/5/8 signaling. Activin B-SMAD1/5/8 signaling occurred selectively in hepatocyte-derived cells and was not enabled by HV in other cell types. Liver Activin B mRNA expression was increased in multiple rodent models of inflammation associated with increased hepcidin and hypoferrernia. Follistatin-315 had no effect on basal hepcidin expression, but blunted hepcidin induction by inflammation in mice.

**Conclusions:** Our data elucidate a novel mechanism for noncanonical SMAD activation by BMP/TGF-β superfamily members, and support a functional role for Activin B in hepatic induction of inflammation in vivo. Targeting the Activin B-hepcidin pathway may lead to new therapies for anemia of inflammation including the anemia of chronic kidney disease.

**Funding:** NIDDK Support

**FR-P088**

**Effects of a Very Low Protein Diet Supplemented with Amino and Keto Acids on Skeletal Muscle Protein Synthesis and Degradation in Patients with Chronic Kidney Disease**

**Background:** Chronic kidney disease (CKD) is characterized by progressive loss of muscle mass, an effect which could be accelerated by low (LPD) and very low protein diets (VLPD), even if essential amino/keto analogue (AA/KA) supplements are used. However, to the best of our knowledge, skeletal muscle protein metabolism adapts to a supplemented VLPD in CKD patients is still unexplored.

**Methods:** To determine the muscle responses to a supplemented VLPD (0.45 g/kg +0.1 g/kg AA/KA, 35 kcal/kg), as compared to a standard LPD (0.55 g/kg 35 kcal/kg), we subjected patients who reached the primary end-point.

**Results:** All patients recorded their daily diets, 24/7 provided 24 hours urine collections. Counseling significantly decreased protein intake (record pre 1.10 ±0.23 g/kg/day post 1.00 ±0.26 p<0.001, urine pre 1.02±0.29 post 0.91±0.22 p=0.04). Although energy intake slightly decreased (record pre 31.9±6.4 kcal/kg/day post 30.1±5.2 p=0.03), this was not below the prescribed optimal calories. Salt intake decreased in recorded data but not in urine data (record pre 8.4±2.8 g/day post 7.6±1.7 p<0.03, urine pre 9.0±4.2 post 9.1±4.4 p<0.86, respectively). There was no significant difference in body mass index, eGFR, HbA1c (diabetic patients), LDL cholesterol, uric acid and blood pressure.

**Conclusions:** iPad and textbook counseling by dieticians is effective in reducing protein intake without compromising necessary caloric requirements, even in clinics without regular nephrologist or dietary staff. Informational technology may be an effective method of delivering on-demand nutritional counseling that can directly benefit patient care.

**Funding:** NIDDK Support

**FR-P089**

**Risk of Anemia and Blood Transfusion following Reduction of Maximum ESA Doses**

**Background:** The cost of providing erythropoietin stimulating agents (ESAs) for renal patients is currently covered in the province of Alberta, Canada. Due to the high costs associated with therapy, the provincial funding agency reduced the maximum weekly ESA dose by 50%. We sought to determine the clinical impact of this policy change on the risk of severe anemia (hemoglobin [HGB] <90 g/L) and transfusions.

**Methods:** All patients in the Southern Alberta Renal Program with a HGB >90g/L and receiving more than darbepoetin 75ug/wk or epoetin 15000 units/wk were reduced to an equivalent of darbepoetin 75ug/wk in September 2013. Serum HGB, iron stores, serum albumin, and parathyroid hormone assessed at baseline, 3 months, and at 6 months (end of study). Blood transfusion data was extracted from provincial electronic records. Patients were returned to a higher ESA dose when the HGB declined to <90g/L. We performed Kaplan-Meier analysis and multivariable regression analysis to calculate the median time to a drop in HGB level to <90g/L (primary outcome) and the receipt of blood transfusions (secondary outcome) following ESA dose reduction. ESA doses were re-established in people who reached the primary end-point.

**Results:** Patients (mean age 61±16 years) met the inclusion criteria. The majority of patients were treated with hemodialysis (75%) and received darbepoetin (81%). The mean baseline darbepoetin dose (or equivalent for those treated with epoetin) was 110±26ug/wk; mean baseline HGB was 106±12g/L. A HGB of 90g/L was reached in 50% of the cohort by 4.1 months (median 1.8 months, IQR 0.4-2.8 months). Blood transfusions occurred in 15% of the cohort during the study and 12% in preceding 3 months (p=0.77). In multivariate analysis, only higher baseline HGB levels were associated with reduced hazard of a drop in HGB to <90g/L. Baseline ESA dose magnitude, and baseline iron stores was not independently associated with our primary outcome.

**Conclusions:** HGB declines below 90 g/L. In about four months following ESA dose reduction. The short-term risk of blood transfusion remains similar. The clinical and economic implications of this policy remain to be determined.

**FR-P090**

**Association of Moderate Ascorbic Acid Supplementation with Plasma Ascorbic Acid and Oxalate Levels in Prevalemt Hemodialysis Patients**

**Background:** Ascorbic acid (AA) supplementation may improve anemia in hemodialysis (HD) patients. Oxalate (Ox), an AA-metabolite, is excreted in the urine and is also removed during HD. When the plasma Ox concentration (plasma [Ox]) reaches 30 µM, Ox may deposit pathologically in organs. Moderate oral AA supplementation—up to 100 mg of AA/day—is often prescribed to HD patients. Of concern, patients who received earlier forms of HD could develop pre-HD Ox levels of 30 µM or higher when taking this moderate AA dose. We hypothesized that moderate AA use is not associated with an increase in pre-HD plasma [Ox] when patients receive high-flux HD.

**Methods:** In 2011, we surveyed outpatients on HD regarding AA supplement use. Pre-HD AA and Ox levels were measured. The treatment group consisted of patients who took moderate AA for more than 4 months. Control patients were patients who did not take moderate AA for more than 4 months.

**Results:** There were no difference in pre-HD plasma [Ox] (mean±SD) between the treatment and the control groups, 21.9±10.1 µM vs. 20.6±10.6 µM, respectively (P=0.42). Median plasma AA concentration was 47.2 µM (IQR 24.6-63.8) in the treatment group and 15.8 µM (IQR 8.5-67) in the control group, (P=0.001).

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

Underline represents presenting author.
FR-PO891

Chronic Kidney Disease Is Associated with Altered Muscle Mitochondrial Energies by Functional MR Spectroscopy and Optical Spectroscopy

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Background: Exercise intolerance and muscle weakness are frequent clinical complications of CKD associated with adverse health outcomes, yet the pathophysiology underlying these conditions is poorly understood.

Methods: Cross-sectional study of in vivo muscle mitochondrial energetics using 31P Magnetic Resonance Spectroscopy and optical spectroscopy (MRS/OS) in 12 subjects with non-diabetic CKD (eGFR<60) and 26 controls. 31P MRS and OS were performed on the hand muscle under controlled ischemia. ATPflux (ATPase rate) was measured from hand muscle using Body Composition Monitor (Fresenius). The primary outcome was the coupling efficiency of mitochondrial oxidative phosphorylation ATP production (ATPflux) per unit of oxygen consumed (O2 uptake) or P/O ratio. Grip strength and timed up and go were assessed. Pearson’s correlation coefficient was calculated for univariable associations. We used multivariable linear regression adjusting for age.

Results: Mean age of CKD patients was 53±13yrs. Physical performance of the CKD group was no different from predicted normal values. Mean P/O values were 1.46±0.3 vs. 1.45±0.3 in controls. Correlation of P/O ratio age (r=-0.42), followed by eGFR (r=0.32). In contrast to controls, patients with CKD had higher O2 uptake (P=0.03) without concomitant change in ATPase rate.

Conclusions: Application of non-invasive tools reveals that CKD is associated with greater muscle O2 uptake reflecting uncoupling of oxidative phosphorylation. These results suggest altered mitochondrial respiration in skeletal muscle of patients with CKD prior to dialysis.

Funding: NIDDK Support

FR-PO892

Improving Outcomes with Nutrition in Older People with Advanced Chronic Kidney Disease – Baseline Data from a Pilot Randomised Controlled Trial

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Background: It is difficult to determine when to start dialysis in older people as creatinine and eGFR can be misleading. Dialysis start is often determined by weight loss, symptoms, potassium and fluid overload, all of which are potentially modifiable with nutrition. This pilot RCT aims to determine whether dietary interventions can result in improved patient outcomes, including time to dialysis, in older people with advanced chronic kidney disease (CKD).

Methods: Patients ≥65 years, with eGFR 10-20mls/min were randomised to an observational or intervention group (greater dietary input). Data will be collected every 6 months for up to 2 years: nutritional status (Subjective Global Assessment), symptoms (Palliative Outcome Scale – Symptoms Renal), function (6 metre walk gait speed test and Jamar handgrip dynamometer) and fluid overload using Body Composition Monitor (Fresenius).

Results: 80 patients were recruited, baseline data presented. The 2 groups have statistically similar baseline demographic and clinical characteristics. Overall, 30% have malnutrition of which 58% are overweight/obese. 28% have nutritionally relevant potentially uraemic symptoms (nausea, vomiting and/or poor appetite). Fluid overload (>2L) was observed in 22% of those that were assessed (n=58).

Conclusions: There is a high prevalence of indications for dietary interventions within older people with advanced CKD at baseline which may positively affect outcomes within two years.

Funding: Government Support - Non-U.S.
High Protein Intake in Relation to Incident End-Stage Renal Disease (ESRD) Among Blacks and Whites in the Southern Community Cohort Study (SCCS) - Rakesh Malhotra, Edmond Kato Kabagambe, Kerri L. Cavanaugh, William J. Blot, Tafat Alp Ikizler, Loren Lipworth. Vanderbilt Univ Medical Center.

Background: Dietary composition could contribute in part to observed racial disparities in ESRD incidence. Diabetes, a major risk factor for ESRD, may lead to differences in dietary intake and metabolism. We examined whether protein intake is associated with ESRD risk and whether the association varies by race and diabetes.

Methods: We conducted a nested case-control study of ESRD within the SCCS, a prospective study of low income blacks and whites in the southeastern US (2002-2009). Through 2012, 1,074 incident ESRD cases were ascertained by linkage with the USRDS, and matched to 3,230 controls on age, sex, and race. A validated food frequency questionnaire was administered at baseline. Odds ratios (OR) and 95% confidence intervals (CI) for ESRD were computed in relation to protein intake, expressed as daily % of total energy intake and modeled in 1 standard deviation (SD) increments in unconditional logistic regression models stratified by race and diabetes. ORs were adjusted for age, sex, BMI, education, income, hypertension, total energy intake and % energy from saturated and polyunsaturated fat.

Results: Median daily % energy intake from protein were higher among whites than blacks and those with vs without diabetes, but differences between ESRD cases and controls were small (15.9 and 15.7%, respectively, for blacks with diabetes, 14.6 and 14.6% for blacks without diabetes, 16.6 and 16.4% for whites with diabetes, and 15.1 and 15.1% for whites without diabetes). For a 1 SD (3.17%) increase in daily % energy intake from protein, adjusted ORs (95% CI) for ESRD were 1.18 (1.05-1.34) for blacks with diabetes, 1.06 (0.93-1.21) for blacks without diabetes, 0.89 (0.61-1.30) for whites with diabetes and 1.00 (0.74-1.33) for whites without diabetes.

Conclusions: Our results raise the possibility that among blacks with diabetes, a diet higher in protein is associated with increased incidence of ESRD. If confirmed, future studies might examine contributors leading to adverse outcomes associated with high protein intake in this subpopulation.

Funding: Other NIH Support - Grant R01 CA92447 from the National Cancer Institute (NCI), including American Recovery and Reinvestment Act funding (3R01 CA029447-08S1)


Background: The intestinal microbial flora consists of diverse bacterial species that inhabit the gastrointestinal tract. These bacteria are integral to the ontology and regulation of the immune system, and maintenance of intestinal homeostasis. In the chronic kidney diseases, changes of the intestinal bacterial flora have been reported, which contribute to nutritional disorder, systemic or local inflammation, and the uremic toxin production. Phosphate promotes a bacterial growth. So, by phosphate adsorption, intestinal bacterial flora may be changed. We examined whether phosphorus adsorption with lanthanum carbonate could change intestinal bacterial flora in renal failure mice.

Methods: We used 5 weeks old male ICR-derived glomerulonephritis (ICGN) mice (n=10) for renal failure group and ICR mice (n=10) for control group. Each group mice were fed with standard diet or diet supplemented with 3% lanthanum carbonate for 10 weeks. Gene expression patterns of a whole bacterial flora in the intestine were analyzed. LogTLR4 protein content in muscle (~4-fold increase vs. controls p<0.05). LogTLR4 protein content in muscle (~4-fold increase vs. controls p<0.05).

FR-PO986

High-Fat Diet Induces the Production of IKKβ by Macrophages to Promote Nephropathy - Xin Wan, Binbin Pan, Changchun Cao.

Background: The NF-κB activation may participate in lipid nephropathy which may be regulated by inhibitor kappa B kinase epsilon (IKKε). To investigate the role of IKKε in this process, mice experiment was performed.

Methods: Mice were grouped into wild-type or with normal fat diet (WN), 2 wild-type with high fat diet (WH), 3 IKKε knockout with normal fat diet (KN), 4 IKKε knockout with high fat diet (KH). Renal function, lipid, histological changes and tubular proliferation were analysed. IL-1β, TNF-β, p50 and p65 were determined by western blot. NF-κB level was tested by EMSA. Expression of IKKε was evaluated via immunohistochemistry and immunofluorescence.

Results: Cystatin C levels were significantly higher in WH group than others. Staining with hematoxylin-eosin revealed that tubular lesions in WH group (3.53 ± 0.21) were more severe than in WN group (0.32 ± 0.11). By Immunohistochemistry, WH group exhibited marked macrophages infiltration than WN, KN and KH groups. Western blot showed significant increase of IL-1β, TNF-β and marked increment in the expression of NF-κB pathway components consists of p50 and p65 in WH group, while these increases were blocked in KN and KH groups. Furthermore, NF-κB level in WH group was higher than other groups. WH group exhibited remarkable macrophages infiltration than other groups by Immunofluorescence. Immunohistochemistry showed remarkable increases in the expression of IKKε in the WH group compared with other groups. Immunofluorescence analysis demonstrated that the expression of IKKε was located around macrophages.

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

Underline represents presenting author.
FR-PO989

Randomized, Double-Blind, Crossover Clinical Trial on Oral Rice Endosperm Protein Supplementation to Patients on Maintenance Hemodialysis Michihiro Hosojima,1 Hisaki Shimada,2 Shigeru Miyazaki,2 Yoshitsugu Obi,1 Hazuki Kondo,3 Mikio Fujii,4 Reiko Watanabe,4 Shoji Kuwahara,1 Ryohei Kaseda,1 Ichici Narita,1 Yoshiki Suzuki,1 Motomi Kadowaki,1 Akihiko Saito.5 1Dept of Clin Nutr Sci, Niigata Univ, Japan; 2Shinrakku-en Hospital, Japan; 3Univ of California; 4Kameda Seika Co., Ltd., Japan; 5Dept of Niigata Prefecture, Japan; 6Dept of Clin Nephrol & Rheumatol, Niigata Univ, Japan; 7Health Administr Center Div, Niigata Univ, Japan; 8Faculty of Agriculture, Niigata Univ, Japan.

Background: Protein-energy wasting, a state of metabolic and nutritional derangements, is an important risk factor that affects outcomes of patients with CKD, particularly in ones with ESRD and on maintenance dialysis (MHD). Purified rice endosperm protein (REP) contains less phosphorus (150 mg/100g) compared with soybean (787 mg/100g) and casein (737 mg/100g) proteins, and may improve nutritional status without imposing further metabolic derangements.

Methods: We carried out a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effect of REP supplementation (5 g day−1 × 4 weeks) on nutritional and metabolic status in 50 MHD patients (UMIN000010876). The primary outcome was the change in urea kinetic-based normalized protein nitrogen appearance (nPNA), an indicator of protein intake in MHD patients. The inclusion criteria were: (1) nPNA < 1.2 g/kg/day; (2) serum albumin concentration ≤ 3.6 mg/dl; (3) body mass index 19 kg/m² and < 23 kg/m²; (4) ≤ 5% variation in dry weight during the period of preceding 6 months; and (5) duration of MHD ≥ 2 years.

Results: By intention-to-treat analyses, REP increased nPNA by 0.07 (95%CI, 0.03-0.11) g/kg/day compared with placebo, whereas Dserum phosphorus concentration was not significantly different between the groups (0.18 (95%CI, -0.23 to 0.58) mg/dl). REP did not show significant effects on other nutritional parameters. Per-protocol analyses yielded similar results. There were no specific complications associated with the REP supplementation.

Conclusions: Purified REP may be useful for dietary supplementation in MHD patients. Further studies are warranted to evaluate its long-term or high-dose efficacy.

Funding: Government Support - Non-U.S.

FR-PO999

Association of Serum Phosphate Levels and Mortality Risk in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis Anawin,1,2 Sikaran Utpila,1,2 1Internal Medicine, Bassett Medical Center and Columbia Univ College of Physicians & Surgeons, Cooperstown, NY; 2Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.

Background: Abnormalities of serum phosphate are associated with increased risk for mortality in end stage renal disease (ESRD) or dialysis patients. Use of phosphate binders has shown to reduce risk of mortality in these population and is recommended in several guidelines. However, there is still controversy on the management of serum phosphate in patients with chronic kidney disease (CKD). This meta-analysis evaluated the impact of serum phosphate on mortality in patients with CKD not requiring dialysis.

Methods: We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published RCT and prospective cohort studies assessing effects of high serum phosphate (compared to normal range) and a 1-mg/dl increase in phosphorus level in patients with CKD (eGFR < 60 ml/min/1.73 m²). We excluded ESRD, dialysis, or renal transplant patients. The primary outcome was risk of all-cause mortality. We used hazard ratio (HR) or risk ratio (RR) in the multivariate model as an effect estimate.

Results: From 15 full-text articles, five studies involving 6,536 patients were included in the meta-analysis. All were prospective cohort studies of CKD stage 3 or 4 patients. There was an increase all-cause mortality risk in higher phosphorus levels (HR = 1.36, 95% CI: 1.24 to 1.49, p=0.001, I²=0%) compared with normal phosphorus levels. A 1-mg/dl increase in serum phosphate also increases mortality risk with HR=1.23 (95% CI: 1.14-1.34, p<0.01, I²=0%).

Conclusions: Elevated serum phosphate levels were independently associated with increased mortality risk among patients with CKD. Randomized controlled trials are needed to assess the benefits of using phosphate lowering therapy in patients with CKD before developing ESRD or dialysis.

Funding: NIDDK Support

FR-PO900

Serum Phosphorus Levels prior to Transition to Dialysis and Early Dialysis Mortality Among U.S. Veterans: A Transition of Care in CKD Study Amanda R. Tortorici,1 Yoshitsugu Obi,1 Melissa Soohoo,1 Connie Rhee,1 Elani Streja,1 Jennie Jing,1 Rajiv Saran,2 Bruce M. Robinson,2 Yi Li,2 Danh V. Nguyen,1 Keith C. Norris,1 Csaba P. Kovedsy,3 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2UM-KECC; 3UCLA; 4UTHSC.

Background: Previous studies have shown that higher phosphorous (Phos) levels were monotonically associated with higher risk of death in patients with chronic kidney disease and end-stage renal disease (ESRD). The impact of the pre-ESRD Phos levels on early post-ESRD mortality is not known.

Methods: In US veterans who transitioned to dialysis between 10/2007 and 9/2011, we identified 10,724 patients with available Phos measurements within the last 6 months pre-ESRD (prior to transition). We examined the association of Phos (averaged over 6 months) as a continuous predictor of all-cause mortality within the first 3 months post transition, using restricted cubic spline analysis and Cox models adjusted for age, sex, race, ethnicity, cause of ESRD, and region of residence.

Results: The median SD age of the cohort was 66±11 years, among whom 34% were African-American, 8% were Hispanic, and 52% had diabetes listed as their primary cause of ESRD. We observed a reverse J-shaped association between pre-ESRD Phos and 3-month post-ESRD mortality risk. Patients with Phos levels <4.7 mg/dl had a higher risk of mortality, and patients with Phos levels >9.0 mg/dl trended towards a higher risk of mortality as well. However, patients with Phos levels between 4.7 and 7.2 mg/dl demonstrated lower mortality risk.

Conclusions: Among veterans transitioning to dialysis, both lower and higher Phos levels were associated with higher risk of early post-ESRD mortality, while patients with Phos levels between 4.7 to 7.2 mg/dl had the lowest risk of mortality. Further studies are needed to determine if using dietary and medication interventions to attain this Phos range confers higher survival in this population.
FR-PO901
The Comparison of Serum Calcium, Phosphorus and Intact Parathyroid Hormone Between Peritoneal Dialysis Patients and Hemodialysis Patients
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Background: In this study, we compared the serum calcium, phosphorus and intact parathyroid hormone between peritoneal dialysis patients and hemodialysis patients to study the difference in MBD biochemical variables between PD and HD.

Methods: 507 patients were enrolled from July 1, 2014 to December 31, 2014, including 148 patients received peritoneal dialysis and 359 patients received hemodialysis patients (HD) more than 3 months. Basic clinical information, data of dialysis, serum calcium, phosphorus and iPTH levels were collected in all patients, and comparative analysis was carried out based on those information.

Results: The age and the dialysis vintage was significantly higher in HD group than in the PD group (P < 0.001). Serum phosphorus was lower, percentage of phosphorus in target was higher and percentage of calcium in target was lower (P = 0.271) in PD group than in HD group (P<0.001). The serum phosphorus levels of PD patients with peritoneal transport characteristics or high average transport were much lower than those with low transport or low average transport (P = 0.0167). The levels of serum phosphorus (P < 0.001), iPTH (P < 0.0167) and alkaline phosphatase (P=0.001) were much lower in women with PD than those with RRF<2ml/min. The levels of serum calcium (P < 0.01), corrected calcium (P<0.01), phosphorus (P = 0.025), iPTH (P<0.001) and alkaline phosphatase (P<0.01) were much lower in patients with urine volume >1000ml/d than those <1000ml/d. There was a negative correlation between RRF and serum phosphorus (r=-0.291, P < 0.001) and iPTH (r=-0.271, <0.01) in PD group. The weekly total Kt/V (r=-0.201, P < 0.019) and weekly total creatinine clearance (CeC (r=-0.407, P<0.001) negatively related to serum phosphorus. The Ccr (r=-0.241, P < 0.01) negatively correlated with serum iPTH.

Conclusions: The serum levels of phosphorus is lower and the percentage of achieving target of phosphorus is higher in PD patients than HD patients. The peritoneal high transport characteristics, RRF>2ml/min, urine volume >1000ml/d and the nutrition status have obvious influence on the serum phosphorus and iPTH levels in PD patients.

FR-PO902
Increased Risk of Cerebral Hemorrhage in Hemodialysis Patients with Hyperphosphatemia: The Q-Cohort Study
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Background: Mounting evidences have shown that hyperphosphatemia, an established component of CKD-MBD, accelerates cardiovascular disorders in dialysis patients. However, previous studies did not separately determine the effects of hyperphosphatemia on the onset of cerebrovascular disorders and cardiovascular disorders in dialysis patients.

Methods: The present study is an observational study consisting of 3431 outpatients undergoing hemodialysis. The associations between the baseline serum phosphate (Pi) level and the onset of cerebral bleeding and infarction were examined. Independent variable was serum Pi level. Dependent variable was the onset of cerebral hemorrhage and infarction. Age, sex, diabetes mellitus, history ofcardiovascular events, diastolic vintage, KtV for urea, systolic blood pressure, hemoglobin, serum levels of calcium, parathyroid hormone, albumin, alkaline phosphatase, creatinine, and C-reactive protein, and use of vitamin D and Pi-binder were used as covariates. Cox proportional hazard model was used for analyses. All statistical analysis was conducted by JMP11.2 (SAS institute).

Results: The mean age of the examined population was 63.7±12.8 years, female was 41%, and the proportion of diabetes mellitus was 29%. Mean serum levels of calcium, Pi, and intact parathyroid hormone were 9.1±0.76 mg/dL, 4.92±1.12 mg/dL, 168±210 mg/dL, respectively. During the mean observational period of 3.1 years, 77 patients newly developed brain hemorrhage and 140 developed brain infarction. Hyperphosphatemia (Pi≥6 mg/dL) did not increase the risk of brain infarction, but increased the risk of brain hemorrhage by 2.2 fold, compared with the target Pi range (3.5£Pi<6.0 mg/dL), even after adjustment for the potential confounders.

Conclusions: Hyperphosphatemia is closely associated with the onset of cerebral hemorrhage but not with cerebral infarction. Our results highlight the importance of Pi management in the prevention of cerebral hemorrhage in dialysis patients.

Funding: Private Foundation Support

FR-PO903
Development and Evaluation of Novel Correction Equations for Serum Calcium Concentrations in Hemodialysis Patients
Yoshitsugu Obi,1 Wei Ling Lau,1 Elaní Streja,1 Connie Rhee,1 Steven M. Brunelli,2 Csaba P. Kovédy,3 Kamyar Kalantar-Zadeh,2, 1UC Irvine; 2DaVita Clinical Research; 3UTHSC.

Background: Ionized calcium (iCa), but not total calcium (tCa), is the physiologically relevant component of blood calcium. However, these measurements correlate poorly in hemodialysis patients even after correction for serum albumin, which may be partly explained by electrolyte and acid-base derangements in this population.

Methods: In 1,366 patients who initiated conventional HD over four years (1/2007-12/2010), we identified 6,830 iCa measurements where serum albumin, tCa, sodium, chloride, phosphorus, and bicarbonate were measured simultaneously. We randomly divided patients into a derivation set (n=681) or a validation set (n=685) to develop and evaluate new correction equations for serum iCa concentrations by comparing correlation r and Bayesian information criterion (BIC) in linear regression analysis as well as receiver operating characteristic (ROC) curves for hypercalcemia determined by iCa (<5.28 mg/dL).

Results: Albumin was associated with iCa, but its coefficient was -0.15, not -0.8 as shown in the conventional correction equation. Furthermore, albumin-corrected iCa showed lower correlation than uncorrected iCa with tCa (r=0.69 and 0.76, respectively). Two equations were developed from the derivation set as follows; [EQ1] 1.1*iCa – 0.12*(phosphorus + 1) and [EQ2] 1.1*iCa – 0.08*(anion gap – 2). In the validation set, EQ1 and EQ2, compared to the conventional correction by albumin, showed better correlation with iCa (<0.78 and 0.80, respectively), lower BIC (96% and 92%, respectively), and higher area under the ROC curve for Ca-defined hypercalcemia (P<0.01 for both).

Conclusions: Novel correction equations for iCa show better association with iCa and hypercalcemia evaluated by iCa. Its clinical usefulness needs to be evaluated in further studies.

Funding: NIDDK Support

FR-PO904
Relationship Between Dietary Phosphorus Intake and Protein and Energy Intakes in Hemodialysis Patients
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Background: Excess dietary phosphorus may contribute to mineral and bone disorders in hemodialysis (HD) patients. However, many high phosphorus foods are also important sources of dietary protein, which raises concerns that phosphorus restriction may compromise protein status.

Methods: We conducted a cross-sectional study of 190 African American and white men and women on intermittent HD for >3 months. Dietary data were collected by three 24-hour recalls, which were analyzed using NDSR®. Only participants who completed all three recalls and reported intakes ≥500 kcal/d were included (n=137).

Results: Dietary phosphorus and protein were highly correlated (R=0.73). Based on linear regression, a 1,000 mg/d phosphorus restriction would provide about 78 g protein/d or 1.1 g protein/kg/d for a 70-kg person. When adjusting for energy intake, the association of dietary phosphorus and protein was far less apparent (R=0.42). Further, the highest phosphorus intake was about two times greater than the lowest phosphorus intake for each energy and protein intake level (500 kcal and 5% of kcal increments), reaching 600 mg/d for some groups.

Figure 1. Ranges in reported dietary phosphorus intake of hemodialysis patients in relation to daily energy and protein intake in the Balance/Wise study (n=137)

Proportion of Daily Dietary Calories from Protein: Intake

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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574A
**Conclusions:** Although dietary phosphorus and protein are highly correlated, this relationship appears to be driven in part by the amount of Calories consumed. Moreover, phosphorus intake ranges widely within energy and protein intake increments, suggesting that reductions in dietary phosphorus may be achieved in many HD patients without compromising the protein status.

**Background:** High phosphorus levels are associated with increased cardiovascular and all-cause mortality but phosphorus control continues to be a challenge amongst dialysis patients. In this study, we conducted a survey to assess phosphorus control and identify barriers to phosphorus control in patients receiving dialysis at Loyola outpatient dialysis unit.

**Methods:** The study consisted of 17 question survey evaluating patients knowledge and understanding of phosphorus control, self care practices and social support as potential barriers to phosphorus control. Patients were approached during dialysis to participate. Objective patient data and laboratory data was collected from electronic medical records. Study was approved by Loyola IRB.

**Results:** Of the 99 eligible subjects, 57 completed the survey. Mean age of the participants was 62 years, 52% were males and 75% were African Americans. Patients were categorized into uncontrolled (phosphorus >5.5 mg/dL) and controlled phosphorus group. The two groups had similar demographics, co-morbidities, dialysis adequacy and medication pill burden. Approximately 80% of patients with uncontrolled phosphorus were aware of normal phosphorus levels in dialysis patients, complications associated with high phosphorus and identified majority of foods with high phosphorus compared to 53% 43% and 57% in the controlled phosphorus group, respectively. Patients with uncontrolled phosphorus frequently identified cheating on diet and missed medication dose as reasons for lack of phosphorus control. There was no difference among the two groups relative to social support or self-care practices. 75% patient in controlled and 55% in uncontrolled group were interested in learning more about phosphorus control.

**Conclusions:** Patients with uncontrolled phosphorus had significantly greater knowledge and understanding of phosphorus control. While continued education of patients regarding phosphorus control is important, qualitative research to study patients’ behavioral aspects is needed to better understand barriers to phosphorus control.

**FR-PO906 Use of a Simple, Widely Available Laboratory Test to Quantify and Explain Variation in Phosphorus Levels in Beverages**

Elizabeth J. Lindley, David Francis Keane,1 Tracey Ying,2 John W. Macd. Agar,3 Gunnar H. Heine,4 Juergen Geisel,3 1Leeds Teaching Hospitals NHS Trust, United Kingdom; 2Geelong Hospital, Australia; 3Saarland Univ Medical Centre, Germany.

**Background:** Restriction of dietary phosphorus (P) is essential in the management of hyperphosphataemia in CKD. Beers and wines contain inorganic P that is readily absorbed but data on these beverages, and less well-known soft drinks, is difficult to obtain. An assay used routinely in hospital laboratories has been validated for measurement of P in a range of beverages (Lindley, J Ren Nutr 2014) enabling renal unit staff to compile information on locally sourced products and investigate variation between brands.

**Methods:** Beverages were processed as if they were urine samples and tested using the standard phosphomolybdate assay. 12 beers popular in the German Saarland were tested to find out if lower P brands could be identified. 10 wines from a micro-winery in New South Wales containing little or no di-ammonium phosphate (DAP, a widely-used yeast nutrient) were compared with 8 Australian wines from UK supermarkets. Classic Coca-Cola, which is strictly regulated world-wide, was used to check agreement between analysers in different countries.

**Results:** The P content of alcoholic beers in the Saarland selection varied from 12 to 27 mg/dL. There was no association between P and alcohol level. P levels in the non-alcoholic beers tested to date were 9 and 18 mg/dL. DAP-free white wines contained 6 to 8 mg/dL. P varied from 14 to 20 mg/dL. DAP increased the P level by about 2 mg/dL, for every 100 mg/mL added to the wine must. Much higher P levels in the supermarket wines (up to 31 mg/dL) suggest routine addition of 500 to 700 mg/L DAP.

**Conclusions:** Phytic acid in cereal grains and grape pips provides P for the seedlings. Inorganic phosphorus is released from this indigestible molecule by the enzyme phytase during malting (sprouting) and fermentation. Biological variation, differences in production that affect the breakdown of phytic acid and addition of DAP contribute to the wide range of P content in beer and wines. Until appropriate labelling becomes mandatory, tables of measured P content by brand could help patients trying to restrict their P intake.

**Funding:** Government Support - Non-U.S.
Serum phosphate in the two groups

Conclusions: 1. Statistically significant separation in serum phosphate was achieved between the two groups (fig 1) with no apparent increase in secondary hyperparathyroidism. 3 patients in the HRG commenced Cinacalcet during the course of the study because serum PTH > 1200ng/dL. 2. As expected, LRG had a significantly larger pill burden than the HRG, with 20 patients in the LRG taking 9 or more binder pills. 3. Despite increased pill burden, albumin levels were not different between groups. 4. Crude mortality 4 times higher in the HRG.

Funding: Pharmaceutical Company Support - Shire pharmaceuticals provided an unrestricted educational grant towards the research fellow’s salary for 12 months.

FR-PO909

Efficacy and Safety of PT20: A Novel Iron-Based Phosphate Binder

Geoffrey A. Block, George G. Hon, Nuno Faria, Jonathan Powell.

Background: PT20, a novel iron based phosphate binder (P-binder), has been specifically engineered with adpic acid substitution to improve phosphate binding capacity and affinity of ferric oxides. PT20 has shown high binding affinity for phosphate in preclinical studies.

Methods: Patients were on hemodialysis with serum phosphate (P) levels between 4.0 and 8.0mg/dL plus serum ferritin levels <1000 mg/dL at their screening visit. All patients were then washed out of previous P-binders and required to have an increase in serum P of at least 1.0 mg/dL to enter study. 153 subjects were randomized to either 400mg, 800mg, 1600mg, 3200mg PT20 or placebo, each taken TID with meals for 28 days. Doses were not modified during the treatment period. Primary end point was change in serum P from Baseline to Day 29. Secondary endpoints assessed safety as well as haematological parameters.

Results: PT20 treatment significantly reduced serum P levels and demonstrated a dose response effect (ITT population; p<0.001). All dose groups showed a reduction in mean serum P levels greater than placebo. Mean reduction in P over the 28 days was (mg/dL) 1.36 / 3200mg; 1.29 / 1600mg; 0.59 / 800mg; 0.40 / 400mg and 0.17 / Placebo dose.

Mean serum P levels greater than placebo. Mean reduction in P over the 28 days was (mg/dL) 1.36 / 3200mg; 1.29 / 1600mg; 0.59 / 800mg; 0.40 / 400mg and 0.17 / Placebo dose.

Conclusion: PT20 treatment significantly reduced serum P levels and demonstrated a dose response effect (ITT population; p<0.001). All dose groups showed a reduction in mean serum P levels greater than placebo. Mean reduction in P over the 28 days was (mg/dL) 1.36 / 3200mg; 1.29 / 1600mg; 0.59 / 800mg; 0.40 / 400mg and 0.17 / Placebo dose.

Funding: Pharmaceutical Company Support - Shire pharmaceutical Co, Ltd

FR-PO911

Phase III Study to Investigate the Long-Term Efficacy, Safety, and Tolerability of PA21 (Sucroferric Oxyhydroxide) in Japanese Hemodialysis Patients with Hyperphosphatemia

Fumihiko Koiwa, Masafumi Fukagawa, Keitaro Yokoyama, Tadao Akizawa, Akira Terao.

Background: PA21 (sucroferric oxyhydroxide: SFOH) after 52-weeks of treatment in Japanese hemodialysis (HD) patients with hyperphosphatemia.

Methods: In total, 161 patients were treated with SFOH (750–3000 mg/day; starting dose 750 mg/day; available as 250 mg and 500 mg tablets). SFOH was administered at Week 0, after treatment with any prior phosphate binders had been discontinued. Doses of SFOH were titrated to maintain predefined serum phosphorus (sP) concentrations of 3.5–6.0 mg/dL.

Results: Mean sP concentrations decreased from 5.46 mg/dL at Week 0 to 5.00 mg/dL at the last evaluation. Mean sP concentrations were maintained within the target range of 3.5–6.0 mg/dL throughout the 52-weeks treatment period. The average number of SFOH tablets was 3.3 tablets/day, and the average dose of SFOH was 1.141 mg/day./

Conclusion: SFOH demonstrated a sustained sP-lowering effect 52-weeks of treatment in Japanese HD patients, and was associated with a low pill burden and good tolerability.

Funding: Pharmaceutical Company Support - Kissey pharmaceutical Co, Ltd

FR-PO912

Improved Serum Phosphorus Control and Decreased Phosphate Binder Pill Burden Amongst African American Hemodialysis Patients Taking Sucroferric Oxyhydroxide

Linda H. Fiscietto, Lin Ma, Vidhya Parameswaran, Claude Mullon, Franklin W. Maddux, Robert J. Kossman.

Background: A retrospective database study was conducted on the real-world effectiveness of sucroferric oxyhydroxide (SO) in controlling serum phosphorus (sP) among hemodialysis (HD) patients (pts). This analysis focuses on the subset of patients who self-reported race as Black or African American.

Methods: All patients were classified as part of standard care at FMCNA clinics and had ≥1 sP measured during SO use. Changes in sP, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and phosphate binder pills per day (PDD) were assessed 3-months before (baseline; BL) and 3-months during SO treatment (SO-TX).

Results: On average, pts (n=1015) were 51 years old with a dialysis vintage of 5.2 years and hyperphosphatemia (BL sP=6.93 mg/dL). BL phosphate binder used were: sevelamer (32.1%), calcium acetate (26.3%), calcium carbonate (4.7%), lanthanum (7.2%), calcium citrate (6.4%) and no PB specified (5.5%). As shown in Figure, pts in-range for sP concentrations at Week 0 as a covariate, P = 0.09. The average number of SFOH tablets was 3.3 tablets/day, and the average dose of SFOH was 1.141 mg/day. Overall, the incidence of adverse events and adverse drug reactions was 94.4% and 32.9%, respectively. Frequently observed adverse drug reactions were diarrhea (22.4%) and constipation (2.5%); no severe diarrhea or constipation was reported. Despite slight increases in serum Ferritin and transferrin saturation, no clinical signs of iron accumulation or overload were observed at 52 weeks.

Conclusion: SFOH demonstrated a sustained sP-lowering effect 52-weeks of treatment in Japanese HD patients, and was associated with a low pill burden and good tolerability.

Funding: Pharmaceutical Company Support - Kissey pharmaceutical Co, Ltd

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Underline represents presenting author.
FR-PO913

Real-World Use of Sucroferric Oxxyydroxide in Hemodialysis Patients: Changes in Serum Phosphorus Control and Phosphate Binder Pill Burden

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Freensius Medical Care North America (FMCNA), Waltham, MA.

Background: Approximately 40% of US dialysis patients (pts) do not achieve serum phosphorus (sPhos) goals (US-DOPPS Practice Monitor, 4/2015). This retrospective database analysis assessed the real-world effectiveness of sucroferric oxxyydroxide (SO) to control sPhos in hemodialysis (HD) pts.

Methods: In-center HD pts prescribed SO as part of routine clinical practice at FMCNA clinics with ≥1 sPhos during SO use were included. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and phosphate binder (PB) pills per day (PPD) were assessed. Pts were assessed at baseline and 3 and 3 months during SO treatment (follow-up).

Results: On average, pts (n=3151) were 54 years old with 4.3 years dialysis vintage and hyperphosphatemia (baseline sPhos = 6.94 mg/dl). PB prescribed at baseline were: sevelamer (47%), calcium acetate (26%), calcium carbonate (6%), lanthanum (7%), other (23% Pb). Pb in with in-range sPhos (3.5-5.5 mg/dl) increased from 13 to 20.4% (57% increase). Mean sPhos (6.94 to 6.73 mg/dl, p<0.001) and mean sCa (9.21 to 9.18 mg/dl, p=0.003) decreased significantly. iPTH changed minimally.

Conclusions: In a cohort of African American hemodialysis patients prescribed sucroferric oxxyydroxide, a 57% increase in patients with in-range (3.5-5.5 mg/dl) serum phosphorus (p<0.001) along with a decrease in pill burden (4.8 fewer pills, p<0.001) was observed.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America.
Conclusions: These results suggest that hyperphosphatemia affects aortic gene expression linked to oxidative stress and inflammation, and that the adverse cardiovascular effects of high serum Pi may be prevented by oral treatment with the phosphate binder VS-505.
Funding: NIDDK Support

FR-PO916

Fractional Excretion of Phosphate Misrepresents Hormonal Effects on Phosphate Reabsorption in Chronic Kidney Disease
Kenneth R. Phelps,
Darius Mason,
Sun J. Kang

Background: The serum P concentration ([P]u) is the sum of Ecr/Cr and TRcr/Cr, where Ecr/Cr and TRcr, are rates of urinary excretion and tubular reabsorption of P per volume of filtrate. Ecr/Cr is proportional to filtrate [P] in the cortical distal nephron ([P]c); we have argued that [PTH] correlates with Ecr/Cr, for this reason in CKD. Fractional excretion of [P] (FEcr), usually calculated as ([P]c)[P]c/(Ecr/Cr)[P]c, also equals 1/(1 + (TRcr/Ecr/Cr)). Since Ecr equals influx of [P]c, the second expression shows that both I and TR determine FEcr. We hypothesized that FEcr correlates with [PTH] and [FGF23] in CKD because I affects all 3 variables.

Methods: We measured fasting [cr], [P]c, [PTH] (1-84 Scantibodies and intact [FGF23]) (Immuntotics) in 30 patients with stages 3-4 CKD. We calculated Ecr/Cr, as [P]c/[Ecr/Cr], TRcr, as [P]c/(Ecr/Cr)[P]c, and FEcr as [P]c/[P]c.[P]c. We performed simple linear regressions as in the table and a multilinear regression of FEcr on [PTH] and [FGF23] did not result from effects of the hormones on TRcr.

Results: FEcr correlated directly with [PTH] and [FGF23] in CKD because I affects all 3 variables. In Bijvoet’s infusion studies, linear regressions as in the table and a multilinear regression of FEcr on [PTH] and [FGF23] did not result from effects of the hormones on TRcr.

Conclusions: FEcr is unrelated to [PTH] and [FGF23] even though both hormones reduce P reabsorption. Although FEcr varied inversely with TRcr/Cr correlations of FEcr with [PTH] and [FGF23] did not show any effect on FEcr, and therefore did not reflect quantitative relationships between hormone concentrations and P reabsorption. The correlations occurred because FEcr and TRcr were correlated with Ecr/Cr. FEcr should not be used to relate P reabsorption to hormones in CKD.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

FR-PO917

Attributes of the Walton-Bijvoet Nomogram at Normal and Reduced Glomerular Filtration Rate
Kenneth R. Phelps,
Darius Mason,
Sun J. Kang

Background: The serum P concentration ([P]) is the sum of Ecr/Cr and TRcr/Cr (urinary excretion and tubular reabsorption of P per volume of filtrate). In Bijvoet’s infusion studies, observed TRcr/Cr equaled maximum TRcr/Cr (Tm/GFR) at fasting fractional P excretion (FEcr) > 20%, as FEcr fell, (Tm/GFR) – TRcr/Cr rose. These observations were incorporated into a nomogram that derives Tmcr from [P]c and FEcr. Although the nomogram was based on data obtained at GFR > 40 mL/min, it is used to assess P reabsorption in CKD.

We examined this practice.

Methods: We collected fasting morning serum (s) and urine (u) from 30 patients with stages 3-4 CKD and 28 controls with MDRD eGFR > 60. We calculated Ecr/Cr, as [P]c/[cr], TRcr, as [P]c, Ecr, and FEcr as [P]c/[cr].[cr]. After ascertaining Tmcr/GFR from [P]c, we determined Ecr/Cr, TRcr/Cr, and FEcr/Cr. We performed group comparisons with the Mann-Whitney U test.

Results: In CKD, Ecr/Cr and FEcr were higher, and eGFR, TRcr/GFR, (Tmcr/GFR)/(TRcr/GFR), (TRcr/GFR)(Ecr/Cr), (Tmcr/GFR – TRcr/Cr), and (Tmcr/GFR)/(TRcr)(Ecr/Cr) were lower than in controls. In [P], was not different in the 2 groups. In CKD, FEcr was > 20% in 27/30 patients; mean (Tmcr/GFR – TRcr/Cr) and (Tmcr/GFR)/(TRcr)(Ecr/Cr) approximated 0 and 1, respectively.

Conclusions: The Walton-Bijvoet nomogram is accurate but unnecessary if (TRcr/Ecr/Cr) < 4. In this circumstance, Tmcr/GFR = TRcr/Cr – [P]c – Ecr/Cr, whether Ecr/Cr is increased by P influx or low Ccr. Use of the nomogram and calculation of TRcr/Cr, require the same variables. In CKD, the nomogram is accurate but unnecessary if (TRcr/Ecr/Cr) < 4.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

FR-PO918

Role of KHSRP and Pin1 in Mediating the Parathyroid Hormone Response in the Proximal Tubule
Rebecca Murray,
Michael Merchant,
Syed J. Khundmiri,
Barbara Clark,
Eleanor D. Lederer

Background: Parathyroid hormone (PTH) regulates the type IIa sodium-phosphate cotransporter (Npt2a), the major regulated proximal tubule phosphate transporter. In both the protein and mRNA level. We previously identified KHSRP as a PTH-responsive phospho-protein that binds Npt2a mRNA and may mediate its degradation. Pin1, a pep-tidyl-prolyl isomerase, is the upstream regulator of KHSRP function and localization.

Methods: We phosphorylated Pin1 binds KHSRP, promoting KHSRP phosphorylation and maintaining its cytosolic localization. We hypothesize that PTH stimulates Npt2a mRNA destabilization through PKA-mediated phosphorylation of Pin1.

Results: A 24-hr increase in Pin1 phosphorylation. IP of KHSRP followed by immunoblot for Pin1 showed that Pin1 associates with KHSRP under basal conditions, but not following 24-hr PTH or 8-hr treatment. Pre-treatment with H-89 blocked the PTH/8-Brc-induced dissociation. 24-hr PTH did not alter total expression of KHSRP, but stimulated its translocation to the nucleus.

Conclusions: We conclude that PTH-mediated destabilization of Npt2a mRNA likely involves PKA-mediated regulation of Pin1 and KHSRP activity. Funding provided by VA to EDL.
Funding: Veterans Administration Support

FR-PO919

Phosphate Depletion-Induced Metabolic Acidosis and Alkali Urine May Be Caused by Inappropriate Stimulation of Apical Cl/HC× Exchanger (Pendrin) in Mouse Kidney Type B Intercalated Cells (IC-B)
Yukiko Yasuoka,
Tomomi Oshima,
Yuuichi Sato,
Hiroshi Nonoughi,
Katsumasa Kawahara

Background: Mice treated with a low phosphate (P) diet can maintain normal levels of plasma P concentration via stimulation of bone reabsorption, but show hypercalcemia, hypercalciuria, and hypophosphatemia. Usually, the Ca-sensing receptor (CaSR) was found to be localized in the basolateral membrane of IC-B as well as in the thick ascending limb of Henle’s loop (Yasuoka et al, 2014). This study was aimed to determine whether hypercalcemia and/or hypercalciuria affect urine pH as expected in mice treated with either dietary P depletor or CaCl2-loading.

Methods: C57Bl/6J mice (10 wks, male) were divided into three groups: (1) normal diet (1% P, n=6), (2) low-P, (LP) diet (0.02% P, n=4), (3) CaCl2-loading (1% P, +1% Ca (CaCl2), n=6). All diets contain 1% Ca (CaCl2). On day 7, a 24-hr urine, blood, and kidney samples were collected.

Results: Serum and urinary Ca were markedly and significantly increased in the LP and CaCl2 groups [serum, 9.1 and 8.9 mg/dl; and urine, 2,400 and 2,140 μg/day], compared with control [serum, 7.6 mg/dl; urine, 105 μg/day]. Although serum pH decreased significantly and specifically to 7.25 and 7.20 in both groups, pH of the urine decreased to 5.6 (P < 0.05) in the CaCl2 group and, surprisingly, increased to 7.4 (P < 0.05) in the LP group (control, serum pH 7.35; urine pH 6.3). Kidney histology and immunohistochemistry showed that

Parameter

<table>
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<th>Controls*</th>
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<tr>
<td>Tmcr/GFR/[TRcr/Cr]</td>
<td>0.02 (0.01)</td>
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</table>

*Values are mean (SEM). P > 0.01 for all other comparisons.

Conclusions: FEcr is > 20% at (TRcr/Ecr/Cr) < 4. In this circumstance, Tmcr/GFR = TRcr/Cr – [P]c – Ecr/Cr, whether Ecr/Cr is increased by P influx or low Ccr. Use of the nomogram and calculation of TRcr/Cr, require the same variables. In CKD, the nomogram is accurate but unnecessary if (TRcr/Ecr/Cr) < 4.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
the IC-A-cell height and basolateral Cl⁻/HCO₃⁻ exchanger type 1 (AE1) staining significantly increased in the CaCl₂ group, whereas the IC-B-cell height and apical Pendrin and basolateral AE4/6 staining significantly increased in the LP group.

**Conclusions:** P₂-depletion induced metabolic acidosis may be due to imbalanced urinary alkalization and acid absorption caused by inappropriate stimulation of Pendrin and AE4 through the hypercalcemia-induced activation of the basolateral CaSR in IC-B.

**FR-PO920**

MUC1 Increases Renal Calcium Channel TRPV5 Activity to Enhance Calcium Reabsorption in a Galectin-3 Dependent Fashion

Mingzhu Nie, 1 Zhufeng Yang, 1 Jie Liu, 1 Denise K. Marciano, 2 Manoj S. Bal, 3 Pediatrics, UTSW Medical Center, Dallas, TX; 1Internal Medicine, UTSW Medical Center, Dallas, TX.

**Background:** MUC1 (MUC1) mutations cause autosomal dominant tubulo-interstitial kidney disease (ADTKD-MUC1), a condition similar to a nephropathy caused by Uromodulin (UMOD) mutations (ADTKD-UMOD). We previously showed that UOMD may protect against calcium-containing kidney stones by increasing TRPV5 cell surface abundance and tubular calcium reabsorption, which may decrease the risk of urinary supersaturation. The role of MUC1 in kidney is unclear. As UOMD and MUC1 share characteristics regarding disease phenotype, protein function, and structure, we examined the hypothesis that MUC1 enhances TRPV5 channel activity.

**Methods:** We expressed TRPV5 and MUC1 variants in HEK293 cells and studied TRPV5 current density by whole-cell patch-clamp recording.

**Results:** MUC1 coexpressed with TRPV5 resulted in a higher TRPV5 current density compared to mutant MUC1-C or control. MUC1 increased TRPV5 current density when applied extracellularly and required TRPV5 N-glycan for upregulation. Immunofluorescence imaging showed apical MUC1 expression along the distal nephron which is compatible with TRPV5 regulation in DCT. To test if MUC1 affects TRPV5 endocytosis, we tested if MUC1 upregulates TRPV5 in caveolin-1 deficient fibroblasts, as TRPV5 undergoes endocytosis via caveolin-1. While MUC1 alone had no effect, cotransfection of recombinant caveolin-1 with MUC1 restored TRPV5 upregulation by MUC1. The extracellular domain of MUC1 contains variable number tandem repeats (VNTRs) which bind galectin-3, a lectin involved in lattice formation of channels. Using galectin-3 siRNA, we identified galectin-3 as a prerequisite for TRPV5 upregulation by MUC1. This was confirmed by the inability of MUC1 lacking VNTR to upregulate TRPV5. In urine samples of patients with calcium-containing kidney stones we found less urinary MUC1 compared to control individuals.

**Conclusions:** MUC1 upregulates TRPV5 by extracellular lattice formation with TRPV5 N-glycan via galectin-3 which impairs TRPV5 channel endocytosis. These data are consistent with MUC1 contributing to protection against calcium-containing kidney stones.

**Funding:** NIDDK Support

**FR-PO921**

NCC Activity Modulation as a Mechanism for PTH Regulation of DCT Calcium Transport

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**Background:** The distal convoluted tubule (DCT) is a major site of both calcium and sodium transport. While altered DCT calcium handling is not required for thiazide-induced hypocalciuria, studies have documented increased DCT calcium reabsorption in response to thiazide administration. This suggests that DCT sodium transport does affect DCT calcium transport, while thiazide-induced hypocalciuria is due to a proximal effect, modulation of NCC activity may affect DCT calcium transport by TRPV5. Since parathyroid hormone (PTH) is known to increase TRPV5 activity and decrease NCC activity, we theorized that decreased NCC-mediated sodium reabsorption may contribute to the enhanced TRPV5 calcium transport, and while thiazide induced hypocalciuria is due to a proximal effect, modulation of NCC mediated sodium reabsorption may contribute to the enhanced TRPV5 calcium transport by PTH from a 45% increase (6.0 ±0.2 to 8.7 ±0.3 nmol/mg/min, n=4, p<0.01 compared to control) as well as a 20% increase (6.1 ±0.7 to 7.3 ±0.2 nmol/mg/min, n=4, p<0.01 compared to non-targeting treated groups)). Inhibition of PKC and PKA, the known pathways by which PTH acts upon TRPV5, resulted in further attenuation of the PTH effect.

**Conclusions:** Here, through the use of a cell model with native NCC and TRPV5 activity, we report that modulation of NCC activity does indeed contribute to the TRPV5 response to PTH, implying a role for hormonal modulation of NCC activity in distal calcium handling. Further study is needed to determine the mechanism for these findings.

**Funding:** NIDDK Support, Veterans Administration Support

**FR-PO922**

How Disruption of Distal Neprhon Salt Reabsorption Causes Calcium Wasting, Tubule Calcification and Skeletal Changes

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**Background:** Carbonic anhydrase II/sodium chloride co-transporter (NCC) and pendrin/NCC double knockout mice (dKO) develop salt wasting and are growth retarded. We propose that the disruption of sodium and chloride reabsorption in these mice causes phosphate and calcium wasting and leads to bone and skeletal anomalies.

**Methods:** Renal alterations that lead to distorted calcium and phosphate reabsorption and contribute to tubular calcification and growth retardation in the dKO mice were examined.

**Results:** dKO mice are volume depleted, exhibit kidney hyperperfusion, and have increased urinary calcium and phosphate excretion. These mice also exhibit skeletal anomalies and osteopenia and develop tubular calcium phosphate deposits. Parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) levels are normal in dKO mice. The urinary content of prostatic glandin E2 (PGE2) is significantly elevated, along with the expression of microsomal prostaglandin E synthase 1, while the sodium phosphate transporter IIa (NaPi-IIa) is downregulated, in the kidneys of dKO mice. qRT-PCR analyses revealed that the expression levels of NCC2 variants A and F were reduced while NCC2-B levels are increased in dKO animals. The latter changes lead to decreased NKCC2 activity in the medullary thick limb and increased calcium excretion, while NaPi-IIa downregulation reduces the reabsorption of phosphate in the proximal tubules. Placement of dKO mice on a high calcium diet or indomethacin corrected the above abnormalities. These results show an important role for salt wasting and dehydrogenase-induced PGE2 synthesis in renal calcium and phosphate excretion as well as in bone calcium mobilization.

**Conclusions:** Our studies suggest the presence of PGE2-mediated pathways, which are responsible for the response to PTH and VDI, to contribute to distal and volume contraction and independent of sodium and calcium wasting. PTH and FGF-23 activity can lead to anomalous mobilization and excretion of calcium and phosphate, and ultimately lead to skeletal abnormalities and growth retardation.

**Funding:** NIDDK Support, Veterans Administration Support

**FR-PO923**

Hypercalcemia-Induced Natriuresis Is Mediated by Endothelin-1 (ET-1) and TGF-β in the NCC Knockout Mice


**Background:** Acute hypercalcemia commonly increases urinary sodium and water excretions. We previously showed that targeting the calcium receptor CaSR does not affect sodium transport in the renal tubule (Loupy, et al., JCI, 2012), suggesting that the natriuretic effect of hypercalcemia does not involve CaSR. Since hypercalcemia increases the renal expression of ET-1, we tested if ET-1 mediates the natriuretic effect of hypercalcemia.

**Methods:** Forty-two 8 week-old, male C57Bl86 mice were studied. Osmostat minipumps were implanted to infuse PTH1-34 and maintain the concentration of PTH to normal range throughout the experiment. Hypercalcemia was induced by the oral administration of dihydroxytachysterol (DHT; 7.5mg/kg food/day). Eighteen mice were treated with an ET-1 receptor antagonist, macitentan (Maci, 27mg/kg BW/day), with or without DHT. Eight mice were treated with DHT for 3 day with cromakalim (Croma, 50mg/kg BW/day, intraperitoneal) alone or with the combination of hypercalcemia (5.0/1 vs 2.4/0.1 mmol/L control mice) and exhibited increased water and sodium excretion as compared to control mice (2.0 ± 0.1 vs 1.4 ± 0.1 mL/day and 46 ± 4 vs 36 ± 2 mmol Na+/mmol creatinine, respectively, p<0.01 for both). Mice treated with Maci+DHT had similar levels of hypercalcemia-induced natriuresis as mice treated with DHT only. However, mice treated with Maci+DHT showed no increase in urinary sodium excretion. Mice treated with Maci only were similar to control mice. A 3-4 fold increase in the renal level of ET-1 mRNA was observed in mice treated with DHT and Maci+DHT.

**Conclusions:** Hypercalcemia increases the renal production of ET-1, which is likely responsible for the increase of urinary sodium excretion. In contrast, ET-1 is not involved in hypercalcemia-induced polyuria.

**Funding:** Government Support - Non-U.S.
Methods: Primary human umbilical vein endothelial cells (HUVECs) were serum starved and treated with an intracellular buffer and preincubated with reverse-mode (Ca2+-influx) NCX1 inhibitors SN-6 or SEAO4000 and the general NCX1 inhibitor ORM-10103. NCX1 protein was knocked down using siRNA. ERK1/2 activation was determined by western blot. [Ca2+]i was measured in ECs loaded with the fluorescent Ca2+ indicator Fluo-4/NGW.

Results: We observed a significant increase (>2-fold; p=0.024) in the plasma of ERK1/2 pathway and extracellular Ca2+ was required for activation. Furthermore, inhibitors of reverse-mode NCX suppressed IS-induced activation of ERK1/2 in a time- and dose-dependent manner and attenuated IS-induced Ca2+ transients. Knock-out of NCX1 (the main NCX isoform in HUVECs) by siRNA confirmed the pharmacological data.

Conclusions: We propose that Ca2+-influx through reverse-mode NCX is required for IS-induced ERK1/2 activation. Given the known role of ERK1/2 activation in the expression of pro-inflammatory molecules such as COX-2 and VCAM-1 in ECs, reverse-mode NCX could be a novel target for improving endothelial function in CKD.

FR-PO925
Chronic Kidney Disease Impairs Myocardial Perfusion and Disturbs Calcium/Calcium Handling Melinda Verkaik,1, 2 Marjetten Oranje,1 Desiree Abdurrahim,1 Pieter M. Ter Wee,1 Etto C. Ertinga,1 Marc G. Vervloet,1 1 Dept of Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; 2 Dept of Physiology, Inst of Cardiovascular Research ICAr-UU, VU Univ Medical Center, Amsterdam, Netherlands; 2 Biomedical NMR, Dept of Biomedical Engineering, Eindhoven Univ of Technology, Eindhoven, Netherlands; On behalf of the NIGRAM Consortium.

Background: The molecular and microcirculatory changes that may underlie the increased prevalence of heart failure and cardiac mortality in CKD are ill-defined. We hypothesized that IS directly impairs both myocardial perfusion and disturbed cardiac diastolic and systolic function due to disturbed calcium fluxes across the myocardial sarcoplasmatic reticulum.

Methods: Eight week old C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery, and after 6 weeks mice were subjected to myocardial contrast echocardiography (MCE) to test myocardial perfusion. Cardiac function was assessed using Cine MRI. In single intact cardiomyocytes diastolic and systolic function, as well as intracellular Ca2+ transients were measured by fura-2 loaded cardiomyocytes.

Results: No difference was found between groups for heart weights over tibia length, neither for ejection fraction, cardiac output, end diastolic and systolic volume, and E/A ratio. The molecular and microcirculatory changes that may underlie the increased prevalence of heart failure and cardiac mortality in CKD are ill-defined. We hypothesized that IS directly impairs both myocardial perfusion and disturbed cardiac diastolic and systolic function due to disturbed calcium fluxes across the myocardial sarcoplasmatic reticulum.

Conclusions: CKD compromises both myocardial microvascular perfusion reserve, and systolic and diastolic function in cardiomyocytes. Calcium fluxes across the sarcoplasmic are disturbed, due to a reduced amount of phosphorylated phospholamban, which activates the sarcoplasmic reticulum Ca2+ channel SERCA.

FR-PO926
Recessive Mutations in SLC34A1 (NaPi-IIa) as a Cause of Idiopathic Infantile Hypocalcemia Karl P. Schlingmann,1 Birgitta Kranz,1 Martin Kaufmann,1 Elisabeth A.M. Cornelissen,1 René J. Bindels,1 Asaf Vivante;1 Robert L. De Vries,1 Elithan N. L. Verkaik,1 1 Dept of Physiology, Inst of Cardiovascular Research ICAr-UU, VU Univ Medical Center, Amsterdam, Netherlands; 2 Biomedical NMR, Dept of Biomedical Engineering, Eindhoven Univ of Technology, Eindhoven, Netherlands; On behalf of the NIGRAM Consortium.

Background: Infantile hypocalcemia (IHH) is characterized by severe hypocalcemia with failure to thrive, vomiting, dehydration, and nephrocalcinosis. Initially mutations in CYP24A1 encoding the vitamin D catabolizing enzyme 25-hydroxyvitamin D2-24-hydroxylation were discovered that lead to an accumulation of active 1,25(OH)2D and subsequent hypocalcemia and hypercalciuria.

Methods: In a subset of IHH patients without mutations in CYP24A1 we now performed a positional candidate gene approach in order to identify a second IHH gene locus. Results: We identified a shared homozygous interval on chromosome 5q35 with a maximum LOD score of 6.91. The sequence analysis of SLC34A1 encoding proximal-tubular sodium-phosphate co-transporter NaPi-IIa revealed recessive mutations in the 4 index cases as well as in 18 additional sporadic IHH patients. The clinical reevaluation revealed renal phosphate wasting but no signs of rickets. Functional studies of mutated NaPi-IIa in Xenopus oocytes and OK cells demonstrated a disturbed membrane trafficking as well as a loss of phosphate transport activity. The reexamination of Slc34a1 knockout mice highlighted the critical role of phosphate depletion and FGF-23 suppression. In affected patients, clinical and laboratory findings persist after omitting vitamin D prophylaxis but rapidly respond to phosphate supplementation.

Conclusions: Therefore, an early differentiation between CYP24A1 (24-hydroxylation) and SLC34A1 (NaPi-IIa) defects appears crucial for a effective therapy in children with IHH.

FR-PO927
Identification of SLC41A3 as a Novel Player in Renal Magnesium Homeostasis Jeroen H.F. De Baati, Anke Lameris, René J. Bindels, Joost Hoenderop. Dept of Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Hypomagnesemia is a common clinical cause of muscle cramps, epilepsy and cardiac arrhythmias. In the distal convoluted tubule (DCT) of the kidney, transcellular reabsorption of Mg2+ regulates the body Mg2+ balance by determining the final urinary Mg2+ excretion. In the DCT, Mg2+ is reabsorbed from the pro-urine via the apical Mg2+ channel TRPM6. Until now, the basolateral Mg2+ extrusion mechanism in DCT is still unknown, but recent findings suggest that proteins of the SLC41A family may contribute to cellular Mg2+ extrusion. The aim of this study was, therefore, to investigate the role of SLC41A3 Mg2+ homeostasis using the Slc41a3 knockout mouse.

Methods: The Slc41a3 knockout mice were studied by serum and urinary electrolyte analysis. To determine the effect of Slc41a3 on intestinal Mg2+ absorption, the Mg2+ absorption capacity was measured using the stable [112Mg] isotope.

Results: Tissue expression screening was performed by RT-PCR, showing that Slc41a3 is the only SLC41 isoform with enriched expression in DCT compared to other segments in the kidney. Interestingly, serum and urinary electrolyte determinations demonstrated that Slc41a3 knockout mice suffer from hypomagnesemia due to renal Mg2+ wasting. Serum and urinary Na+, K+ and Ca2+ levels were not affected. Mg2+ uptake was similar in wild type and knockout mouse, although Slc41a3 knockout animals exhibited increased intestinal expression of Mg2+ transporters Trpm6 and Slc41a1. Remarkably, 10% of the Slc41a3 knockout mice developed severe unilateral hydropnephrosis, as demonstrated by the presence of transitional epithelium lining the fluid cavity. Feeding the Slc41a3 knockout mice a low Mg2+ diet may have instigated the formation of hydropnephrosis.

Conclusions: In conclusion, SLc41A3 was established as a new important factor for renal Mg2+ handling, suggesting that Slc41a3 is the basolateral Mg2+ extrusion mechanism in DCT. These mice provide the first mouse model with isolated hypomagnesemia, without concomitant electrolyte disturbances. In the future, SLc41A3 mutations should be considered in patients with unilateral hydropnephrosis and/or hypomagnesemia.

Funding: Government Support - Non-U.S.

FR-PO928
Diuretic Inulin Supplementation Stimulates Magnesium Absorption in Patients with Proton Pump Induced Hypomagnesemia Jeroen H.F. De Baati,1 Mark Wilhelm Hess,2 Joost Hoenderop,2 Joost P.H. Drenth,3 René J. Bindels,3 1 Dept of Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2 Dept of Gastroenterology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: Hypomagnesemia is a common and severe side effect of patients using proton pump inhibitors (PPI). For the first time we provide a successful alternative for oral Mg2+ supplementation. Methods: This clinical trial prospectively determined serum Mg2+ concentrations in 133 patients using PPIs. Under maintenance of PPIs, eleven identified cases of PPI-induced hypomagnesemia were exposed to 2 repetitive dietary suppletions with inulin for 14 days was washed out and compared to 10 healthy non-PPI users. The primary endpoint was serum Mg2+. Secondary endpoints were serum Ca2+, K+, and Na+ levels.

Results: Hypomagnesemia is present in 13% of the study population. Dietary supplementation with inulin significantly enhanced mean serum Mg2+ levels by +0.1 mmol/L in patients and Ca2+ by +0.1 mmol/L in healthy controls. Moreover, in patients with PPIH concomitant treatment effects were observed for serum Ca2+ (+ 0.09 mmol/L) and serum K+ (+ 0.07 mmol/L), no effects were seen on serum Na+. Patients with PPIH had adequately renal excretion of Mg2+ and Ca2+, which increased due to inulin following increases in serum levels. Additionally, two SNPs in TRPM6 (rs3770425 and c.2274024A) were identified that cause a 4.75 times higher risk to develop hypomagnesemia.

Conclusions: Inulin fibers are a promising prebiotic treatment strategy to treat intestinal- and renal-caused hypomagnesemia. For the first time we provide a successful alternative for oral Mg2+ supplementation.

Funding: Government Support - Non-U.S.

FR-PO929
The Distal Convoluted Tubule Plays a Key Role in Tacrolimus-Induced Hypomagnesemia and Hypercalcemia Rebecca A. Laerle,1 Sabina K. Jelen,2 Chao-Ling Yang,1 Joost Hoenderop,2 René J. Bindels,2 David H. Ellison,1 1 Div of Nephrology & Hypertension, Oregon Health and Science Univ, Portland, OR; 2 Radboud Inst for Molecular Life Sciences, Radboud Univ Medical Center, Nijmegen, Netherlands; 3 Renal Section, Portland VA Medical Center, Portland, OR.

Background: The immunosuppressive drug tacrolimus, used to prevent graft rejection, often leads to hypomagnesemia and can also cause hypercalcemia. A decrease in renal Mg2+ and Ca2+ reabsorption is thought to be involved, but the molecular mechanisms are unclear. Tacrolimus requires a binding partner, FKBP12, to inhibit its canonical target, calcineurin. We generated a mouse model in which FKBP12 can be deleted along the whole body.

Results: We found that the distal convoluted tubule (DCT) was knockdown using siRNA. ERK1/2 activation was determined by western blot. 

Conclusions: Therefore, an early differentiation between CYP24A1 (24-hydroxylation) and SLC34A1 (NaPi-IIa) defects appears crucial for a effective therapy in children with IHH.

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

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580A
neprin (KS-FKBPI2). We then tested if either FKBPI2 disruption or calcineurin inhibition alleviated the nephrotoxic effects on the mRNA abundance of renal ion transport proteins leading to hypomagnesemia and hypercalciuria.

**Methods:** KS-FKBPI2 mice were generated using an inducible CRE/LOX system driven by the Pax8 promoter. Mice were treated with doxycycline (KS-FKBPI2) or vehicle (control). Mice were fed a high phosphate diet (3%) for 24 days on plasma [Mg^2+], urinary Ca^2+ excretion, and mRNA abundance of renal proteins involved in ion transport using metabolic cages, colorimetric assays and qRT-PCR.

**Results:** As expected, tacrolimus caused hypomagnesemia and hypercalciuria in control mice, which was not the case in KS-FKBPI2 mice. Compared to KS-FKBPI2 mice, tacrolimus reduced the mRNA abundance of proteins involved in Mg^2+ and Ca^2+ transport by the distal convoluted tubule (DCT) including, TRPM6, calbindin-28K and the Sodium Calcium Exchanger-1. In contrast, tacrolimus had no effect in KS-FKBPI2 mice (p<0.05 for all comparisons). The abundance of mRNA encoding Claudin 16 and 19, thick ascending limb (TAL) proteins involved in Mg^2+ and Ca^2+ handling, were not affected by tacrolimus treatment in either group.

**Conclusions:** Tacrolimus reduces the abundance of mRNA encoding proteins involved in Mg^2+ and Ca^2+ transport by the DCT. These effects require FKBPI2, suggesting that calcineurin inhibition is essential. The results show that the DCT plays a key role in these troubling side effects.

**Funding:** NIDDK Support, Private Foundation Support

**FR-P0930**

**Regulation of Magnesium Reabsorption and Transient Receptor Potential M6 Channel Activity by Protein Kinase A Signaling** 

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**Background:** The transient receptor potential melastatin type 6 (TRPM6) epithelial channel participates in Mg^2+ reabsorption in the distal convoluted tubule. Using patch clamp, cell surface biotinylation and Total Internal Reflection Fluorescence (TIRF) live cell imaging of transfected HEK293 cells, TRPM6 channel activity was measured.

**Results:** Urinary Mg^2+ excretion was increased (~1.7-fold) in AC3 deleted mice compared to controls where as serum Mg^2+ concentrations were not different. Renal TRPM6 mRNA levels were increased by ~3-fold, Mg^2+ excretion was increased by ~2-fold in AC3 deleted mice. Serum Mg^2+ was significantly lower in AC3 deleted animals for 7 days on the low Mg^2+ diet compared to the control animals. In HEK293 cells, it was demonstrated that cAMP signaling rapidly potentiates the activity of TRPM6 by promoting its accumulation at the plasma membrane and by increasing its single channel conductance. Comparison of electrophysiological data between the phosphorylation-deficient S1252A and phosphomimetic S1252D mutants suggests that phosphorylation at this intracellular residue participates in the observed stimulation of channel activity.

**Conclusions:** These data support a physiologically relevant magnesiumotropic role of cAMP signaling in the direct stimulation of Mg^2+ transport in the kidney membrane trafficking and function of TRPM6 ion channels in the distal convoluted tubule.

**Funding:** Government Support - Non-U.S.

**FR-P0931**

**Renal Handling of Magnesium in Individuals on Long Term Proton Pump Inhibitor Therapy** 

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**Background:** Proton Pump Inhibitors (PPI) are a group of very commonly used medication. Recently the US-FDA has issued warning regarding the risk of high serum magnesium are associated with an increased risk of SCD. Although serum magnesium levels showed a negative correlation with the duration of PPI therapy (r = 0.502; p < 0.01). The FE—Mg of the PPI group is significantly reduced suggesting increased renal conservation of magnesium in order to maintain near normal serum levels.

**Conclusions:** Compensatory renal conservation of Mg occurs in long term PPI receiving patients. Thus if patients with impaired renal handling of Mg (diabetes; CKD or those on diuretics) receive long term PPI therapy they might possibly be at a greater risk of clinically significant hypomagnesemia.

**FR-P0932**

**Magnesium Prophylaxis against Phosphate-Induced Kidney Injury in Mice with Uninephrectomy** 

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**Takayuki Hamano,** 

**Isao Matsui,** 

**Akihiro Shimomura,** 

**Yasuo Kusunoki,** 

**Takayuki Hamano,** 

**Yusuke Sakaguchi.** 

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**Background:** We have recently reported that the risk of progression of CKD associated with high serum phosphate (P) was significantly attenuated in patients who had higher serum magnesium (Mg) levels (Kidney International in press), although the causality remains unclear. Here we studied whether Mg protects against kidney injury induced by P overload.

**Methods:** Eight-week-old C57BL6 mice underwent uninephrectomy and were divided into 4 groups: 1. high P (1.25% P)-normal Mg (0.05% Mg) diet; 2. high P (1.25%) -low Mg (0.005% Mg) diet, 3. low P (0.2%) -normal Mg (0.05% Mg) diet; 4. low P (0.25%) -low Mg (0.005% Mg) diet. Twenty-four-hour urine samples were collected for the measurement of daily urinary excretion of P. After 6 weeks of dietary intervention, mice were sacrificed and kidney tissues were harvested for histological analysis and mRNA quantification.

**Results:** Mice fed with the high P-low Mg diet showed severe tubular injury, interstitial fibrosis, and a marked accumulation of F4/80 positive cells in the interstitium; these changes were largely attenuated in mice in the high P-normal Mg diet group. Creatinine clearance in the high P-low Mg diet group was significantly lower than that in the high P-high Mg diet group (0.04±0.02 vs 0.27±0.14; p<0.05). Both TGF-β/Smad and TNF-α mRNA expression levels in the whole kidney were upregulated in the high P-low Mg diet group compared with those in the high P-normal Mg diet group. No histological evidence of kidney injury was found in both of the low P groups. Since urinary P excretion in the high P-low Mg diet group was equivalent (at 3 weeks) to or even lower (at 6 weeks) than that in the high P-normal Mg diet group, it is unlikely that the exacerbation of kidney injury in the high P-low Mg diet group was owing to an increased intestinal absorption of P.

**Conclusions:** Low Mg diet aggravates phosphate-induced kidney injury. Mg may be beneficial to reduce the phosphate toxicity to the kidney.

**FR-P0933**

**Low Serum Magnesium Is Associated with an Increased Risk of Death from Coronary Heart Disease and Sudden Cardiac Death** 

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**Robert Zietse,** 

**Oscar Franco,** 

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**Bruno H. Stricker,** 

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**Background:** Low serum magnesium has been associated with cardiovascular disease (CVD) mortality in population-based studies. However, results are conflicting and it remains unclear if this effect is mediated by an effect on atherosclerosis or heart rhythm.

**Methods:** We examined the relationship between serum magnesium and CVD mortality in 9,820 participants aged ≥ 45 years from the population-based Rotterdam Study. We used multivariable-adjusted Cox proportional hazard regression models and divided serum magnesium into quartiles, with the second and third quartile combined as reference group.

**Results:** During a median follow-up of 8.7 years, 780 participants died of CVD, including 431 deaths from coronary heart disease (CHD) and 217 sudden cardiac deaths (SCD). Low serum magnesium (0.80 mmol/L) was associated with an increased CVD mortality risk (HR 1.25, 95%CI 1.10-1.41) and SCD (HR 1.68, 95%CI 1.20-2.37). Low serum magnesium was associated with an increased QT-interval, due to a strong effect on heart rate (RR interval -7.7 ms, 95%CI -14.7 to -0.7), but additional adjustment for heart rate did not change the association with SCD. Low serum magnesium was associated with increased intima media thickness (0.01 mm, 95%CI 0.004-0.020), and this explained part of the effect of magnesium on CVD mortality. Notable, high serum magnesium (≥ 0.89 mmol/L) was also associated with an increased risk of death from SCD (HR 1.50, 95%CI 1.05-2.16), but reduced risk of death from CHD (HR 0.64, 95%CI 0.43-0.95).

**Conclusions:** Low serum magnesium is associated with an increased risk of death from SCD, which is partly explained by an effect on atherosclerosis. Both low and high serum magnesium are associated with an increased risk of SCD. Although serum magnesium strongly affects heart rate, this did not explain the relationship between serum magnesium and SCD.
FR-PO934
Oral Magnesium Supplementation Improves Serum Calcium Propensity in Chronic Kidney Disease Stage 3-4
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Background: In previous experimental studies of chronic kidney disease (CKD) magnesium has been shown to improve vascular calcification. Serum calcium propension was measured using the T50 analysis which has been shown to predict all-cause mortality among patients with chronic kidney disease (CKD) stage 3-4.

Methods: In a proof-of-concept randomized placebo-controlled double-blinded trial of placebo versus slow-release magnesium oxide at two different doses (360 mg daily or 360 mg twice daily) for eight weeks in 34 subjects with CKD stage 3-4 and plasma magnesium <0.82 mmol/L, T50 was measured to examine whether magnesium supplementation affects serum calcification propensity.

Results: In subjects randomized to magnesium 360 mg twice daily (n = 11) plasma magnesium increased by 0.11 mmol/L (confidence interval: 0.05 - 0.17, p = 0.003) and T50 increased by 40 minutes (confidence interval: 18 - 63, p = 0.003) after eight weeks of treatment (Figure 1), while there were no changes in plasma phosphate, calcium or parathyroid hormone. There were no significant changes in T50 in the placebo (n = 12) or magnesium 360 mg once daily (n = 11) groups.

Conclusions: Oral magnesium oxide 360 mg twice daily improves serum calcification propensity in CKD stage 3-4 after eight weeks of treatment. Larger, long-term trials are needed to assess whether this translates into reductions in vascular calcification (e.g. coronary artery calcium score or pulse wave velocity) and cardiovascular endpoints.

FR-PO935
The Novel NaPi-IIb Inhibitor ASP3325 Does Not Mitigate Hyper-phosphatemia in Chronic Kidney Disease Patients on Hemodialysis
Tobias F. Larsen, Chiasso Kameoka, Ikumi Nakajo, Yuta Tanishi, Satoshi Yoshida, Tadao Akizawa, Ronald Alfonso Smulders, Astellas Pharma Europe BV, Leiden, Netherlands; 1 Astellas Pharma Inc., Tokyo, Japan; 2 Dept of Nephrology, Showa Univ School of Medicine, Tokyo, Japan.

Background: The sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) is considered an important mediator of active inorganic phosphate (Pi) absorption and therefore recognized as a target molecule for treatment of hyperphosphatemia. We evaluated the pharmacological characteristics of ASP3325, a novel NaPi-IIb inhibitor being developed to treat hyperphosphatemia in chronic kidney disease (CKD).

Methods: The inhibition ratio of P-Pi uptake during ASP3325 (0.03-1000 nmol/L) treatment was measured in HEK293 cells stably expressing rat or human NaPi-IIb. To assess the competitive inhibition of NaPi-IIb to intestinal Pi absorption, ASP3325 and 32P-Pi were orally administered in sequence, and then serum 32P-Pi levels were measured. For normal rats, an ASP3325 containing-diet was provided for three days and the rate of Pi excretion in urine was measured on the final day. For rats with adenine-induced renal failure, an ASP3325 containing-diet was provided for two weeks after which plasma levels of phosphorus were measured.

Results: ASP3325 inhibited 32P-Pi uptake with an IC50 value of 7.0 mmol/L in HEK293 cells expressing human NaPi-IIb and an IC50 value of 88 mmol/L in HEK293 cells expressing rat NaPi-IIb. In normal rats, oral administration of ASP3325 at 1 and 3 mg/kg significantly reduced the area under the concentration curve of serum 32P-Pi levels from 0 to 30 min post oral administration. ASP3325 (0.001%-0.01%) reduced urinary Pi excretion dose-proportionally, and treated with 0.01% ASP3325 reduced excretion by 31.2% compared to vehicle (P=0.01). In rat with adenine-induced renal failure, ASP3325 (0.001%-0.01%) exhibited a dose-related reduction in plasma levels of phosphorus. Following two weeks of treatment, plasma level of phosphorus in the vehicle-treated group was 11.43 ± 0.66 mg/dL, and in the 0.01% ASP3325-treated group was 6.61 ± 0.47 mg/dL (P=0.01).

Conclusions: ASP3325 inhibited NaPi-IIb-mediated Pi transport and decreased plasma levels of phosphorus in rats with renal failure as well as urinary Pi excretion in normal rats. ASP3325 might therefore be a novel candidate for the treatment of hyperphosphatemia in humans.

FR-PO936
Novel NaPi-IIb Inhibitor ASP3325 Inhibits Phosphate Absorption in Intestine and Reduces Plasma Phosphorus Level in Rats with Renal Failure
Kazuhiro Terai, Yoshiharu Tomura, Showa University, Tokyo, Japan.

Background: The sodium-dependent phosphate co-transporter type 2b (NaPi-IIb) is considered an important mediator of intestinal inorganic phosphate (Pi) absorption and therefore recognized as a target molecule for treatment of hyperphosphatemia. We evaluated the pharmacological characteristics of ASP3325, a novel NaPi-IIb inhibitor being developed to treat hyperphosphatemia in chronic kidney disease (CKD).

Methods: The inhibition ratio of P-Pi uptake during ASP3325 (0.03-1000 nmol/L) treatment was measured in HEK293 cells stably expressing rat or human NaPi-IIb. To assess the competitive inhibition of NaPi-IIb to intestinal Pi absorption, ASP3325 and 32P-Pi were orally administered in sequence, and then serum 32P-Pi levels were measured. For normal rats, an ASP3325 containing-diet was provided for three days and the rate of Pi excretion in urine was measured on the final day. For rats with adenine-induced renal failure, an ASP3325 containing-diet was provided for two weeks after which plasma levels of phosphorus were measured.

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Conclusions: ASP3325 inhibited NaPi-IIb-mediated Pi transport and decreased plasma levels of phosphorus in rats with renal failure as well as urinary Pi excretion in normal rats. ASP3325 might therefore be a novel candidate for the treatment of hyperphosphatemia in humans.

FR-PO937
Statin Therapy Reduces Phosphate Levels in Dialysis Patients: Results from the Epidemiological Vitamin K Italian Study (VIKI Study)
Maria Fusaro, Sandro Giannini, Marianna Noale, Giovanni Tripipi, Piergiorgio Messa, Andrea Aghi, Nicola Veronesi, Maurizio Gallieni, Sabina Zambon, CNR, Padua; 2 Univ of Padua; 3 Ospedale Maggiore Policlinico, Milan; 4 CNR, Reggio Calabria; 5 San Carlo Borromeo, Milan.

Background: Statin therapy is the mainstay approach to reduce VC and prevent CV events in patients with dyslipidemia. The aim of this study was to investigate an association between statin therapy and plasma phosphate levels in patients on hemodialysis recruited in the VIKI Study.

Methods: The VIKI Study is a multicenter, cross-sectional study in 387 CKD patients on hemodialysis from 18 hospitals in Italy. We determined plasma levels of vitamin 25(OH)D, vitamin K, osteocalcin (bone-Glia-Protein or BGP), matrix-Glia-protein (MGP) and routine biochemistry. Assessment of VC was centralized (Witteman’s method: by measuring the length of calcific deposits along the anterior and posterior wall of the aorta). Plasma phosphate levels were dichotomized according to the median value (≥4.6 vs <4.6 mg/dL).

Results: 33% of the VIKI Study population (n=126) was on statin therapy. Patients on simvastatin had significantly lower HDL cholesterol (meanSD: 40.4±11.1 vs 43.5±13.4 mg/dL, p=0.0473) and higher plasma triglyceride levels (median: 164.0 vs 142.0 mg/dL, p=0.0041) compared to those not on statin. Plasma phosphate levels were significantly lower in patients on statin therapy (4.57±1.2 vs 4.86±1.33 mg/dL, p=0.0365). The analysis of the vitamin K components showed that patients on statin therapy had higher plasma MK7 levels (median: 1.16 vs 0.84 ng/mL, p=0.0241), while concentrations of vitamin 25(OH)D were significantly reduced (median: 26.0 vs 30.7 ng/mL, p=0.0198). In a multivariate analysis adjusted for BMI, angina, LDL, BGP and antibiotics, statin therapy was significantly associated with lower plasma phosphate levels (OR 0.61, 95%CI 0.38-0.98, p=0.0411), while BMI (OR 1.06, 95%CI 1.01-1.12, p=0.0250) and serum BGP levels ≥ 182 mcg/L (OR 1.58, 95%CI 1.01-2.48, p=0.0472) were associated with higher phosphate concentrations.

Conclusions: To our knowledge this is the first evidence of an association between statin therapy and reduced plasma phosphate levels in CKD patients.

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Underline represents presenting author.
582A
Epidemiology of Kidney Stone Disease in Icelandic Children 1985-2013
Solborg E. Ingvarsdottr, Olafur S. Indridason, Runolfur Palsson, Vidar O. Edvardsson, Children’s Medical Center, Landspitali – The National Univ Hospital of Iceland; Div of Nephrology, Landspitali – The National Univ Hospital of Iceland, Faculty of Medicine, Univ of Iceland, Reykjavik, NA, Iceland.

Background: The aim of the study was to examine time trends in the prevalence and incidence of kidney stone disease in Icelandic children and adolescents over the past 3 decades.

Methods: Computerized databases of all major hospitals and medical imaging centers in Iceland covering the years 1985 to 2013, were searched for ICD, radiology and surgical procedure codes indicative of kidney stones for subjects aged 0-18 years of age. Incidence was calculated for the time periods 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009 and 2010-2013, based on population information for Icelandic children in these years. Prevalence was calculated for the years 1999-2013.

Results: From 1985 to 2013, there were 186 incident patients, 110 (59%) of whom were female. Median (range) age at diagnosis was 15.0 (2.1-17.9) years. The annual incidence increased from a mean of 3.7/100,000 in the first 5 years to 11.0/100,000 in the years 1995-2004, but decreased thereafter and was 7.8/100,000 in 2010-2013. This trend was more pronounced in boys, for whom the incidence was 4.7/100,000 in the first time period, 11.0/100,000 during 2000-2004 and only 2.4/100,000 in 2010-2013. The incidence for girls increased from 2.7/100,000 in the first time period to 14.2/100,000 in 1995-1999 and has since then leveled off and was 13.6/100,000 in 2010-2013. The mean annual prevalence of kidney stone disease in 1999-2013 was 44/100,000 for boys and 51/100,000 for girls.

Conclusions: The incidence rise observed and current incidence of kidney stones in Icelandic children is similar to that recently reported in the USA. A significant incidence increase was observed for females in the early 1990’s but this did not trend downwards in boys and remained stable in girls. These trends can not be adequately explained and warrant further study.

Funding: Government Support - Non-U.S.

Kidney Stone Recurrence in Icelandic Children
Solborg E. Ingvarsdottr, Olafur S. Indridason, Runolfur Palsson, Vidar O. Edvardsson, Children’s Medical Center; Div of Nephrology, Landspitali – The National Univ Hospital of Iceland; Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland.

Background: The 5-year recurrence rate of kidney stones in adults is in the range of 30-50%. No population-based data are available on the recurrence of childhood kidney stone disease. The purpose of this study was to examine the recurrence rate of stone disease in Icelandic children.

Methods: Patients were identified by searching computerized databases of all the major hospitals and the only freestanding radiology clinic in Iceland for diagnostic, radiology and surgical codes indicating kidney stones in 1985-2013. We subsequently examined medical records of patients with kidney stone disease for information on stone recurrence. A recurrent stone event was defined as radiologic signs of a new stone or a new episode of flank pain and hematuria. The Kaplan-Meier method was used to assess stone-free survival and the log-rank test to compare groups.

Results: We identified 186 children with stone disease during the study period. There were 76 boys with a median (range) age of 14.6 (0.2-17.9) years and 110 girls aged 15.4 (8.1-17.9) years. The follow-up time was 13.0 (0-36) years. A total of 67 children (37%) experienced a second stone event, at a median of 1.9 (0.9-18.9) years after the initial diagnosis. The recurrence rate was 26%, 35%, 41% and 46% after 5, 10, 15 and 20 years of follow-up, respectively. There was no significant difference in recurrence rate between boys and girls (p=0.24) and those aged under and over 13 years at diagnosis (p=0.56), but a significant difference between patients diagnosed in 1985-1994, 1995-2004 and 2005-2013 was observed, with a 5-year recurrence rate of 9%, 24% and 8% respectively (p=0.002).

Conclusions: In our population-based pediatric study, the recurrence rate of kidney stones is similar to that reported in adults. Further, the rate of recurrence appears to be increasing as has recently been reported for the incidence of childhood stone disease. Increased recurrence rate may be related to improved diagnosis and documentation of stone events and/or environmental factors affecting urinary lithogenicity.

Funding: Government Support - Non-U.S.

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Results: We identified 186 children with stone disease during the study period. There were 76 boys with a median (range) age of 14.6 (0.2-17.9) years and 110 girls aged 15.4 (8.1-17.9) years. The follow-up time was 13.0 (0-36) years. A total of 67 children (37%) experienced a second stone event, at a median of 1.9 (0.9-18.9) years after the initial diagnosis. The recurrence rate was 26%, 35%, 41% and 46% after 5, 10, 15 and 20 years of follow-up, respectively. There was no significant difference in recurrence rate between boys and girls (p=0.24) and those aged under and over 13 years at diagnosis (p=0.56), but a significant difference between patients diagnosed in 1985-1994, 1995-2004 and 2005-2013 was observed, with a 5-year recurrence rate of 9%, 24% and 8% respectively (p=0.002).

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Funding: Government Support - Non-U.S.

Assessment of Health-Related Quality of Life (HRQoL) in Rare Kidney Stone Formers (RKSF)
Frank Modularitz, Alicia Meck, David S. Goldfarb, Medicine, New York Univ School of Medicine, New York, NY; Medicine, Mayo Clinic, Rochester, MN.

Background: Assessment of HRQoL in RKSF is important for following disease course and evaluating treatments. We previously showed that SF with cystinuria reported lower SF than non-cystinuric subjects 5.5 years ago. We now report on population-based assessment of HRQoL in the Rare Kidney Stone Consortium (RKSC) Registries, to be followed prospectively.

Methods: Patients were enrolled from 3 RKSC registries: primary hyperoxaluria (PH), cystinuria and Dent disease. In adults, HRQoL is measured using the SF-36v2 and in children the SF-10. Participants chose between online assessment or paper-based questionnaire. Results are calculated as norm-based scores (NBS) based on US Standard Population = 50.

Results: 280 participants were enrolled; 200 adults, 80 children; 163 males, 118 females. Mean age was 34 years: for adults 44y and children 10y. 189 adults and 68 children were included in the baseline analysis: PH: 145, cystinuria: 71, Dent: 41. Domain scores for children are presented without cystinuria (n=10). For all participants, SF-36 NBS and summary scores for adults are below 50, except for the domain Physical Functioning (mean = 51.2). The lowest total domain score was in General Health with 45.8 ± 11.8. Adult and significantly different results in Role-Physical, Bodily Pain, Vitality, Social Functioning, Mental Health and Mental Component Score based on disorder. The lowest score was found in cystinuria for General Health (mean = 43.9). The summary scores for Physical Health (PHS) and Psychosocial (PSS) in children were 47.4 ± 14.2 and 51.80 ± 9.6 with

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583A
FR-PO943
Supplemental Calcium Increases the Growth Rate of Renal Calculi in Stone Formers

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Background: Though dietary calcium is associated with a decreased risk of stone formation, post-menopausal women supplemented with calcium have an increased risk of urinary tract stones. Prior studies have examined the effect of supplemental calcium on the risk of passing symptomatic stones but its role in the pathogenesis of stone formation is not clear.

Methods: We retrospectively identified 6059 patients with a history of urolithiasis. Eligible patients had 2 or more CT scans greater than 30 days but less than 2 years apart during the time of the stone event. For those on no supplementation, the most recent urine sample was used. Of these, 626 patients met the criteria: 195 on calcium, 127 on vitamin D only, and 104 on none. Patients on calcium received 46mg/d of 2703IU vitamin D3/d or 5607IU D2/d and patients on vitamin D only received 3085 IU D3/d or 6296 IU D2/d. Urine calcium was calculated as the sum of the maximum of all stones on CT, and rate of stone growth was calculated by the change in consecutive stone burdens divided by the elapsed time between scans.

Results: Stone composition was similar among all groups: 65.5% calcium oxalate, 20.0% calcium phosphate, and 11.8% uric acid. Stone formation rate in mm/year: standard deviation was 7.8±10.8 for calcium group, 3.3±11.4 for vitamin D, and 4.49±13.8 for none. Those supplemented with calcium had a higher rate of stone formation than those supplemented with vitamin D or none, p<0.01. Serum calcium was statistically significant when controlling for serum PTH and calcium on multiple logistic regression. BMI, gender, age and dose of calcium were not significantly associated with stone formation rate while dose of vitamin D had an inverse association, p=0.0490.

Conclusions: Supplementation with calcium was associated with a significant increase in stone growth rate in stone formers. Vitamin D supplementation showed no added risk and may potentially have a protective effect. Though the pathophysiology is unclear, these data suggest patients at risk of stone formation should be cautious of supplementation use.

Funding: Private Foundation Support

FR-PO944
Effects of Calcium and Vitamin D Supplementation on Known Stone Formers

Felicity T. Enders, John R. Asplin, Deepa A. Malieckal, David S. Goldfarb. Internal Medicine, Div of Nephrology, NY Harbor VA Healthcare System, New York, NY; Internal Medicine, Div of Nephrology, New York Univ School of Medicine, New York, NY; *Internal Medicine, Div of Nephrology, NY Harbor VA Healthcare System, New York, NY; †Health Sciences Research, Div of Biomedical Statistics & Informatics, Mayo Clinic, Rochester, MN; ‡Liholink Corp, Chicago, IL.

Background: While high dietary calcium has protective effects against kidney stone formation, the effect of supplementation with calcium and vitamin D on the risk of kidney stone formation remains unclear. Post-menopausal women supplemented with calcium have an increased risk of urinary tract stones; however, there is conflicting evidence for the effects of supplementation on urinary excretion of calcium.

Methods: We identified 6059 patients with a history of urolithiasis by CT scan, 2061 of which had 24-hour urine collections before and after starting supplementation. For patients on no supplementation, the most recent urine was used. A total of 1486 patients were supplemented with calcium, 417 with vitamin D only, and 158 with no supplementation. Patients on calcium received an average of 600mg/d of 2702IU vitamin D3/d or 5678IU D2/d and patients on vitamin D only received 3005IU D3/d or 6307IU D2/d.

Results: Stone composition did not differ among groups: 70.0% calcium oxalate, 16.6% calcium phosphate, and 10.8% uric acid stones. There was a significant decrease in urinary calcium excretion in patients supplemented with calcium (p=0.021) and vitamin D (p=0.011) and significant decreases in urinary oxalate in those supplemented with calcium (p=0.0001) and vitamin D (p=0.0001). No differences were seen in the amount of change between supplemented groups for any urinary excretion values.

<table>
<thead>
<tr>
<th>Calcium</th>
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</tr>
<tr>
<td>serum Vitamin D (ng/mL)</td>
<td>3.7</td>
<td>7.6</td>
<td>-1.2</td>
</tr>
<tr>
<td>serum PTH (pg/mL)</td>
<td>8.1</td>
<td>4.3</td>
<td>-3.3</td>
</tr>
<tr>
<td>urinary Calcium (mg/d)</td>
<td>-5.1</td>
<td>-8.9</td>
<td>5.3</td>
</tr>
<tr>
<td>urinary Oxalate (mg/d)</td>
<td>-4.2</td>
<td>-3.1</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

The table shows changes from baseline. Among all groups, higher serum calcium was associated with higher urinary calcium excretion (p=0.0001); higher serum calcium (p=0.0007)and vitamin D (p=0.026) were associated with lower oxalate excretion.

Conclusions: Both calcium and vitamin D supplementation decreased urinary calcium excretion. High serum calcium and vitamin D was associated with higher urinary calcium excretion in both men and women.

Funding: Private Foundation Support

FR-PO945
Tolvaptan Therapy Effectively Decreases Urinary Calcium Oxalate, Calcium Phosphate, and Uric Acid Supersaturations in Stone Formers

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Background: Drinking large amounts of fluids is universally recommended for urinary stone prevention but can be difficult to do for many stone formers. Tolvaptan, a V2 receptor antagonist, blocks water reabsorption in the collecting duct. This in turn should increase serum osmolality and stimulate thirst. The net effect should be lower supersaturation of stone forming salts, but this has not been proven.

Methods: This double blind, randomized, placebo-controlled, crossover study was conducted in 21 adult calcium urinary stone formers, stratified as major calcium oxalate (CaOx, n=10) or calcium phosphate (CaP, n=11). Patients were randomized to receive tolvaptan 45 mg/day or placebo for week 1, followed by washout week 2, and then crossover to drug or placebo for week 3. The 24 hr urine volume and chemistries were assessed at the end of week 1 and week 3.

Results: Tolvaptan versus placebo decreased urinary calcium oxalate (204±96 vs 529±213 mOsm/kg, P<0.0001) and increased urinary volume (4.8±12.9 vs 1.8±0.9 L, P<0.0001). However, the majority of urinary salt excretion rates (mg/24 hrs) including sodium and calcium did not significantly change. Thus, urinary CaOx SS (-0.01±1.1 vs 0.95±0.87, P<0.001) and CaP SS (-1.6±17 vs -0.13±1.02, P=0.001) both decreased. Urinary Uric Acid (UA) SS also fell (-2.05±0.45 vs -5.24±3.12, P=0.03). The tolvaptan treatment effect on urinary supersaturation did not differ between CaOx and CaP stone types (P=0.05 for all interactions). Serum sodium increased slightly while on tolvaptan (142±3 vs 141±2 mEq/L, P=0.01).

Conclusions: Use of tolvaptan increased urinary volume but did not appreciably change daily excretion of urinary constituents. The net effect was thus a fall in CaOx, CaP and UA SS. This study highlights the dramatic benefit increased free water ingestion alone can have on urinary supersaturation. Use of tolvaptan or other V2 receptor antagonists could be a useful strategy for selected stone formers not responsive to intensive dietary and/or behavioral counseling.

Funding: Other NIH Support - The investigators acknowledge support from the Rare Kidney Stone Consortium (U54DK083908), a member of the NIH Rare Diseases Clinical Research Network (RDCRN), funded by the NIDDK and the National Center for Advancing Translational Sciences (NCATS), and the Mayo Clinic O’Brien Urology Research Center (U54 DK100227). Pharmaceutical Company Support - Research work for this review was supported by Onsuka America Pharmaceutical, Inc.
FR-PO947

Claudin-14 Gene Polymorphisms May Regulate Urine Calcium Excretion
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Background: Claudins are a family of proteins that form paracellular calcium channels in tight junctions and may thus regulate tubular permeability to divalent cations. Claudin-14 is expressed in the ascending limb of Henle’s loop and inhibits calcium reabsorption. A previous GWA showed that two polymorphisms (SNPs) of CLDN14 (rs219778 and rs219781) were associated with kidney stones and calcium excretion in an Iceland population. The present study is aimed to explore the effect of CLDN14 SNPs on calcium excretion.

Methods: We have performed a retrospective study on 380 hypertensive patients never treated with antihypertensive drugs. These patients underwent a saline load test (i.v. infusion of NaCl 0.9% 2 litres in 2 hours) to evaluate sodium sensitivity. Kidney stones in their clinical history was ascertained by interview. Calcium was measured in 24-h urine and oxalate excretion was obtained from the GWA data.

Results: Kidney stones were reported by 9.3% of patients. No association was found between CLDN14 SNPs and stones. As previously observed, rs219778 was associated with kidney stones and calcium excretion in an Iceland population. The most significant association occurred with rs219778 (GG 5.62 ± 2.49, GA 4.86 ± 3.67, AA 3.67 ± 2.82, p = 0.0001). The association with calcium excretion was also observed when calcium excretion after saline load was considered (considering rs219755: AA 3.10 ± 0.36, GA 3.12 ± 0.21, GG 0.75 ± 0.51, p = 0.0008).

Conclusions: The CLDN14 genotype is associated with calcium excretion. This association is observed even after saline load test, a well known stimulus to urinary calcium excretion. Minor alleles of these SNPs could cause a reduction of calcium excretion and could be protective against kidney stones and hypercalciuria. The lack of association among stones and CLDN14 SNPs could be due to the method used to identify stone formers.

FR-PO948

Independent Effect of Blood Glucose Level on Urinary Citrate and pH
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Background: Urinary citrate is an important kidney stone inhibitor and its excretion is influenced by systemic acid base status and diet. However, the effects of demographies and other factors on urinary citrate excretion are not well defined, including the independent influence of blood glucose.

Methods: Twenty-four hour urine samples were collected from non-Hispanic white sibships in Rochester, MN. Height, weight, blood pressure, blood glucose, serum creatinine and cystatin C were measured. Diet was assessed using the Viocare food frequency questionnaire. The effects of blood glucose, demographics and diet on urinary citrate excretion, urine pH and net gastrointestinal (GI) alkali absorption were evaluated in bivariate and multivariable models, plus interaction models that included age, sex, and weight.

Results: Samples were available from 709 individuals (mean age 66±9 years). In general urine citrate and urine pH correlated positively with higher net alkali absorption (p<0.0001). Urine pH was higher in women for any given net alkali absorption value, but not after adjustment for covariates. In multivariable models urinary pH decreased with higher serum creatinine, blood glucose, dietary protein and increased with dietary potassium. Meanwhile, in multivariable models urinary citrate increased with age, weight, eGFR, urine pH and increased with loop diuretic and thiazide use. Association of urinary citrate and age was influenced by blood glucose (p<0.01).

Conclusions: In our study urinary citrate and pH correlated positively with net GI alkali absorption. Blood glucose had independent effects on urine pH and urinary citrate. This study provides the first evidence that blood glucose could influence stone risk independent of urinary pH and urine citrate crystallization. These observations could provide new insights into the association of obesity and urinary stone disease.

Funding: Other NIH Support - This work was supported by R01 DK077950, R01 DK073537, U01 HL054457, R01 HL087660, the Mayo Clinic O’Brien Urology Research Center P50 DK083007, and Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), all funded by the National Institutes of Health.

FR-PO949

Renal Oxalate Secretion Reduces Risk of Systemic Oxalosis in Primary Hyperoxaluria
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Background: Primary Hyperoxaluria (PH) is a rare genetic disease causing high hepatic production of oxalate. Renal excretion of oxalate keeps plasma oxalate (Pox) controlled but leads to stones and often ESRD. Systemic oxalosis occurs when GFR is reduced and Pox rises above the supersaturation threshold (approximately 45 mmol/L). Renal handling of oxalate in relation to GFR is poorly understood.

Methods: 16 patients ≥ 12 years without ESRD were identified from the Rare Kidney Stone Consortium registry. We used the most recent simultaneous Pox, serum creatinine and 24 hour urine oxalate (Uox). Net oxalate secretion (Sox) equals Uox-eGFR×Pox. Proximal tubular oxalate (PTox) is Uox corrected for creatinine and estimated proximal tubule water absorption, eGFR is by CKD-EPI (adults) or modified Schwarz (adolescents).

Results: 45 patients were identified (37 PH-1; 5 PH-2; 7 PH-3). Median age was 23.2 (IQR: 16.7, 32.9) and eGFR was 66.1 mL/min/BSA (54.8, 80.8). Pox, Sox and Uox rose sharply when eGFR fell below 45 mL/min. Similar results were seen in eGFR groups. PTox and Pox increased proportionally (p<0.001).

Conclusions: Compensation for high oxalate production in PH is maintained through CKD stage 3a. Higher PTox in CKD stage 3b may accelerate proximal tubular CaOx crystallization. Risk for systemic oxalosis is low until at least CKD stage 4.

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585A
FR-PO950
Effect of Antibiotic Treatment on Oxalobacter formigenes Colonization

Background: Kidney stones are a disease of worldwide prevalence with significant public health implications. About 60-80% of stones are composed of calcium oxalate (CaOx). Hyperoxaluria is a major risk factor. Oxalobacter formigenes (OF), a member of the normal gastric microbiota plays a major role in net colonic oxalate absorption and secretion. We now report OF colonization rates in a young healthy population, the stability of colonization, and the effects of antibiotic treatment on OF colonization.

Methods: We followed 64 healthy subjects tested for Helicobacter pylori (HP), who were stratified with antibiotics (Amoxicillin and clarithromycin for 2 weeks) for HP eradication. Using species-specific PCR, we tested for OF colonization at baseline and at follow-up.

Results: Of the 64 subjects (MF: 24/40; mean age 25.0 ± 5.5y) tested for OF, 25 (32%) subjects were positive at baseline. Subject to HP elimination, 6 became OF-negative at 6 weeks, only 2 reverted to positive at week 24, and 4 patients remained negative at follow up (Mean 21.0 ± 6wks). Of 16 untreated positive people, 12 (75%) remained positive at follow up (Mean 18.8 ± 7.7wks), but of 26 untreated negative subjects, only 6 (23%) were positive at follow up (mean 19.7 ± 6.6wks), significantly fewer than the untreated positives (p=0.001 by Fisher exact test).

Conclusions: We conclude that OF status remains stable over a follow-up period of several months, with antibiotics suppressing colonization in the majority of people in the short term. The differential long-term effect of antibiotics on OF colonization and its effect on urinary oxalate excretion, will be important to evaluate.

FR-PO951
Identification of Calcium-Oxalate Binding Proteins in Human Urine That Prevent Crystal Adhesion: An In Vitro Model of Kidney Stone Formation
Scott C. Norcott, J. Feng, F. Koenig, Quixin Guo, Katelynn H. Moor, Paul F. Austin. Dept of Surgery, Div of Urology, Washington St, Louis, MO.

Background: There are limited therapeutic options for the treatment of stone disease and about 50% of patients experience at least one recurrence. Existing treatment protocols focus on altering urine concentrations, which presents challenges due to the idiosyncratic nature of many stones and the variety of underlying factors. In this study, we examine the hypothesis that there are naturally occurring urinary proteins capable of binding calcium oxalate crystals, promoting their clearance, and preventing stone formation. Elucidating these interactions may provide novel therapies.

Methods: Calcium oxalate monohydrate (COM) crystals and fluorescently-labeled derivatives (COM-FITC) were synthesized in vitro. Stone formation was modeled in vitro by assessing the FITC-COM crystals to confluent monolayers of inner medullary collecting duct (IMCD) epithelial cells. Affinity chromatography was used to isolate COM-binding proteins from human urine.

Results: COM and COM-FITC crystals synthesized in vitro exhibited the typical prismatic morphology of urinary crystals. Incubation of IMCD cells with COM-FITC crystals resulted in rapid binding to the cell surface with high affinity. The addition of urinary proteins purified from human urine inhibited COM-FITC binding by 76.2%. Furthermore, urinary proteins inhibited the growth of COM crystals in free solution by 63.7%. In using this affinity chromatography to isolate COM-binding proteins, we found that this technique may facilitate the design of peptide-based therapies that prevent crystal adhesion and stone formation, as well as the development of diagnostic biomarkers that stratify patients and guide treatment decisions in at-risk populations.

Funding: NIDDK Support, Private Foundation Support

FR-PO952
Hydroxyapatite Induces Tolerance in Primary Human Monocytes Exposed to Calcium Oxalate Crystals
Benjamin Canales,1 Paul R. Dominguez Gutierrez,2 Sergei Kusmartsev,1 Katherine M. Lowney,1 Ammon B. Peck,2 Scott A. Koenig,3 Qiusha Guo,1 Katelynn H. Moore,3 and Paul F. Austin.1

Background: Although most crystal deposits within tissue produce inflammation, renal interstitial hydroxyapatite deposits do not, accumulating as Randall’s plaque. To further explore this lack of response, we investigated the effect of oxalate, hydroxyapatite, and combination of both on time dependent, immunological responses in human THP-1 (monocyte) cells, the precursors to tissue macrophages.

Methods: Using 1 mg/ml LPS and untreated as positive and negative controls, THP-1 cells were exposed to varying concentrations of soluble potassium oxalate (KOx) or CaOx and treated (10, 100, and 1000 ug/ml). In addition, a group of primary human monocytes were pre-treated with 100 ug/ml of HA or CaOx followed by secondary treatment with 100 ug/ml HA, 100 ug/ml CaOx, and 1 mg/ml LPS. THP-1 cells were collected at 2, 4, and 8 hours after various treatments, and RNA was analyzed by quantitative real time PCR.

Results: Pre-exposed THP-1 cells responded strongly at baseline, demonstrating marked suppression of TNFα, IL-1β, IL-8, and IL-10 secretion. However, at 4 hours, a dose depended response was observed at 100 ug/ml LPS exposure of human monocytes to HA had little effect on cytokine response to subsequent CAOx and LPS exposure; however, pre-exposure to CAOx followed by HA negated all further cytokine production.

Conclusions: In our human monocyte model, the order of CAOx and HA exposure affects myosin response. HA neither stimulates cytokine production nor inhibits demonstrated production when pre-exposing monocytes prior to CAOx exposure. Pre-exposed CAOx monocytes, however, had decreased cytokine and chemokine expression when secondarily treated with HA. This tolerance mechanism may partially explain the lack of papillary inflammation in the pathogenesis of Randall’s plaque.

Funding: NIDDK Support, Other NIH Support - T32

FR-PO953
A Low Sodium Diet Inhibits Stone Formation in Genetic Hypercalciuric Stone-Forming Rats
Benjamin S. Scott1

Background: About 60–80% of stones are composed of calcium oxalate (CaOx) and about 50% of patients experience at least one recurrence. Existing treatment protocols on urinary oxalate excretion, will be important to evaluate. We conclude that of dietary Na restriction reduces kidney stone formation, we utilized 101 generation genetic hypercalciuric stone-forming (GHS) rats fed either a low (LNa, 0.05%) or normal (NNa, 0.4%) Na diet for 18 weeks. Urine was collected at 6 wk intervals; a mean was determined for each analyte and then an overall 18 w week mean calculated. Radiographic analysis for stone formation was done at 18 wks.

Results: As anticipated, the decreased mean uNa (NNa=2.48±0.3 mmol/24h; LNa=0.9±0.2 mmol/24h) and uCa (NNa=2.65±0.13 mmol/24h; LNa=1.9±0.06, p<0.001) in the LNa group resulted in significantly lower overall mean uCa was lower with LNa than NNa (NNa=17.3±3.5 mg/dL; LNa=15.2±0.5, p<0.01) as was u phosphate (P) (NNa=16.5±0.6 mg/dL; LNa=13.8±0.4, p<0.001). Urine oxalate (Ox) and citrate (C) increased in LNa, citrate and volume did not differ with diet Nna. There were no significant differences in a u NaP characterization with respect to CaOx or CaOx. Serum Ca was significantly increased with LNa (NNa=10.9±0.1 mg/dL; LNa=11.4±0.1, p<0.01) while there were no differences in urine P, PTH or FGF23. Radiographic analysis of kidneys demonstrated a significant decrease in calcification with LNa (calcification scores with a range of 0-3: NNa=1.4±0.15; LNa=0.5±0.12, p<0.001).

Conclusions: Thus a low Na diet reduced uCa and stone formation in GHS rats even though urine supersaturation was not altered. These data, in a genetic model of hyperoxaluria and stone formation, lend support to the use of dietary Na restriction to prevent recurrent Ca nephrolithiasis.

Funding: NIDDK Support

FR-PO954
Ethylene Glycol Induced Hyperoxaluria in Rats: A Transcriptional Study

Background: Hyperoxaluria, if remains undiagnosed, can cause renal injury and inflammation leading to a number of diseases including advanced stages of renal failure. In order to look into the different pathways and molecular mechanisms involved in the kidneys of hyperoxaluric rats, we performed genome wide analysis of differentially expressed genes in the kidneys of rats fed ethylene glycol (EG).

Methods: Male rats were divided into two groups. Rats in one group were fed normal diet and the other group diet supplemented with 1.25% EG. Urinary assays were done at different time intervals and after 14 and 28 days rats were euthanized, kidneys explanted and total RNA extracted for micro array analysis using Agilent 8 x 60k single color arrays. Data was analyzed using bio-conductor Limma (Linear models for micro array analysis) package using R. Gene ontology (GO) and KEGG pathway analyses were also performed. Immunohistochemical (IHC) and Eosin and Hematoxylin (E & H) staining was also done for highly significant genes.

Results: All rats became hyperoxaluric from day 7 and had crystal deposition at different time intervals. Urinary LDH, sodium and creatinine were significantly different in the EG group as compared to the control. There was significant expression of different genes encoding for macromolecular modulators such as osteopontin (OPN), monocye chemoattractant protein-1 (MCP-1), lipocalin 2 (Lcn-2), fibroin (Fn-1), clusterin (CLU) and kidney injury molecule-1 (KIM-1) along with nicotine amide dinucleotide phosphate (NADPH) oxidase-4 (NOX-4) and glutathione peroxidase (Gpx-2). Gene analysis showed 17 and differentially expressed pathways for day 14 and day 28 respectively.

Conclusions: Results highlight that the EG treated rats showed heavy deposition of crystals and there were 15 pathways that were common between day 14 and day 28 giving a deep insight into the molecular mechanisms and pathways activated in hyperoxaluric rats.

Funding: Other NIH Support - R01-DK078602 and R01-DK092311

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Underline represents presenting author.
Sucrose and Thiosulfate Competitively Inhibit Oxalate Transport via a Drosophila Prestin (dPrestin, dSIC26α)-Dependent Mechanism Greg M. Landry,1,2,3 Taku Hira,1,4 Jacob B. Anderson,1 Christopher Joseph roel Gallo,1 Michael Francis Romero,1,2,3,5 Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN; Nephropathy and Hypertension, Mayo Clinic College of Medicine, Rochester, MN; O’Brien Urology Research Center, Mayo Clinic College of Medicine, Rochester, MN.

Background: Nephrolithiasis affects approximately 12% of men and 6% of women in industrialized countries with the majority of stones being composed of calcium oxalate (CaOx).

Methods: Using Drosophila melanogaster as a robust and translatable model of CaOx nephrolithiasis, we studied the effects of sucrose and thiosulfate on oxalate transport, and subsequent CaOx crystal formation, as a proof of principle in providing a nidus to identify new therapeutic interventions.

Results: Results indicate that dPrestin transports thiosulfate with a much higher affinity than sucrose (dPrestin sucrose Kₚₒₓ = 8.65 ± 3.87 mM compared to dPrestin thiosulfate Kₚₒₓ = 0.23 ± 0.03 mM). Additionally, both sucrose (48 h) and thiosulfate (24 and 48 h) were effective at decreasing Malpighian tubule CaOx crystallization with the opposite results observed at 48 h in Malpighian tubules where dPrestin was not expressing a role indicating differentiation for cell-specific dPrestin in luminal oxalate transport.

Conclusions: Given the higher affinity of thiosulfate for dPrestin when compared to those which are reported for oxalate (dPrestin average Kᵢₚₒₓ for oxalate = 0.87 ± 0.16 mM and for thiosulfate = 0.22 ± 0.03 mM), we have concluded that the ability of thiosulfate to act as a competitive inhibitor of oxalate at the transporter level, specifically dPrestin, may explain the regulatory role in CaOx stabilization seen in the absence of thiosulfate. Overall, our findings predict that thiosulfate or oxalate-mimics may be effective as therapeutic competitive inhibitors of CaOx crystallization.

Funding: NIDDK Support

FR-PO956


Background: C3 glomerulopathy (C3G) is a progressive form of glomerulonephritis (GN) characterized by antibodies associated with abnormalities in regulation of the alternative pathway (AP) of complement. Mice with deficiency of factor H (Cfh⁻/⁻), a negative AP regulator, are an established experimental model of C3G in which abundant complement C3 accumulates along the glomerular basement membrane.

Methods: We examined the spontaneous renal phenotype in Cfh⁻/⁻ mice with and without accompanying deficiency of complement receptor 3 (CR3), the main receptor for iC3b. We performed accelerated serum nephrotoxic nephritis (ANTN) in CR3-deficient mice, accompanying CR3 deficiency was associated with significantly increased albuminuria, glomerular hypercellularity and macrophage influx, and mortality. We performed bone marrow transplantation experiments in Cfh⁻/⁻ recipients indicated that the protective effect of CR3 was dependent on BM-derived cells. ANTN produced severe, significant increased albuminuria, glomerular hypercellularity and macrophage influx, and mortality. Bone marrow (BM) transplantation experiments in C3G patients, which do not score in the standard C3NeF assay. Here we compare how 50-80% of C3G patients. Notably also autoantibodies but lack C3Nef. Some C3 convertase antibodies deregulate the C3 convertase and additional C3 convertase inhibition.

Results: Among the 34 C3G patients, 19 patients were identified with autoantibodies which bind to the C3 convertase, but lack C3Nef. 15 patients were identified C3NeF positive according to the binding to the C3 convertase, high titer (HT) and low titer (LT) antibodies were identified among isolated autoantibodies from all 34 C3G patients. HT as well as LT antibodies strongly activated the C5 convertase and enhanced C5a generation. Interestingly all antibodies bound to the C3 convertase, but only HT and not LT antibodies complement C5 convertase activity. The HT but not the LT antibodies increased C3 convertase assembly, stabilized the convertase and increased C3a generation.

Conclusions: Two classes, HT and LT, of complement C3 convertase binding autoantibodies were identified in C3NeF-positive and negative C3G patients. These antibodies deregulate complement by two different mechanisms: HT antibodies activate complement on the C3- and C5 convertase levels, while LT antibodies activate only on C5 convertase level. We speculate that these functional different autoimmune forms explain responder and non-responder types to therapeutic C5 inhibitors.

Funding: Government Support - Non-U.S.

FR-PO959

Autoimmune C3 Glomerulopathy: Can Complement Inhibiting Drugs Reduce Complement Activation by C3 Convertase Autoantibodies? Friederike Sophie Schulze,1 Fei Zhao,1 Giuseppe Remuzzi,2 Marina Noris,3 Christine Skerka,1 Peter F. Zipfel,1,3 Hans Knoll Inst, Jena; 1Mario Negri Inst for Pharmacological Research, Bergamo; 1Friedrich Schiller Univ, Jena.

Background: C3 glomerulopathy is a severe kidney disorder that is caused by deregulation of the alternative complement pathway. Pathways are important in the development of new autoantibodies cause complement deregulation and how complement inhibitors affect the action of these autoantibodies.

Methods: IgGs were purified from patients with C3 convertase antibodies lacking C3NeF (n=19) and also from C3NeF+ patients (n= 15). These purified IgGs were tested for their impact on complement activity and the effect of soluble CR1 (sCR1) and Eculizumab was examined by ELISA, Western blot and complement activation assays.

Results: C3 convertase antibodies from patients lacking C3NeF deregulated complement only in the absence of autoantibodies stabilized the C3 convertase and all activated the terminal complement pathway. C3NeFs activated complement in a related manner. In probes with C3 convertase antibodies sCR1 did inhibit excessive complement activity. Also Eculizumab prevented antibody mediated complement activation. Both inhibitors blocked C3NeF-mediated complement deregulation in a related manner. For some probes from either C3NeF+ or C3NeF- patients a higher dose of sCR1 was necessary to affect C3 convertase activity.

Conclusions: A subgroup of C3G patients present with C3 convertase-binding antibodies but lack C3NeF. Some C3 convertase antibodies deregulate the C3 convertase and all stabilize the C5 convertase. The complement inhibitors sCR1 and Eculizumab reduced complement activity. Patients with antibodies causing only excessive C5 convertase activity may benefit from Eculizumab, whereas patients with excessive C3 convertase may require additional C3 convertase inhibitors.

Funding: Government Support - Non-U.S.

FR-PO957

Two Autoimmune Forms of C3-Glomerulopathy Are Defined by Complement Convertases Deregulating Autoantibodies Christine Skerka,1 Fei Zhao,1 Giuseppe Remuzzi,2 Rossella Piras,2 Peter F. Zipfel,1,3 Dept of Infection Biology, Leibniz Inst for Natural Product Research and Infection Biology, Jena, Germany; 3Laboratory of Immunology and Genetics of Transplantation and Rare Diseases, IRCCS- Istituto di Ricerche Farmacologiche, Bergamo, Italy; 1Friedrich Schiller Univ, Jena, Germany.

Background: In C3Glomerulopathy (C3G) defective complement activation on level of the C3 convertase is caused by mutations in genes coding for complement components and or regulators as well as by autoantibodies. C3 nephritic factor (C3NeF) has been reported in 50-80% of C3G patients. Notably also autoantibodies to C3b and Factor B were identified in C3G patients, which do not score in the standard C3NeF assay. Here we compare how the new C3 convertase reacting antibodies and also C3NeF affect complement regulation on the level of the C3- and the C5 convertases.

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587A

FR-PO958

Respiratory Syncytial Virus May Exacerbate Kidney Damage in IgA Nephropathy Through C3a/C5aR and C5a/C5aR Signaling Amplifying the Effects of Th17 Cells Xiaozhao Li,1 Xinyue Hu,2 Ting Meng,3 Juntao Feng,2 Qiaoling Zhou.1 1Dept of Nephrology, Xiangya Hospital of Central South Univ, Changsha, Hunan, China; 2Dept of Clinical Laboratory, Xiangya Hospital, Central South Univ, Changsha, Hunan, China.

Background: The exacerbation of IgA nephropathy (IgAN) is related to respiratory tract infection with respiratory syncytial virus (RSV), but the mechanism is unknown. In this study we investigated the role of complement activation products C3a and C5a (C3aR and C5aR) in response to the effect of T-helper 17 (Th17) cells in the pathogenesis of IgAN associated with RSV.

Methods: IgA nephropathy was induced in BALB/c mice with lipopolysaccharide, carbon tetrachloride and bovine serum albumin. Then the mice were sensitized with C3aR-Antigen (C3aRA) and C5aR-Antigen (C5aRA) respectively and infected with respiratory syncytial virus (RSV) in sequence. Urine Albumin-Creatinine ratio and sediments were measured. The pathological changes in kidney and lung tissues were observed under microscopy. C3aR and C5aR proteins in kidney tissue were examined by immunohistochemical staining. Th17 cell regulatory T cells (Tregs) in kidneys were tested by flow cytometry. C3a-C5a, IL-17A, IL-6 and IL-21, IL-22 in the kidneys were detected by ELISA.

Results: The IgAN mice had albuminuria and microscopic hematuria, renal mesangial proliferation and C3a deposition, high electron dense deposition in glomerular mesangial region, decreased frequency of Tregs, increased frequency of Th17 and Th17-Treg ratio. Furthermore, C3a, C5a, C3aR, C5aR and Th17-related cytokines IL-17A, IL-6 and IL-21 were all increased in the kidneys of IgAN mice. Compared with IgAN mice, the manifestations in RSV-IgAN mice were more severe, but alleviated in C3aR-treated groups and C5aR-treated groups respectively.

Funding: Government Support - Non-U.S.
Conclusions: RSV infections may exacerbate kidney damage in IgAN through C3a/C3aR signaling amplifying the Effects of Th17 Cells. The first two authors contributed equally to this work.

Funding: Government Support - Non-U.S.

FR-PO960

Functional Glomerular Deceleration Accelerating Factor Induction by Heme: Role of HO-1
Maria Detours, Giouli Makri, Vasileios Atsalas, Pu Diann, Elias A. Lianos.
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Background: In hemolytic disorders and glomerular injury associated with hematuria intraglomerular free heme increases and may activate the alternative complement (C)-pathway. Rat glomeruli express deceleration factor (DAF) in glomerular epithelial cells (GEC). We assessed whether heme upregulates glomerular DAF to minimize C activation and explored underlying mechanisms.

Methods: hmox1-/- and hmox1 +/+ rats were generated by Zinc Finger Nuclease (ZNF)-mediated HO-1 gene disruption and rats with GEC targeted HO-1 overexpression (GEC-hmox1) by Sleeping Beauty Transposon mediated transgenesis using a nephrit promoter. Wild-type (WT) or hmox1 +/+ , hmox1-/- or GEC-hmox1 glomeruli were treated for 18 h with heme (hemin, FePP) or non-iron porphyrins with opposite effects on HO activity: 1) HO inducers, Cobalt (CoPP) and the non-metal protoporphyrin IX (PPIX) and 2) HO inhibitors: Zinc (ZnPP), Tin (SnPP) protoporphyrins, Tin (SnMP) and Chromium (CrMP) mesoporphyrins. C3b deposition in glomeruli was triggered by exposure to 10% rat serum. DAF, HO-1 and C3b levels were assessed by western blotting or Real-time PCR. HO enzyme activity was measured by standard methods.

Results: Constitutive DAF (mRNA and protein) decreased in both hmox1 -/- and hmox1 +/+ and increased in GEC-hmox1 glomeruli. Heme, at concentrations encountered in hemolytic disorders (50-400 µM), increased DAF expression in WT glomeruli. This effect was attenuated in both hmox1 -/- and hmox1 +/+ and augmented in GEC-hmox1 glomeruli. Heme-mediated DAF induction in hmox1 +/+ glomeruli persisted despite complete HO-1 absence. Of the non-Fe porphyrins, CoPP, ZnPP and PPIX increased DAF and HO-1. SnPP induced DAF but not HO-1. SnMP and CrMP had no effect on either heme. Tin or SnPP-mediated DAF induction reduced C3b deposition. This was reversed by PI-PLC which removed membrane bound DAF.

Conclusions: HO-1 regulates constitutive DAF expression and heme-mediated DAF induction. The latter is independent of metal moiety and HO enzyme activity, requires the porphyrin ring and may also occur via a HO-1 independent mechanism. DAF induction by heme is functional and attenuates C-activation.

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FR-PO961

Complement Activation Impairs Endothelial Cell Migration – Possible Role in TMA Pathogenesis
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Background: Cell migration is a key requirement in multiple physiological scenarios including angiogenesis and endothelial cell repair. Thrombotic microangiopathy (TMA) is characterized by endothelial cell (EC) activation and injury, in atypical hemolytic urticemic syndrome caused by complement activation on ECs. We hypothesized that EC injury in aHUS was at least in part – caused by complement-mediated inhibition of cell migration. Methods: To test this hypothesis blood outgrowth ECs were exposed to complement by blocking EC surface regulators (CD46, CD55, CD59) and incubating ECs with 50% normal human serum (NHS; complement active). Heat inactivated serum (HIS; complement inactive), C5-depleted serum (terminal pathway inactive) and media served as controls.

Results: Wound healing assay in fluidic conditions (wound infliction via trypsin/EDTA) showed within 1.5 h a wound area decrease to 62.5±1.5% when perfused with media. Subsequent (1.5h) HIS perfusion allowed for further wound area reduction to 38±6.5%, similar to C5-depleted serum (46±5%). In contrast, exposure to complement (NHS) inhibited further wound closure (wound area 63±7%, p<0.05). The proliferation rate (% BsdU+ positive cells after 2 h) was similar between controls and complement-exposed ECs (20±2 vs. 21.1±3%), and no apoptosis or necrosis was detected within a 30min - 4h observation period (Annexin V, live dead aque dye). However, we demonstrated an instantaneous but transient cell membrane perfusion, suggesting a role for PIP3 signaling in impaired cell migration leading to EC injury and defective EC repair – findings extending our current concept of TMA pathogenesis.

Conclusions: Our data suggest that sublethal EC complement exposure results in impaired cell migration leading to EC injury and defective EC repair – findings extending our current concept of TMA pathogenesis.

FR-PO962

Uncommon Features in Antibody Binding Sites of Human Anti-Glomerular Basement Membrane Autoantibodies
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Background: Detection of pathogenic anti-α3(IV)NC1 collagen autoAb in the serum or kidneys is required for diagnosis of anti-GBM nephritis and Goodpasture Syndrome, yet little is known about the origin and structure of human anti-α2/α3/α4 in these diseases. The heterogeneity of serum Ig, lack of ready access to kidney tissues in patients, and inability to reproduce complex immunological microenvironments in vitro present formidable barriers. Humanized models provide a novel platform to circumvent these obstacles.

Methods: We generated Hu-HSC mice by injection of human CD34+ hematopoietic stem cells into immunodeficient NOD-scid-gamma hosts. Mice with an established human immune system (mean blood chimerism 15.0±15.9% at 3 mons post-injection) were immunized twice with α3(IV)NC1 collagen prior to tissue harvest. Human C amplified EBV transformed using Cpe oligos and kinase inhibitors, screened for antigen binding, electrophoresed with a human heterohybridoma, and subcloned. The mAb sequences were determined using PCR of cDNA with published primer panels and analyzed using IMGT/TV-QUEST.

Results: Sequence analysis of 6 non-clonally related human anti-α3(IV)NC1 mAb revealed skewed gene use and unusual motifs in the critical HCDR3 that is predominantly responsible for antigen binding. 4 of 6 (67%) human mAb are encoded by an IgH J6 allele, the extended sequence of which enriches for aromatic tyrosine residues in HCDR3. The HCDR3 are exceptionally long, with mean length 26.4 amino acids (a.a.) compared to average human HCDR3 of 15.2 a.a., and include hydrophobic motifs, an autoimmune signature uncommon in Ig repertoires of healthy individuals and of unimmunized Hu-HSC mice. Similar motifs were observed in murine anti-α3(IV)NC1 mAb, despite substantial species differences in Ig gene loci and a.a. composition.

Conclusions: Our results suggest that binding of α3(IV)NC1 collagen by human anti-GBM autoAb requires unusual structural motifs that can access recessed hydrophobic epitopes and that are normally excluded from the healthy human immune repertoire. Similar motifs in man and mouse suggest origins by convergent selection.

Funding: NIDDK Support, Veterans Administration Support

FR-PO963

Antigenicity Alteration of Deglycosylated Myeloperoxidase
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Background: Myeloperoxidase (MPO) is a kind of enzyme located in the azurophilic granules of neutrophils, which is the most common target antigen of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in Chinese patients. Native MPO possesses five N-glycans at positions 323, 355, 381, 483 and 729. The alteration of MPO antigenicity after deglycosylation of these glycans is not elucidated.

Methods: We prepared deglycosylated MPOs via glycosidases based on commercial human-derived intact MPO, and then detected the antigenicity of deglycosylated MPOs in 40 patients with anti-glomerular basement membrane (GBM) disease without MPO-ANCAs.

Results: We found antibodies against deglycosylated MPOs existed in patients with antigranulocyte disease. 12/40 (30%) patients were positive for MPO treated with PNGase F naked MPO without hydrocarbon side-chain. 12 (30%) patients were positive for MPO treated with Endo H (MPO with one GluNac only). Antibody against the intact native MPO was not detectable in all these patients. Furthermore, clinical analysis presented that the deglycosylated antibodies against deglycosylated MPOs were positively associated with renal dysfunction. The plasma levels of antibodies against naked MPO without glycan were positively correlated with the concentrations of serum creatinine (P<0.006, R=−0.178). The plasma levels of antibodies against MPO with one GluNac only were also positively correlated with the concentrations of serum creatinine (P=0.002, R=−0.234).

Conclusions: The existence of patients’ antibodies towards deglycosylated MPO first discovered the new epitope exposure of MPO after the loss of hydrocarbon side-chain, explicating the possible reasons for antigenicity alteration, and then prompting some clinical significance of these antibodies.

Funding: Government Support - Non-U.S.

FR-PO964

Autoantibodies to a Cryptic Myeloperoxidase-Specific Immunodominant Epitope Correlate with Disease Activity in Patients with MPO-ANCA Vasculitis
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Background: ANCA vasculitis is commonly characterized by polyclonal autoantibody reactivity to one of two autoantigens, proteinase 3 (PR3) and/or myeloperoxidase (MPO). ANCA positivity has been observed in patients with active and quiescent disease. A subset of MPO-ANCA in many patients recognizes a cryptic epitope which is normally buried within MPO suggesting that this epitope may be exposed by mechanisms that are not yet understood. We assessed human anti-KV reactive longevity in a large cohort of patients with MPO-ANCA vasculitis to better understand the temporal association of the anti-ANCA antibody response.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Methods: Serum, plasma, and extensive clinical data from patients with ANCA vasculitis were prospectively collected every 3 months. A highly sensitive and specific indirect ELISA using KIV peptide was developed to longitudinally screen patient samples for reactivity over their disease course. To minimize non-specific antibody signal, reactivity to a scrambled peptide of the same amino acid composition was also measured. A positive signal was defined as two standard deviations above the healthy control mean (HC n=85).

Results: Of 67 patients with MPO-ANCA vasculitis, 28 were positive for human anti-KIV autoantibodies at least once during their disease course spanning an average follow-up of 3.3 years. The majority of these patients displayed positivity during initial stages of disease, while others exhibited a persistence of reactivity. Further structural analysis of autoantibody binding to native MPO confirmed this peptide to be a cryptic epitope.

Conclusions: These findings suggest that conformational changes in MPO that expose this cryptic epitope may be important in the pathogenesis of the MPO-ANCA vasculitis and may provide insight into the etiology of this disease. Furthermore, this assay could help to more clearly define temporal disease activity.

FR-P0965
An Anti-GBM Autoantibody Gene Contributes Risk to Distinct Auto-Collagen Responses
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Background: The mechanism by which anti-GBM nephritis is initiated and regulated remains an enigma. Recent studies indicate that anti-GBM patients’ serum IgG react with multiple collagen chains and with atypical alpha3(V)NC1 epitopes, and that diverse marine anti-collagen antibodies auto-antigenically linked. We examined these relationships in a novel autoantib IgG transgenic model expressing a human GBM gene at low frequency in adult mice but enriched in anti-GBM IgG and arthrogryphic anti-collagen II IgG.

Methods: Mice expressing an IgK-encoding kappa light chain Tg were bred with mice expressing a collagen II alpha1 chain. Both anti-collagen and anti-alpha3(V)NC1 collagen I antibodies were detected by western blot, dot blot, and ELISA and characterized by their ability to react in situ with anti-GBM antigens. We assessed the contribution of anti-alpha3(V)NC1 antibodies to the development of collagen I and II autoantibodies by assessing serum samples from Tg mice versus wild type controls.

Results: Differences in collagen II and III reactivity were observed with anti-collagen II antibodies being stronger than those anti-collagen III. Anti-alpha3(V)NC1 collagen I antibodies were present in both Tg and non-Tg mice, but were more strongly expressed in Tg mice. These results suggest that anti-collagen II antibodies are regulated by the absence of anti-collagen III autoantibodies.

Conclusions: Our results demonstrate the potential of this transgenic model to study the role of distinct autoantibody responses in the development of anti-GBM nephritis.

FR-P0966
Autoantibodies Target Multiple Epitopes in THSD7A in Primary Membranous Nephropathy
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Background: Thrombospondin type-1 domain-containing 7A (THSD7A) is a large type 1 transmembrane glycoprotein expressed by the podocyte. It serves as the in situ antigen in a subset of primary membranous nephropathy patients. Its extracellular domain consists of a regularly repeating structure composed of thrombospondin type-1 and F-spondin repeats, as well as a highly basic region. We sought to investigate the location(s) of the humoral epitopes targeted by anti-THSD7A antibodies in membranous nephropathy.

Methods: N- and C-terminal truncation mutants of THSD7A, as well as constructs comprising single or multiple adjacent domains, were expressed in HEK293T cells. Reactivity with human autoantibodies was assessed by western blot, dot blot, and immunoprecipitation.

Results: Patient sera displayed varying degrees of reactivity to these recombinant constructs, with most sera reacting with 2 or more distinct domains in the more C-terminal, extracellular domain of the molecule. A subset of sera recognized an additional epitope in the N-terminal portion of the molecule. Reactivity with the larger constructs, such as THSD7A serially truncated from the N- or C-terminus, was stronger than that against constructs composed of 1 to 4 adjacent domains, and could be detected by western blot, dot blot, and immunoprecipitation.

Conclusions: As in PLA2R associated membranous nephropathy, the humoral response to the target antigen THSD7A involves multiple epitopes within the molecule. Reactivity with autoantibody appears to depend on the conformation of an extended THSD7A extracellular region. Further analysis of additional anti-THSD7A positive sera will help to define the epitopes within the molecule, underlie the pathogenesis of this autoimmune disease, and identify potential targets for novel therapeutic strategies.

Funding: NIDDK Support

IRF-P0967
Intramolecular Epitope Spreading in Phospholipase A2 Receptor, in IMN Patient En Route to End-Stage Renal Disease
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Background: Clinical studies have established that over 70% of patients with idiopathic membranous nephropathy (IMN) possess high levels of circulating autoimmune antibodies targeting phospholipase A2 receptor (PLA2R) in the glomerular visceral epithelial cells. Our recent studies demonstrated that over 70% of IMN patients are circulating autoantibodies that target PLA2R triggering immune complexes formation in situ and deposition in the glomerular subepithelial spaces. The immunodominant epitope in PLA2R was recently located to the extreme N-terminus of the receptor encompassing the THSD1-C3 region. In the rat model of MN, epitope spreading was detected in the antigenic protein, megalin that is correlated with the disease progresses. Whether epitope spreading occurs in human IMN and its relationship to disease progresses is unclear.

Methods: Serum samples from biopsy-proven IMN patients were collected and screened for anti-PLA2R antibodies using Western-blot and epitope-specific ELISA assays. The reaction of autoantibody and PLA2R protein was further analyzed using immunoprecipitation and immunoblotting assays.

Results: Western-blot analysis using patient sera against full-length PLA2R or the dominant epitope region indicated that, 3 of the 12 serum samples that were positive with anti-PLA2R autoantibodies failed to recognize the dominant epitope protein. Further test of these 3 samples against a series of truncated PLA2R extracellular domains on Western-blot demonstrated that the autoantibodies bind strongly to the Cys-R-FnII-CTLD1-3 region of PLA2R. Interestingly, serial analysis of sera from a patient with worsening proteinuria showed, that the autoantibodies first recognized the Cys-R-FnII-CTLD1-3 region and then spread to the CysR-FnII-CTLD1 region, suggesting epitope spreading is associated with the disease progresses.

Conclusions: Our results demonstrate for the first time that intramolecular epitope spreading occurs in PLA2R in IMN. This finding supports the important role of the dominant epitope in IMN pathogenesis and disease progresses.

FR-P0968
Demonstration of a High Titer Low Affinity Anti-PLA2R Autoantibody in an IMN Patient En Route to End-Stage Renal Disease
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Background: Circulating immune complexes (IC) deposit in the glomeruli of the kidney in many autoimmune diseases, leading to proliferative glomerulonephritis. IC binding can promote proliferation or induce apoptosis in human macrovascular EnCs.

Conclusions: As in PLA2R associated membranous nephropathy, the humoral response to the target antigen THSD7A involves multiple epitopes within the molecule. Reactivity with autoantibody appears to dependent on the conformation of an extended THSD7A
Kidney diseases.

Methods: Renal ENCs were cultured from C57BL/6 mice and primary human glomerular ENCs were obtained commercially. Cells were treated with heat aggregated IgG (anti-β2m) or IC. Quantitative RT-PCR was used to measure mRNA levels of TNF superfamily members. A cellular ELISA was used to assess TRAIL protein expression on ENCs. Apoptosis was assessed using annexin V and H2AX phosphorylation, and caspase 3 activity assays, as well as TUNEL staining. In vivo findings were validated in a renal inflammatory mouse model of acute IC kidney injury.

Results: TRAIL mRNA expression is up-regulated by renal endothelial cells in vitro in the presence of IC binding and in vivo. Membrane TRAIL expression on ENCs also increases after treatment with IC in a dose dependent manner. Receptors for TRAIL, DR5, DR4, and the receptor for TRAIL-R1 (TRAIL-R1) are expressed by ENCs at RNA and protein levels. Using XTT cell proliferation assays, there is a modest decrease in EnC metabolism or proliferation after treatment with IC. Caspase 3 activity and DNA double strand breaks were both increased in cultured ENCs after treatment with IC in a dose dependent manner. Results were similar for both murine and human glomerular ENCs.

Conclusions: Results suggest that IC binding to glomerular ENCs in vitro is pro-apoptotic. Several TNF superfamily members known to promote apoptosis and their receptors are also up-regulated on ENCs treated with IC. Targeting TRAIL binding to DR5 and its downstream signaling pathways may reduce EnC activation or injury in IC kidney diseases.

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FR-PO970

Paired Immunoglobulin-Like Type2 Receptor α (PILRα) Negatively Regulates Immune Complex-Mediated Glomerulonephritis

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Background: PILRα expressed mainly on macrophages, dendritic cells and granulocytes, has been described for its regulatory functions for leukocyte β2 integrin activation in acute inflammation including LPS-induced endotox shock model. Here, we investigated roles of PILRα in immune complex (IC)-mediated glomerulonephritis.

Methods: IC-mediated glomerulonephritis was induced by intravenous administration of nephrotic serum (NTS) after pre-conditioning with rabbit IgG in C57BL/6 (WT) and PILRα−/− mice. Functional analysis for renal injury was performed by urine albumin and serum creatinine (creatinine) concentrations at day 7, 14 and 21. Diseased kidneys from both mouse strains were harvested for histology, renal leukocyte infiltrates by flow cytometry and renal cytokine profiles by ELISA after induction of NTS glomerulonephritis. In vitro, α4β7 integrin-dependent neutrophil adhesion on IC was evaluated in both mouse strains.

Results: BUN and Cr concentrations were significantly elevated in PILRα−/− mice compared to wild type mice at day 14 and day 21 and those were highly associated with deteriorated proteinuria. In histological analysis, glomerular damages, corroborated with both glomerular PAS deposits and glomerular crescent formation, were more severe in PILRα−/− mice at day 21 (p<0.05). Moreover, glomerular neutrophil accumulation was remarkably observed in PILRα−/− mice compared to WT mice at day 21. In addition, total infiltration of Ly6G+ neutrophils, F4/80+ macrophages and CD3+CD4+ T cells in whole kidneys were increased in PILRα−/− mice than WT mice at day 14 and day 21. Renal pro-inflammatory cytokine production for IL-1β and IL-6 on day 7, 14 and 21 also demonstrated severe renal inflammation in PILRα−/− mice. In vitro, PILRα−/− deficient neutrophils showed enhanced adhesion and spreading on IC compared to WT.

Conclusions: PILRα−/− deficiency resulted in deteriorated renal damage in mouse IC-mediated glomerulonephritis compared to WT mice, indicating that PILRα negatively regulates IC-mediated leukocyte recruitment by inhibition of α4β7 integrin activation.

FR-PO971

Role of Interferon Regulatory Factor 5 and Toll-Like Receptor 7 in Immune Complex Glomerulonephritis

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Background: Immune-complex glomerulonephritis (ICGN) is a common cause of glomerular inflammation characterized by in situ formation of immune complexes and activation of the complement cascade. Interferon regulatory factor 5 (IRF5) is a transcription factor acting downstream of toll-like receptors 7 (TLR7) to trigger an inflammatory response. Recent genetic studies have associated systemic lupus erythematosus (SLE), and other autoimmune syndromes with gain-of-function polymorphisms in the IRF5 gene. We therefore hypothesized that deletion of IRF5 or TLR7 would ameliorate ICGN.

Methods: We induced nephritic nephropathy using an endotoxin-free IgG1 fraction of sheep nephritic serum (SNS) in FgRiBv−/− mice that either express (Control) or do not express IRF5 (IRF5−/− or TLR7−/−). During the first five days following tail-vein injection of NTS, at a time when the heterologous antibody response peaked, we euthanized the mice and compared histology, albuminuria, renal immune cell infiltration and renal cytokine expression.

Results: The control mice developed severe glomerulonephritis characterized by massive albuminuria, prominent kidney mononuclear cell infiltration and presence of crescents or necrosis in 28±6% of glomeruli. In contrast, TLR7−/− and IRF5−/− developed significantly less severe disease with crescents/necrosis in only 6±2% of glomeruli (p<0.01), and significantly decreased monoclonal cell infiltration (including both patrolling and infiltrating monocytes). IRF5−/− mice showed a similar pattern in the control and IRF5−/−KO, but not in the IRF5−/−KO mice. Therefore, TLR7-independent pathways downstream of TLR7 is responsible for the proteinuria. Consequently, we conclude that the TLR7/IRF7 pathway may represent a novel therapeutic target for the control of glomerular inflammation.

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FR-PO972

Therapeutic TLR9 Inhibition Prevents the Establishment of Anti Myeloperoxidase Autoimmunity and the Development of Glomerulonephritis in Mice with Established Autoimmunity

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Background: We have shown TLR9 ligations enhances anti-myeloperoxidase (MPO) autoimmunity (AI) and glomerulonephritis (GN) through dendritic cell (DC) activation. We assessed therapeutic TLR9 inhibition on both the development of anti-MPO AI induced through DC vaccination and subsequent development of GN by TLR9 responsive innate effector cells.

Methods: Injection of MPO/Freud’s Adjuvant or transfer of MPO/CpG (TLR9 ligand) pulsed bone marrow derived DCs established anti-MPO AI. To stimulate effector cells, intraperitoneal (IP) CpG or MPO/Freud’s Adjuvant was injected after inducing anti-MPO AI, triggering renal glomerulonephritis and anti-glomerular basement membrane glomerulonephritis (GN).

Results: TLR9 signaling was inhibited with an inhibitory oligodeoxynucleotide before both induction of AI and triggering renal injury.

Results: Mice receiving MPO/CpG/DCs + IP CpG compared to MPO/CpG/DCs + IP CpG (Control) developed heightened immune responses (cells/spleen: 5.4±6 vs 6.1±5.1×10^6, p<0.05) and renal injury (area:3.1±7 vs 11±3μm²/L, p<0.05; abnormal glomeruli:93±3 vs 15±3%, p<0.001) confirming effector cell TLR9 ligand is required for disease induction and a target for therapeutic inhibition. TLR9 inhibition prevented MPO/CA induced systemic and MPO/autoimmunity measured by MPO specific dermal DTH swelling (2.6±18.6±3Dmm, p<0.05) and decreased frequency of MPO stimulated IL-17A producing cells (6±1 vs 21±3cells, p<0.01) compared to control. TLR9 inhibition prevented IL-17A driven mice in receiving MPO/CpG/DCs (DTTH:3.2±3 vs 18.6±3Dmm, p<0.001, IL-17A:21±6 vs 3±0.9, p<0.001) and significantly decreased mononuclear cell infiltration (including both patrolling and infiltrating monocytes) when given to mice with established anti-MPO AI compared to control (DTTH:3±1 vs 13±4mm footpad swelling, p<0.05, area:26±1 vs 34±3μm²/L, p<0.05; abnormal glomeruli:43±9 vs 79±5%, p<0.01).

Conclusions: Therapeutic TLR9 inhibition prevents the development of anti-MPO AI and is a therapeutic option to prevent the development of renal injury once anti-MPO AI is established.

Funding: Government Support - Non-U.S.

FR-PO973

TLR9 Activation Aggravates Murine IgA Nephropathy; Possible Role of BAFF Mediated Pathway

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Background: Contribution of Toll like receptors (TLRs) which play a key role in the innate immune system has been discussed in the pathogenesis of IgAN. We recently demonstrated that TLR9 is importantly involved in progression of kidney injuries in IgAN prone mice. On the other hand, role of B cell activating factor (BAFF) is discussed in the pathogenesis of human IgAN. Present study examined the contribution of BAFF in the TLR9 mediated progression of IgAN using IgAN prone mice.

Methods: Commercially available quiescent IgAN prone mice (ddY mice) at 4 weeks of age were used for this study. They were divided into two groups with (n=8) or without (n=8) TLR9 ligand (CpG-ODN) for 12 weeks. Renal histological lesions and serum levels of IgA, IgG and IgA-IgG immune complexes (IC) were evaluated at 16 weeks of age. Serum levels of aberrantly glycosylated IgA was measured by the binding of Sambucus nigra bark lectin and Ricinus communis agglutinin I. Splenic expressions of TLR9, MyD88, BAFF and its receptor (TACI) were also quantitatively evaluated.

Results: CpG-ODN treated, but not non-treated mice, showed mesangial deposition of IgA, IgG and IgA-IgG immune complexes (IC) were evaluated at 16 weeks of age. Serum levels of aberrantly glycosylated IgA was measured by the binding of Sambucus nigra bark lectin and Ricinus communis agglutinin I. Splenic expressions of TLR9, MyD88, BAFF and its receptor (TACI) were also quantitatively evaluated.

Conclusions: Present study indicated that TLR9 activation exacerbates murine IgAN via increase of aberrantly glycosylated IgA and nephritogenic IC. In addition, present findings also suggested that TLR9 mediated BAFF expression may be involved in the nephritogenic IgA and IC production.
FR-PO974

Key Role of Apoptosis Inhibitor of Macrophage in Phlogenic Action of Glomerular Nephritogenic IgA in IgA Nephropathy

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Background: Apoptosis inhibitor of macrophage (AIM), a protein mainly produced by macrophages, has been reported to be related to autoimmune diseases as well as arteriosclerosis.

Methods: We evaluated the role of AIM in IgA nephropathy (IgAN) using IgAN prone mice, grouped ddY (gddY) (J Am Soc Nephrol.2012;3:1364-74). Serum of gddY mice was injected to AIMKO and wild-type (WT) mice, and proteinuria and glomerular depositions were evaluated over time. In addition, nephritogenic IgA, produced by gddY splenic B cells hybridomas, was injected to AIMKO and WT to perform the same evaluation.

Results: We found excessive expression of AIM in gddY, which were co-localized with glomerular IgA. Glomerular IgA depositions were observed in AIMKO and WT 2h after the injections of gddY serum and purified nephritogenic IgA. The depositions were cleared soon thereafter in WT but later in KO after being accumulated. However, proteinuria was not noticed in WT, but noticed in KO. Moreover, CD45 soon thereafter in WT but later in KO after being accumulated. However, proteinuria was not noticed in WT, but noticed in KO. Moreover, CD45 was accumulated by CD45-negative cells by IgA1-secretive cells by IgA1-secretive patients. Our study defines how these signaling pathways influence IgA1 O-glycosylation.

Methods: IgA1-secretating cells from IgAN patients and healthy controls (HC) were stimulated with IL-6/LOF/OSM with or without JAK-STAK inhibitors. Gd-IgA1 levels were determined by lectin ELISA. Cell lysates from IgAN and HC cells were analyzed by global tyrosine-kinome profiling using PamStation®12 platform and Western blotting. The role of STAT3 or STAT1 in mediating IL-6/LOF/OSM, signaling was confirmed by siRNA knock-down (k/d).

Results: siRNA k/d of STAT3 and STAT1 reduced production of Gd-IgA1 in IgAN cells induced by IL-6 and LOF/OSM, respectively. A specific inhibitor of JAK/STAT signaling reduced IL-6/LOF-enhanced production of Gd-IgA1, but only in IgAN cells. Global tyrosine-kinome profiling identified nine target peptides that were selectively inhibited by the tested JAK/STAT inhibitor in the IgAN cell lysates. Bioinformatics analyses and pathway mapping identified abnormal signaling in JAK/STAT and MAPK cascades as the highest ranked pathway.

Conclusions: IL-6/LOF/OSM cytokines enhanced production of Gd-IgA1 via over-activating JAK/STAT pathways in IgAN cells. Global tyrosine kinome profiling validated this finding and also indicated participation of MAPK. Elucidating the mechanisms of abnormal signaling associated with Gd-IgA1 production in IgAN-secreting cells may provide new targets for treatment of IgAN.

Funding: NIDDK Support

FR-PO975

Expression of Mesangial Tissue Transglutaminase Is Independent of Abrerrantly Glycosylated IgA in Patients with IgA Nephropathy

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Background: It has been reported that tissue transglutaminase (TG2) is essential for mesangial deposition of IgA1 and development of mesangial inflammation in a mouse model of IgA nephropathy (IgAN). We have shown that some IgAN patients have an active form of TG2 in the mesangial area and that mesangial TG2 activity is associated with elevated proteinuria and proliferation of mesangial cells (MC). The impact of aberrantly glycosylated IgA1 on mesangial TG2 expression merits investigation, as circulating immune complexes, including those containing aberrantly glycosylated IgA1, are deposited in the mesangium in IgAN.

Methods: To understand the role of mesangial TG2 in IgAN, expression of TG2 in cultured MC stimulated by sera from IgAN patients with mesangial TG2 activity (IgAN-TG2A), IgAN patients without mesangial TG2 activity (IgAN-TG2N), disease controls (DC), or healthy controls (HC) were assessed. Expression of TG2 in MC stimulated by purified serum IgA1 or enzymatically deglycosylated IgA1 was also assessed. Furthermore, we characterized hinge-region (HR) O-glycosylation profiles of serum IgA1 from IgAN-TG2A and IgAN-TG2N using high-resolution mass spectrometry.

Results: MC stimulated with sera from IgAN-TG2A showed more binding of IgA1 and expressed more TG2 than those stimulated with sera from IgAN-TG2N, DC, or HC (P>0.01). Mass spectrometry analysis identified 13 IgA1 HR O-glycosylomics with up to 3 galactose-deficient glycans. The number of galactose-deficient glycans was not significantly different between IgA1 from IgAN-TG2A and IgA1 from IgAN-TG2N (0.76 vs. 0.79 mol/HR). Enzymatically deglycosylated IgA1 did not change TG2 expression on MC compared to IgA1 from HC.

Conclusions: Sera from IgAN patients enhanced mesangial TG2 expression. Aberrantly glycosylated IgA1 alone was insufficient to increase TG2 expression by MC.

FR-PO979
ACNA Disease Patients Demonstrate a Higher Frequency of CD33+ Myeloid Cells with Variable Suppressive Abilities. Meghan E. Free, Katie Stember, Julie Anne G. McGregor, J. Charles Jennette, Ronald J. Falk, Maureen Su. 1UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 2Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 3Pediatrics, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Myeloid-derived suppressor cells (MDSCs), or CD33+ myeloid cells, have been extensively studied in cancer as potent suppressors of T cell activation. Regulatory T cells do not control T cell proliferation in patients with ANCA disease as an alternative suppressive mechanism.

Methods: Analyses were performed using flow cytometry on peripheral blood mononuclear cells (PBMC) from 63 patients stained with relevant antibodies. Suppressor potential of CD33+ myeloid cells was assessed with a standard T cell suppression assay.

Results: Flow cytometric analysis of PBMCs revealed an increased population of lineage negative, HLA-DR negative, CD11bhigh and CD33+ myeloid cells in patients with ACNA disease compared to healthy controls (mean 2.72% versus 0.18% of PBMCs). This CD33+ myeloid cell population also contained MPO and PR3. Suppression assays utilizing patient CD33+ myeloid cells and autologous T cells have demonstrated variable suppressive capacities with the majority of patients exhibiting modest (30-60%) suppression.

Conclusions: CD33+ myeloid cells are increased in patients with ACNA disease and represent a potential source of T cell suppression not previously investigated. Intriguingly, the patients who demonstrated the highest frequency of CD33+ myeloid cells were those who had sequentially received rituximab and cyclophosphamide.

Funding: NIDDK Support

FR-PO980
Endothelial NF-κB Induction by ACNA-Activated Neutrophils. Mira Choi, 1Adrian Schreiber, 2Claudia Eulebenberg, 2Ralph Kettritz, 3Claus Scheidereit. 1Dept of Nephrology, Charite, Berlin, ECR; 2Charite, Berlin, Germany; 3Experimental and Clinical Research Center (ECRC), Berlin, Germany.

Background: Activation of the NF-κB/Rel family and subsequent transcriptional upregulation of inflammatory mediators plays a central role in vascular diseases. ACNA vasculitis is an inflammatory condition where ACNA-activated neutrophils (PMN) interact with the endothelium resulting in necrotizing vasculitis. We hypothesized that ACNA-activated PMN promote endothelial NF-κB and vascular inflammation.

Methods: NF-κB activation was assessed by IkBα degradation, EMSA, RT-PCR and IHC. NF-κB was studied in renal tissue from mice with ACNA-induced NGN, ACNA-stimulated PMN and endothelial cells.

Results: In kidney extracts from mice in which we had induced anti-MPO Ab-mediated NCGN, we observed a significant correlation between the percentage of crescents and NF-κB activity by EMSA (R²=0.72, n=20). Similar correlations were found for crescents and upregulation of the NF-κB dependent genes TNFa and IkBα. In renal biopsies from patients with ACNA-induced NCGN, we observed strong phospho-p65 staining in the glomerular convolute. Regarding the importance of PMN-EC interactions in ACNA vasculitis, we studied NF-κB activation in PMN and ECs in vitro. Low-dose TNFa priming resulted in a significant increase in NF-κB activity in EC when co-incubated with mAb-stimulated PMN and observed significant IkBα degradation in EC (n=10). We confirmed this with human ACNA preparations. Cell-free PMN supernatants were sufficient for endothelial NF-κB activation indicating that direct cell-cell contact was not required. Consequences of endothelial NF-κB activation were the upregulation of endothelial TNFa and IL-6 mRNA and its release as cytokines into the supernatant, which lead to increased recruitment and adhesion of new PMN.

Conclusions: Renal NF-κB activation and NCGN severity were closely correlated. Our in vitro data demonstrate that ACNA-activated PMN induce endothelial NF-κB activity thereby promoting vascular inflammation by recruiting more PMN. Inducing endothelial NF-κB may help limiting the ACNA-mediated damage.

Funding: Government Support - Non-U.S.

FR-PO981
Ubiquitin C-Terminal Hydrolase-L1 Controls Dendritic Cell Cross Priming of the CD8+ T Cell Response. Anna Reinicke, 1Malte Mühlig, 1Pina Schmucker, 2Tim Otto, 2Christian Kurts, 1Hans-willli Mittrücker, 2Catherine Meyer-Schewig. 1Nephrology, III. Medical Clinic, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2Immunology, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Background: Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) is a central deubiquitinating enzyme of the ubiquitin proteasomal system. UCH-L1 is thought to regulate the pool of ubiquitin. Within the kidney, UCH-L1 is de novo expressed in glomerular podocytes in human and rodent glomerulonephritis. Mice with constitutive UCH-L1 deficiency exhibit an exacerbated course of immune-complex nephritis suggesting that UCH-L1 deficiency may alter the ability to generate effective renal immune responses. The current study was undertaken to identify the origin of renal tubulo-interstitial UCH-L1-expressing cells, 2. To analyze the response of UCH-L1-deficient mice to a bacterial infection, 3. To analyze the role of UCH-L1 in dendritic cells (DCs). Method: Constitutive UCH-L1-deficient mice were generated by Cre-Lox technology. The immunologic phenotype was investigated by challenging UCH-L1-deficient mice with Listeria monocytogenes. Cross presentation and cross priming assays were performed in vitro and in vivo. The DC phenotype was assessed in naive and stimulated DCs by FACS, Western, protemal and deubiquitinate-based activity assays, and real-time PCR.

Results: UCH-L1 is expressed in DCs isolated from kidney and spleen, and in bone-marrow derived cultured DCs. UCH-L1 expression in bmDCs is regulated by IFN-γ and LPS. UCH-L1 activity is upregulated by LPS stimulation while other deubiquitinating enzymes down-regulate their activity in the absence of UCH-L1. DCs are specially equipped to cross present antigen to stimulate a CD8+ T cell response. Cross-presentation of cell-associated antigen in UCH-L1-deficient DCs is significantly reduced in vitro and in vivo while activation of a CD4+ T cell response is unaffected. Finally, exposure to L. monocytogenes results in a significantly decreased generation of antigen-specific CD8+ T cells.

Conclusions: We describe a hitherto unrecognized role for UCH-L1 in controlling CD8+ T cell activation by DCs.

Funding: Government Support - Non-U.S.

FR-PO982
CD103+ Dendritic Cells Elicit CD8+ T Cell Responses to Accelerate Kidney Injury in Adiriamycin Nephropathy. Qiao Cao, 1Qing Li, 1Xin M. Wang, 2Chenguang Wang, 1Yuan Min Wang, 2Stephen L. Alexander, 1Yiping Wang, 2Bijan C. Harris. 1Centre for Transplant and Renal Research, Westmead Millennium Inst for Medical Research, The Univ of Sydney, Sydney, NSW, Australia; 2Flow Cytometry Facility, Westmead Millennium Inst for Medical Research, The Univ of Sydney, Sydney, NSW, Australia; 3Centre for Kidney Research, Children's Hospital at Westmead, Sydney, NSW, Australia.

Background: CD103+ dendritic cells (DCs) in non-lymphoid organs exhibit two main types of function, namely maintaining tolerance by induction of regulatory T cells and protecting against tissue infection through activation of CD8+ T cells. However, the characteristics and functions of CD103+ DCs in kidney remain unclear.

Methods: Adiriamycin nephropathy (AN) was induced in BALB/c mice. The distribution, phenotype and function of kidney CD103+ DCs were assessed in normal and AN mice. CD103+ DCs were depleted by neutralizing CD103-saporin (SAP) antibody in AN mice to examine their role in vivo.

Results: In the present study, we showed that CD103+ DCs are one of four subpopulations of renal mononuclear phagocytes in normal kidney; they expressed DC-markers CD103 and CD86, but down regulation of VDR. Podocytes in renal cortical sections of Tg26 mice displayed enhanced expression of SNAIL and down regulation of VDR. NF-κB and NF-κB237 displayed upregulation of SNAIL but down regulation of VDR. HIV-IPs displayed H3K4 trimethylation at SNAIL promoter and enhanced expression of histone deacetylase (HDAC) 1, DNA methyl transferase (Dnmt) 3b. IP studies revealed the association of HDAC1, Dnmt3b, Dnmt1, and mSin3A with the SNAIL, VDR agonts, HDAC inhibitor, and demethylating agents alone could not reverse NF-κB expression optimally, but could do so, when used in combination. In summary, SNAIL recruits multiple chromatin enzymes to form a repressor complexes that down regulate VDR expression in HIV milieu. To upregulate VDR optimally, reversal of VDR expression is needed.

Conclusions: SNAIL recruits multiple chromatin enzymes to form a repressor complexes that down regulate VDR expression in HIV milieu. To upregulate VDR optimally, reversal of VDR expression is needed.

Funding: NIDDK Support

FR-PO983
Advanced Glycation End Products Induced the Imbalance Between Th17 and Treg Cells via RAGE Pathway in Diabetic Nephropathy. Yanlin Zhang, Ao Cheng. Dept of Nephrology, The First Affiliated Hospital of Xiamen Univ, Xiamen, Fujian, China.

Background: There was imbalance of Th17/Treg cells in patients with diabetic nephropathy, but the mechanism was still unclear. Advanced glycation products (AGEs) often accumulated in the patients with diabetic nephropathy. The main purpose of this experiment is to explore whether AGEs can cause the imbalance of Th17/Treg cells through RAGE signaling pathway.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Methods: (1) Recruitment of 20 healthy adults and 40 diabetic nephropathy patients of CKD stages 3 to 5. AGEs content of CD4+ T cells/ Th17 cells/ Treg cells to verify the correlation. (2) Prepared AGE-HSA in vitro and isolated the initial CD4+ T cells from healthy volunteers peripheral blood to explore the effect of AGE-HSA on the differentiation of initial CD4+ T cell: AGE-HSA with different dose and time stimulated initial CD4+ T cells, or for RAGE neutralization, blocking and to detect the ratio of Th17 cell and Treg cells by flow cytometry and determine the expression mRNA of RORgt and Foxp3, and the expression of mRNA and protein of STAT3 and HIF-1α.

Results: In patients with diabetic nephropathy, there is accumulation of AGEs and increasing of Th17 cells and the reduction of Treg cells. The ratio of Th17 cells and Treg cell is imbalance (increase in the proportion). There was a positive correlation between the concentration of AGEs and ratio of Th17 cells and Treg cells; (2) The AGE-HSA in a dose dependent manner inhibited the CD4+ T cells differentiation to Th17 cells, or for RAGE neutralization, blocking RAGE could mitigate this effect; (3) AGE-HSA increased the expression of RORgt in the initial CD4+ T cells, but no effect on Foxp3. After blocking RAGE, it could inhibits the expression of RORgt induced by AGE-HSA; (4) the expression of STAT3 and HIF-1α was raised in the initial CD4+ T cells induced by AGE-HSA, while blocking RAGE, expression of STAT3 and HIF-1α. induced by AGE-HSA was inhibited.

Conclusions: In patients with diabetic nephropathy, there was positively correlated between the content of AGEs and the proportion of Th17 cells and Treg cells, and AGE-HSA of STAT3 and HIF-1α. induced by AGE-HSA was inhibited.

Histological injury in the biTreg 5 months showed severe proliferative glomerulonephritis in pristane injected wild type mice. As one possible explanation for the improved outcome, we found that biTregs from wild type mice produced less inflammatory cytokines. Studies in a model of acute crescentic glomerulonephritis demonstrated that activation of RORgt in the kidney is imbalance (increase in the proportion). There was a positive correlation between the content of AGEs and the proportion of Th17 cells and Treg cells, and AGE-HSA of STAT3 and HIF-1α. induced by AGE-HSA was inhibited.

Conclusions: In patients with diabetic nephropathy, there was positively correlated between the content of AGEs and the proportion of Th17 cells and Treg cells, and AGE-HSA of STAT3 and HIF-1α. induced by AGE-HSA was inhibited.

FR-P0984


Background: We recently characterized Foxp3+ regulatory T cells, co-expressing the Th17 characteristic transcription factor RORγt, as an independent and bi-functional T-cell lineage (biTregs). biTregs secrete both, anti-inflammatory (IL-10, IL-35), but also pro-inflammatory (IL-17) cytokines. Studies in a model of acute crescentic glomerulonephritis suggest that pro-inflammatory biTreg functions are mediated by RORγt. This is of high clinical relevance, since multiple RORgt blocking agents are currently under development.

Methods: Systemic lupus erythematosus (SLE)-Pristane in biTregγ+/mice.

Results: Time course analyses showed increasing infiltration of biTregs into kidneys of pristane injected mice with a maximum at around 5 months. Subsequently percentages decreased and were back to baseline at 8 months. To study the functional role of RORγt in biTregs, Foxp3γ- x RORCγ- mice were generated (biTregγ-). Renal histology at 8 months showed severe proliferative glomerulonephritis in pristane injected wild type mice. Histological injury in the biTregγ- group, in contrast, was significantly ameliorated.

Conclusions: Depletion of Tregs with anti-CD25 antibodies abrogated the beneficial effects of IL-2C treatment. Significant recovery of all 3 activation subsets occurred 3 months post-rituximab treatment. Using ROC curve analysis, activatedCD154+CD45RA- CD4+ T cells (P<0.01) were upregulated in responders (75.7±1.2%). IFN-γ+CD8+ T cells were similarly decreased in responders (73.6±1.2%) and non-responders (72.6±1.1%) (p=0.005) and controls (72.6±1.25%). IL-2+CD8+ subs were lower in responders (24.0±14%) compared to non-responders (44.2±15%) (p=0.007) and controls (63.1±5%) (p=0.03). Significant recovery of all 3 activation subsets occurred 3 months post-rituximab treatment.

Conclusions: We have identified prognostic markers which define a subset of FSGS patients bearing an immunological signature representing hyperresponsiveness to T-cell stimulation, with good response to rituximab therapy.

FR-P0987

Cytokine Profiling in Rituximab-Treated Pediatric Focal Segmental Glomerulosclerotic Nephrotic Patients Wee Song Yeo, Chang-Yien Chan, Hui Kim Yap. Pediatrics, Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore, Singapore.

Background: Focal segmental glomerulosclerosis (FGS) is the most common histological pattern seen in pediatric steroid-dependent and steroid-resistant nephrotic patients. In recent years, rituximab is increasingly used in nephrotic patients who have failed therapy with conventional immunosuppressants. This study aimed to examine the cytokine profile in rituximab-treated pediatric FSGS nephrotic patients and elucidate the cytokine profile differences between responders and non-responders.

Methods: We study population consisted of 13 pediatric FSGS patients who underwent rituximab therapy. Plasma cytokine profiling was performed on each of these patients utilizing multiplexed Luminex® Cytokine Human 27-plex assay pre- and post-rituximab therapy.

Results: Five (38%) of the patients responded to rituximab, defined as having achieved complete resolution of proteinuria accompanied by cessation of prednisolone and calcineurin inhibitors within 3 months. All patients in the study demonstrated an increase in plasma interferon-gamma-inducible protein (IP)-10 levels post-rituximab therapy (554.3±62.4 pg/ml (pre) vs 793.4±125.5 pg/ml (post), p<0.008). Comparing the cytokine profile between responders and non-responders, responders demonstrated a positive mean-fold change in macrophage inflammatory protein (MIP)-1α, in contrast to non-responders which demonstrated a negative mean fold change (0.23±0.16 vs -0.17±0.08, p=0.04). There were, otherwise, no noted significant differences in the other cytokines i.e. pre- (post-rituximab and ii) between responders and non-responders.

Conclusions: Our study results suggest the development of a pro-inflammatory state in our patients post-rituximab therapy. The increase in plasma IP-10 in patient post-rituximab may account for the phenomenon of rituximab-associated colitis. The finding of increased plasma IP-10 in responders compared to non-responders is novel. Further mechanistic studies are required to ascertain the role of MIP-1α in the mechanism of action of rituximab.

Funding: Government Support - Non-U.S.
FR-P0988
Gut-Kidney Axis in the Pathogenesis of IgA Nephropathy
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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. It is characterized by deposition of deoxyribonucleated IgA1 and IgA antibodies in the glomeruli and its pathogenesis is only partially defined. Intestinal microbiota could be involved in IgAN, as suggested by the observation that B-cell activation factor (BAFF) transgenic mice had high levels of aberrantly glycosylated serum IgA, the presence of commensal flora and the circulation of corresponding specific IgA antibodies being essential for the development of IgA deposits. BAFF is an important regulator of B cell maturation, survival and function. The aim of the study was to analyze the role played by gut kidney axis in the pathogenesis of IgAN.

Methods: 16 healthy controls (HC) and 32 IgA patients (16 non-progressors - NP and 16 progressors - P) were included in the study. Serum creatinine, estimated Glomerular Filtration Rate, 24h-proteinuria and histological descriptions following Oxford Classification (MEST score) were analyzed. Gut microbiota, urinary and fecal metabolome of all subjects were characterized by 16S sequencing, Biochrom 30 series amino acid analyzer and gas-chromatography mass spectrometry/solid-phase microextraction (GC-MS/SPME).

Results: Serum BAFF levels were positively correlated with 24h-proteinuria (**P <0.01 P vs HC). IgAN patients with histological grade at diagnosis M1, E1, S1 and T1 had significantly higher levels of serum BAFF than HC. Moreover, serum BAFF levels were positively correlated with 24h-proteinuria (r=0.47, **P <0.0069) and with the levels of fecal phenolic metabolites (r=0.61, ***P <0.0003).

Conclusions: Gut kidney axis might play an important role in the pathogenesis of IgAN.

FR-P0989
Intestinal Macrophages Polarized to Activation of Pro-Inflammatory and Had Dysfunction of Phagocytosis Leading to Aggravate Microinflammation and Assist Bacterial Translocation as Carrier in Uremia Rats
Lingshuang Sun, Hongli Jiang, Hua Liu, Meng Wei. Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of Medicine School.

Background: This study investigated whether intestinal macrophages are related to low-grade inflammation and bacterial translocation (BT) during uremia, and whether probiotics can alter the macrophage activity.

Methods: Male Sprague-Dawley rats were randomly divided into 3 treatment groups: sham, uremia (untreated), and uremia + probiotic. The expression of cell surface antigen CD11a (a.k.a., lymphocyte function-associated antigen 1 [LFA1]), inducible nitric oxide synthase (iNOS), ICAM1, and TGF-β were analyzed by immunohistochemistry. Gene and protein expression of early growth response protein 1 (EGR1) and TLR4 in intestinal specimens were determined. Density of labeled macrophages and tracer bacteria in intestinal and extraintestinal tissues were examined by immunofluorescent microscopy, and macrophage micromorphology were examined by transmission electron microscopy. In addition, the intestinal LPS levels were measured. Intestinal uremia exhibited significantly high intensity of expression of iNOS, ICAM1, and TGF-β staining. Gene and protein expression levels of intestinal TLR4 and EGR1 were also highest in this group. Intestinal segments of uremic rats exhibited high density and broad distribution of tracer bacteria and macrophages. Intestinal macrophages in untreated rats showed fewer cytoplasmic protrusions and pseudopodia. Administration of probiotics resulted in restoration of macrophage classic activation and phagocytosis that was associated with a reduction in BT.

Conclusions: In the uremic state, intestinal macrophages are polarized toward a proinflammatory phenotype that results in low-grade inflammation. Abnormal intestinal macrophage activation and impaired phagocytic function are associated with increased BT. Probiotics may reduce BT by enhancing phagocytosis of intestinal macrophages.

Funding: Government Support - Non-U.S.

FR-P0990
Linking PI3K/AKT Signaling to RNase 7 Production and Urinary Tract Sterility
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Background: Antimicrobial peptides (AP) play a role in shielding the uroepithelium from uropathogenic E. coli (UPEC). We have identified RNase 7 (RNase 7) as a potent, epithelial-derived AP that is secreted by the bladder uroepithelium and renal intercalated cells. RN7 serves as an immune sensor for the uroepithelium from UPEC. Currently, there is a limited understanding of the mechanisms that regulate RN7 production, and if disrupted RN7 production increases UTI risk. Using a chemical inhibitors transcriptome PCR array, we identified the PI3K/AKT pathway as a unique regulator of RN7. Here, we confirm that PI3K/AKT regulates RN7 expression and relate changes in RN7 to UTI pathogenesis.

Methods: To evaluate the role of PI3K/AKT in regulating RN7, we treated primary human renal epithelial cells (REC) with insulin, a known PI3K agonist and/or insulin+wortmannin (wort), a PI3K/AKT inhibitor. PI3K/AKT activation was confirmed by Western blot. qRT-PCR and ELISA quantitated RN7. UPEC growth in urine inoculated with and/or insulin+wort was measured.

Results: Insulin-dependent phosphorylation of the PI3K/AKT in RFC was detected by 1hr. Insulin induced RN7 gene expression and protein expression 3-fold (25.23±3.51ng/mL vs 0.05±0.06 ng/mL). RN7 induction was abolished with wort, confirming PI3K/AKT involvement in RN7 production. Media from insulin treated RFC suppressed UPEC growth compared to media from RFC pretreated with wort or vehicle control, suggesting that PI3K/AKT and RN7 is involved in UTI pathogenesis. Urinary RN7 levels were significantly higher during disease flare compared to levels during remission. Serum LPS level correlated with acetate level (r=0.52, **P <0.01). Renal LBP, GPR-41 and GPR-43 expression showed markedly increased in nephritis patients compared to healthy controls, and was predominantly detected in the tubulo-interstitium, associated with inflammatory cell infiltration, fibrosis and tubular atrophy. LBP, GPR-41 and GPR-43 expression showed similar staining intensities and localization in patients with nephritis and those with non-glomerulus diseases.

Conclusions: Our data suggest that acetate and LPS may be involved in the pathogenesis of lupus nephritis and non-glomerulus diseases.

Funding: NIDDK Support

FR-P0991
Serum Acetate and Lipopolysaccharide Levels Correlate with Disease Activity in Patients With Lupus Nephritis
Daniel Tak Mao Chang, Ping Lung Chan, Qing Zhang, Yin Yi Au, Desmond Y.H. Yap, Mel Chau, Susan Yung. Dept of Medicine, The Univ of Hong Kong, Hong Kong.

Background: Lupus nephritis is a severe manifestation of systemic lupus erythematosus and is associated with poor prognosis. The gut microbiota has been implicated in the etiology of autoimmune diseases. Bacterial products from the gut may enter the circulation and induce inflammatory responses. Acetate is a short chain fatty acid (SCFA) produced by gut microbiota and lipopolysaccharide (LPS) is a component of the outer wall of Gram-negative bacteria. We measured serum acetate and LPS levels and intra-renal expression of their cell surface receptors in lupus nephritis patients to investigate the potential relationship between gut microbiota and lupus nephritis pathogenesis.

Methods: Serum acetate and LPS levels were measured in patients with biopsy-proven severe proliferative lupus nephritis, patients with non-lupus glomerular diseases and healthy controls (n=50 for each group). Intra-renal expression of LPS-binding protein (LBP) and GPR-41 and GPR-43 (SCFA receptors) was also examined.

Results: Serum acetate and LPS levels were significantly higher in patients with lupus nephritis compared to levels in patients with non-lupus renal diseases (P<0.05, for both) and healthy subjects (P<0.01, for both). In lupus nephritis patients, serum acetate and LPS levels were significantly higher during disease flare (P=0.04 and P=0.0015 respectively compared to levels during remission). Serum LPS level correlated with acetate level (r=0.52, P=0.0001), and inversely correlated with that of IgG (r=−0.61, P=0.01). Renal LBP, GPR-41 and GPR-43 expression was markedly increased in lupus nephritis patients compared to healthy controls, and was predominantly detected in the tubulo-interstitium, associated with inflammatory cell infiltration, fibrosis and tubular atrophy. LBP, GPR-41 and GPR-43 expression showed similar staining intensities and localization in patients with lupus nephritis and those with non-lupus renal diseases.

Conclusions: We propose that acetate may be involved in the pathogenesis of lupus nephritis and non-glomerulus diseases.

Funding: Government Support - Non-U.S.

FR-P0992
Noninvasive Assessment of Macrophage Activation in Experimental Glomerulonephritis Using Optical Imaging with Near-Infrared Light as a Surrogate of Disease Activity
Sebastian Braehler, Dongyue Huang, Matthew David Cheung, Walter J. Akers, Alfred Hyoungjui Kim. Washington Univ School of Medicine, St. Louis, MO.

Background: Glomerulonephritis (GN) represents a major cause of morbidity & mortality. The standard for diagnosing GN is through renal biopsy, but this is not performed uniformly across many centers. There is an unmet need to identify a noninvasive approach for detecting disease activity in patients with GN. Recent advances in deep tissue imaging using probes detected by near-infrared (NIR) wavelengths have enabled the noninvasive probing of biologic activity. Macrophage infiltration of the kidney is observed in early GN and once activated, express the cysteine protease cathepsin B. Thus, renal macrophage activation can be assessed by detecting urinary RNase7 levels that reflect macrophage infiltration.

Methods: RNase7 was induced in 129 mice by nephrotoxic serum (NTS) delivered intravenously. RNase7 induction was assessed using albumin ELISA & chromogenic creatinine assay. H&E and PAS stained slides of mouse kidneys were observed using light microscopy. Presence of renal macrophages was confirmed using FACS. NIR optical imaging of anesthetized mice was performed following IV administration of a cleavable fluorophore for imaging macrophages. We performed serial urinary RNase7 levels to monitor macrophage infiltration.

Results: In mice with uninflamed kidneys, we confirmed the paucity of renal macrophages. Accordingly, there was minimal renal fluorescence signal as determined by renal fluorescence intensity signal in NTS mice compared to control mice.
FR-PO993  
Improved Tissue Clearing and 2-Photon Imaging of Mouse Kidneys Reveals Immune Cell Architecture in Nephrotic Nephritis  
Matthew David Cheung, Dongyue Huang, Alfred Hyongjui Kim.  
Background: Tissue clearing approaches such as CLARITY renders tissue transparent, and in combination with two-photon microscopy, enables microscopic visualization deep internal structures in unaltered organs. These cutting edge approaches have drastically improved the understanding of cellular circuits in the brain. However, application of this approach has only recently been described for the kidney. Here, we clear mouse kidneys to better understand the immune cell architecture following induction of nephrotic nephritis (NTN) using a modified lipid removal approach that also worked for human kidney fragments.  
Methods: 129 mice were injected intravenously with nephrotic serum to induce NTN. Mice were perfused with an acrylamide monomer solution to form the basis of the hydrogel. Lipid removal was accomplished using 8% sodium dodecyl sulfate (SDS). An acrylamide solution was used to quench light absorbing heme in red blood cells trapped within the tissue. Cleared mouse kidneys were stained with antibodies specific for B cells, T cells, macrophages, and dendritic cells (DCs). Human kidney fragments were incubated in acrylamide monomer solution then cleared as mentioned above. Cleared tissue was imaged using two-photon microscopy.

Results: Compared to previously published protocols, perfusion of acrylamide monomers into mice significantly accelerated the tissue clearing process. Enhanced tissue clearing was observed when we incubated kidneys in aminoalcohols. We observed vast networks of lymphocytes, macrophages, and DCs cleared NTN kidneys compared to DC-deficient control kidneys. Human kidneys also were cleared using this approach, and we noted DC networks in healthy donor controls.

Conclusions: We identified a new protocol that enhanced and accelerated tissue clearing in mouse and human kidneys. Using this approach, we found elaborate networks of lymphocytes and monocyte-derived cells in NTN mouse kidneys. We also observed DC networks in healthy human donor fragments. These data demonstrate the utility of tissue clearing in evaluating cellular architecture in mouse and human kidneys.  
Funding: Private Foundation Support

FR-PO994  
Natural IgM Mediates Ischemic AKI  
Lindsey R. Goetz, Jennifer Laskowski, 1 Brandon Renner, 1 Rachel A. Woolaver, 1 Liudmila Kulik, 2 Kazue Takahashi, 3 Matthew C. Pickering, 1 Joshua M. Thurman.  
Background: Glomerular IgM deposition occurs in numerous “non-immunologic” kidney diseases and has been shown in chemical and inflammatory models of injury. We recently demonstrated that complement activation within the kidney leads to neo-epitope formation. Because the alternative complement pathway is activated in renal ischemia reperfusion (IR) injury, we hypothesized that complement activation during renal IR generates neo-epitopes recognized by natural IgM antibodies that then exacerbate inflammatory injury.

Methods: To investigate this hypothesis, we used a 24 minute IR model. Results: We first subjected soluble IgM deficient (sIgM) mice to renal IR and found a trend toward less severe injury in these mice vs. wild type (wt) controls (mean BUN of 135 ± 39 [SD] and 152 ± 26 mg/dL, respectively; n ≥ 7, p = NS). To accentuate complement activation in this model, we then exposed mice heterozygous for complement regulatory protein factor H (B6/±) to the same IR protocol and found that the B6/± mice sustained worse renal injury and had greater glomerular IgM deposition than wt controls (mean BUN of 114 ± 46 and 63 ± 48 mg/dL, respectively; n ≥ 14, p = 0.009 and mean glomerular IgM RFUs of 44 ± 7 and 22 ± 7, respectively; n ≥ 8, p = 0.0002). To further evaluate IgM pathogenicity, we induced IR injury in mice deficient in both factor H and IgM (B6/± IgM-) and noted a trend toward attenuation of renal injury in the B6/± vs. B6/± mice (mean BUN of 106 ± 69 and 127 ± 52 mg/dL, respectively; n ≥ 7, p = NS) with data collection ongoing.

Conclusions: These data suggest that natural IgM contributes to ischemic renal injury by binding neo-epitopes generated during complement activation in the kidney. This adds to a growing body of evidence suggesting a common final pathway of IgM-mediated glomerular injury in a variety of “non-immunologic” renal disorders and offers a novel therapeutic target for the treatment of these diseases.  
Funding: NIDDK Support

FR-PO995  
Activation of Toll-Like Receptor 2 in the Pathogenesis of Contrast-Induced Nephropathy  
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Background: Innate immunity mediated by Toll-like receptors (TLRs) is involved in the pathophysiology of contrast-induced nephropathy (CIN). We studied the expression of TLRs and associated molecules in CIN using human renal proximal tubule epithelial cells (RPTECs) and aged diabetic (db/db) mice.  
Methods: We cultured RPTECs in normal (5mM) or high (35mM) glucose media for 24 h and then exposed them to nonionic (iodixanol or iohexol) and ionic (Urografin) contrast media (CM) at a dose of 25–100 mg iodine/ml for another 24 h. Then we cleaved the same media. 24-wk-old male db/db mice were given nonionic CM i.v. (3 g of iodine/kg bw) after 24 h water deprivation. All mice were sacrificed 24 h after CM injection.

Results: The mRNA expressions of TLR2 increased by 2.5 fold (p < 0.05), TICAM-1 by 1.7 fold (p < 0.05) in RPTECs exposed to iohexol compared to untreated RPTECs in a dose-dependent fashion. RPTECs in high glucose for 48 h and exposed to ioxanol showed significantly increased apoptosis compared to RPTECs in normal glucose. 24-wk-old db/db mice became obese, polyuric, glucosuric, ketonuric, and had increased GFR, systolic blood pressure, urine NGAL, and renal tubular damage compared to nondiabetic (db/m) control mice. 24 h after iohexol injection, db/db mice showed a significant decrease in GFR, metabolic acidosis and significant increases in serum creatinine, urine and kidney KIM-1 levels and kidney damage histologically compared to control db/d mice. After iohexol administration, the mRNA level of TLR2 was significantly increased by 2.4 fold (p < 0.01) in kidney compared to control but there was no change in TLR4 expression. The expression of CD11b and CD68 were also significantly upregulated in kidney.

Conclusions: High glucose RPTECs and diabetic (db/db) mice are vulnerable to CIN. Innate immunity mediated by TLR2 plays a major role in the pathogenesis of CIN as demonstrated by in vitro and in vivo studies. TLR2 may prove to be a promising drug target for the development of new therapeutics against CIN.

Funding: Private Foundation Support

FR-PO996  
Heparanase Deficiency Improves Renal Function During Experimental Glomerulonephritis  
Marileen Garson, 1 Marinell Benner, 1 Henry Dijkman, 1 Jinxing Li, 1 Ton J. Rabolink, 1 Israël Vladovský, 2 Jo H.M. Berden, 1 Angelique Roep, 1 Michael Elkin, 3 Joris A. Smits, 1, 3 Centre for Complement and Inflammation Research, Imperial College London, London, United Kingdom.

Background: Heparanase (HPSE), a heparan sulfate (HS)-specific endoglucuronidase, mediates the onset of proteinuria and renal damage during experimental diabetic nephropathy. Glomerular HPSE expression is increased in the majority of proteinuric diseases. The exact role of HPSE in the development of other inflammatory glomerular diseases is still unknown.

Methods: Here, we evaluated the role of HPSE in two models of experimental glomerulonephritis, being a murine basement membrane and lipopolysaccharide (LPS)-induced glomerulonephritis, in wild type (WT) and HPSE-deficient mice.

Results: Induction of experimental glomerulonephritis led to an increased HPSE expression in WT mice, which was associated with a decreased glomerular HS expression and albuminuria. Albuminuria was reduced in the HPSE-deficient mice in both models, which was accompanied by a better renal function and less renal damage. Notably, glomerular HS expression was preserved in the HPSE-deficient mice. Glomerular leukocyte and macrophage influx was reduced in the HPSE-deficient mice, which was accompanied by a reduced expression of both Th1 and Th2 cytokines. In vivo, tumor necrosis factor (TNF)-α and LPS directly induced HPSE expression and increased transendothelial albumin passage in a HPSE-dependent manner.

Conclusions: Our study shows that HPSE deficiency ameliorates proteinuria and renal damage in experimental glomerulonephritis by preserving glomerular HS expression, and reducing leukocyte and macrophage influx, and by affecting the local cytokine milieu.

FR-PO997  
Iron Chelation as a Novel Renoprotective Strategy in Lupus Nephritis  
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Background: Poorly liganded iron damages tissue via several mechanisms. Multiple iron homeostasis proteins have been proposed as urinary biomarkers of lupus nephritis, and we have previously found that renal tissue iron levels are increased in the (NZBxNZW)F1 mouse model of lupus nephritis. Anemia is also common in lupus patients. Together, these data suggest that dysregulation of body iron homeostasis may occur in lupus. This pilot data suggests that dysregulated body iron homeostasis affects hematological parameters.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.
**FR-PO998**

IKK2 Inhibition Inhibits the Initiation, but Aggravates the Progression of the Disease in a Mouse Model of Lupus Nephritis. 

Miki Yatabe,1,2,3 Chihiro Nishimura,2 Tetsuhiro Kato,4 Ryo Kubo,4 Takanori Maruo,4 Michihiro Horiuchi,4 Takeshi Yamazaki,4 Takeshi Okada,4 Masaki Matsuzaki,4 Masayasu Mutoh,4 Shoko Yamanaka,4 Masahiro Takahashi,5 Masato Kato,2,6 Masahito Kato,2,7 Akiko Ito,2,8 Toshio Kishimoto,2,9 Minoru Sato,2,10 Takeshi Ozaki,2,11 Masayuki Yonezawa,1,2,3

**Background:** The NF-kB transcription factor family facilitates the activation of dendritic cells (DC) and CD4+ T helper (Th) cells, which are important for protective adaptive immunity. Inappropriate activation of these immune cells may cause inflammatory disease, and NF-kB inhibitors are promising candidate drugs.

**Methods:** Here, we investigated whether inhibiting the NF-kB component IKK2 can attenuate crescentic glomerulonephritis, a severe DC- and Th-cell dependent kidney disease by induction of the passive and the accelerated NTN mouse model.

**Results:** Prophylactic pharmacological IKK2 inhibition reduced DC activation, Th cell activation and ameliorated glomerulonephritis in mice. However, therapeutic IKK2 inhibition during ongoing disease, which is relevant for clinical situations, unexpectedly aggravated the nephritogenic immune response and disease symptoms. This resulted from systemic loss of regulatory T cells (Tregs), which have been previously shown to protect against crescentic glomerulonephritis and which require IKK2 as well.

**Conclusions:** In conclusion, although IKK2 inhibition can suppress the induction of nephritogenic immune responses in vivo, it may aggravate such responses in clinically relevant situations, because it also impairs Treg, and thereby unleashes pre-existing nephritogenic responses. Our findings argue against using IKK2 inhibitors in chronic glomerulonephritis, and perhaps also in other immune-mediated diseases.

**Funding:** Government Support - Non-U.S.

**FR-PO999**

Transfused M2 Macrophages Ameliorate Renal Injury in Murine Nephrotoxic Serum Nephritis. 

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**Background:** Glomerular leukocyte infiltration is a hallmark of glomerulonephritis. In addition to the effector roles of glomerular macrophages (M2a) for tissue injury, recent studies found involvement of alternatively activated macrophages (M2b Mø) in resolution of kidney inflammation. The aim of this study is to directly assess the potential of M2b Mø to protect against renal injury in murine nephrotoxic serum (NTS) nephritis.

**Methods:** Bone marrow (BM)-derived Mø and mouse iPS-derived Mø were obtained under the stimulation of IL-4/IL-13 to differentiate M2b Mø with high expression of arginase-1 and IL-10. M2b Mø were co-cultured with vehicle-treated mice (median onset of albuminuria 39 and 32 weeks, respectively).

Liver iron concentration was significantly lower in deferiprone-treated mice than vehicle-treated mice, consistent with effective iron chelation. Renal cortical and outer medullary iron concentrations were not significantly different between groups. Unexpectedly, hematocrit was significantly improved by treatment with deferiprone (48% increase versus 39% increase in vehicle-treated mice; P<0.01), whereas red cell hemoglobin and plasma non-heme iron concentrations were not different between groups.

**Conclusions:** Our pilot data suggest that iron chelation may delay the onset of albuminuria in a mouse model of lupus nephritis without adversely affecting hematological parameters.

**Funding:** Private Foundation Support

**FR-PO1000**

A Randomized Multicomponent Intervention to Reduce Disparities in Transplant Referral: Results from the RaDIANT Community Study

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**Background:** The Reducing Disparities In Access to kidney transplantation (RaDIANT) Community Study is a dialysis facility-level randomized clinical trial to test the effectiveness of a multicomponent intervention in improving kidney transplant (KTx) referral and reducing racial disparities in referral in Georgia.

**Methods:** In 2013, 134 dialysis facilities were randomized to receive either usual KTx education (n=67) or a multicomponent intervention conducted by, consisting of KT education and engagement activities targeting dialysis facility leadership, staff, and patients (n=67) over 12 months. Paired t tests, overall and by race [white and African-American (AA)], were used to compare referral at 9 months of intervention vs. baseline, in intervention and control facilities.

**Results:** Facilities that received the intervention had a greater absolute increase in referral over 9 months than facilities that performed usual KTx education (+7.8% vs. -2.5%).
A total of 51 of the 67 (76.1%) intervention facilities improved their percentage of patients referred for KTxs over the 9 month study period. Intervention vs. control facilities had a greater increase in referral among AA (+7.3% vs. -2.5%) than white (+0.4% vs. -1.2%) patients over 9 months. Among the 26 dialysis facilities that had an AA vs. white racial disparity in referral at baseline, 69.2% no longer had a racial disparity in referrals by 9 months.

Conclusions: Data from RaDIANT Community Study intervention facilities suggest that a large, randomized, quality improvement program among dialysis facilities in GA may improve KTxs access. Availability of data after 12 months of the intervention will allow final assessment of the effectiveness of the intervention.

FR-PO1002
Association of Neighborhood Poverty and Living Donor Kidney Transplant Rates by Race
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Background: Despite a growing shortage of deceased donor kidneys in the US, living donation (LD) rates have declined steadily since 2004. We sought to understand the impact of candidate socioeconomic environment on living donation rates.

Methods: We identified all candidates listed for kidney or kidney pancreas transplant in the SRTR database from 2000-2010. Data was linked to US census data on median income of candidate zip code. Neighborhood poverty was defined as neighborhoods with median income below $25,000.

Results: Neighborhood poverty was associated with lower LD rates for all racial and ethnic groups. Overall LD rates were highest among Caucasians and lowest among AA. Efforts should be made to remove financial disincentives to living donation to address racial and socioeconomic disparities in access to the life-saving treatment of transplant.

FR-PO1003
Deceased Donor Renal Transplant eGFR at Six Months Has Improved in the Last 13 Years in Spite of Declining Donor Quality
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Background: Deceased donor quality has declined in the last decade but long-term graft outcomes are improving. We sought to analyze the trend in graft function at six months post-transplant in relation to this improvement.

Methods: All adult deceased donor kidney transplant recipients with at least six months graft survival recorded in the SRTR database between 2000 and 2012 were analyzed. The CKD EPI eGFR was determined based on the patient characteristics and serum creatinine at six months post-transplant. KDPI of the donors was also calculated. Linear regression was used to determine the effect of covariates on eGFR.

Results: 111,678 deceased donor recipients were identified. 4918 (4.4%) recipients with no six month creatinine time record were excluded. The median eGFR improved from 54.5 ml/min./1.72m2 in 2000 to 58.9 in 2012 (p=0.001) while the median KDPI increased from 41% to 46%(p=0.001). The use of tacrolimus/mycophenolate derivative also increased from 33.1% to 89.8%. Every 10 unit increase in KDPI resulted in a 3 ml/min./1.72m2 decline in eGFR.

FR-PO1004
Recipient Age and KDPI Are the Most Potent Predictors of Early Acute Rejection in Deceased Donor Kidney Transplantation
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Background: The rate of acute rejection in first six months after deceased donor kidney transplant is now under 10% in the modern era of immunosuppression. We sought to determine the factors predictive of acute rejection in this era.

Methods: All recipients transplanted between 2001 and 2012 in the SRTR database were included in the analysis. Logistic regression was performed to determine the odds ratio of acute rejection in the first six months adjusting for multiple covariates.

Results: The acute rejection rate was 7.1% during the study period. KDPI and recipient age were the most important factors influencing rejection rates with recipients under 30 years old having a rate of rejection more than double that of recipients 60 years or older and recipients receiving donor kidneys with a KDPI over 90% having a 2 fold increase in rejection rate over those receiving a kidney with a KDPI less than 30%.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
No vascular complications, rejection or allograft loss was noted. All of the donors were aged 0 to 5 years of age. Younger age and low weight of the donors did not adversely affect our results. The average serum creatinine remains at 0.89 to date. Kidney size 0.3 to 1.2 cm on average at 3-6 months in follow up. There were no perioperative complications, allograft failure, rejection, vascular complications or recurrence of the primary disease. The average serum creatinine remains at 0.89 to date.

Conclusions: KDPI and recipient age are the most important factors associated with rejection. Risk stratification for donor recipient pairs based on age and KDPI should be considered when determining induction and maintenance immunosuppression needs.

The only factors in the KDPI determination associated with rejection were donor age, donor hypertension, HCV seropositivity, and black donor race, with age accounting for most of the effect.

Conclusions: KDPI and recipient age are the most important factors associated with rejection. Risk stratification for donor recipient pairs based on age and KDPI should be considered when determining induction and maintenance immunosuppression needs.

FR-PO1005

Transplantation of Cadaveric Kidneys from Infants and Toddlers into Adults in the Era of Extreme Donor Shortage

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Background: Kidney transplantation is the treatment of choice for patients with ESRD. The number of patients in the waiting list for a deceased donor kidney transplant continues to increase. In this era of extreme donor shortage we present our experience with transplantation of cadaveric kidneys from infant and toddler into adult recipients.

Methods: This was a retrospective study of twelve adult deceased donor kidney transplant recipients from pediatric donors ages 0-5 years. Medical records were reviewed from visits previous to transplantation to the most recent follow up after transplant.

Results: Twelve consecutive adult patients were transplanted with pediatric en bloc kidneys from donors 0-5 years between February 2014 to February 2015. Ten of the donors were standard criteria brain death (DBD) and two were donors with cardiac death (DCD), KDPI scores ranged from 47 to 87%, donor age from 6 months to 5 years, weight 6 to 15 Kg. Recipients were equally distributed by gender, average age 56 years, mean BMI 22. All patients were followed in average 6 months to 1 year. In the early post transplant period 9 recipients were noted to have glaucosuria with normal blood glucose and mild metabolic acidosis. These findings were noted on average up to 3 to 6 months after transplant and resolved thereafter. Nine patients had follow up renal ultrasound with finding of increase in kidney size 0.3 to 1.2 cm on average at 3-6 months in follow up. There were no perioperative complications, allograft failure, rejection, vascular complications or recurrence of the primary disease. The average serum creatinine remains at 0.89 to date.

Conclusions: We report excellent outcomes after adult kidney transplant from cadaveric donors aged 0 to 5 years of age. Younger age and low weight of the donors did not adversely affect our results. No vascular complications, rejection or allograft loss was noted. All of our patients have excellent allograft function 6-12 months post transplant.

FR-PO1006

The Role of Dobutamine Stress Echo in Identifying Cardiac Ischaemia, Cardiovascular Events and Role of Subsequent Cardiac Angiography

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Background: Dobutamine Stress Echo (DSE) is an established method of identifying cardiovascular (CV) risk in patients undergoing kidney transplantation, however the role of coronary angiography (CA) is not clear. The aim of this study was to investigate the role of DSE and CA in predicting cardiac ischaemia and CV events in this population.

Conclusions: DSE is a suitable method to stratify cardiovascular risk and predict significant CAD on CA, however subsequent PCI does not conclusively show decreased event rates. Larger studies are required to establish the role of revascularisation.

FR-PO1007

Racial Differences in Survival of Incident Home Hemodialysis and Kidney Transplant Patients

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Background: Previous studies have indicated that patients on maintenance dialysis have worse survival compared to kidney transplant (KTx) recipients. However, none of these studies have compared mortality in United States(US) patients using alternative dialysis modalities such as home hemodialysis(HD) with KTx recipients.

Methods: Comparing patients who started home HD with those who received KTx in the US between 2007-2011, we created a 1:1 propensity-matched cohort of 4,000 patients and examined the association between treatment modality and mortality using Cox proportional hazard models.

Results: The mean±SD age of the matched home HD and KTx patients at baseline were 54±15 and 54±14 years, 65% were male (both groups), 70% and 72% of patients were white and 19% were African American (both groups), respectively. Over 5 years of follow-up, home HD patients had 4-times higher mortality risk compared to KTx recipients in the entire patient population (HR=4.06, 95%CI:3.27-5.04), and similar differences were found across each race stratum (Figure).
Survival of Elderly Incident Home Hemodialysis and Kidney Transplant Patients  
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Background: The proportion of elderly (≥65 years) patients with kidney failure is increasing. Previous data suggest that the projected increases in the life spans of kidney transplant (KTx) patients compared to conventional dialysis were 2.8 and 1.1 years for patients aged 65-69 and 70-74 years, respectively. However, no studies have compared mortality of elderly patients using alternative dialysis modalities such as home hemodialysis (HD) with KTx recipients.

Methods: Comparing elderly patients, who started home HD with those who received KTx in the US between 2007-2011, we created a 1:1 propensity score (PS) matched cohort of 960 elderly patients (480 KTx and 480 HD) and examined the association between treatment modality and all-cause mortality using Cox proportional hazard models.

Results: The mean±SD age of the PS matched home HD and KTx patients at baseline were 71±6 years and 71±5 years, 69% were male (both groups), and 81% and 79% of patients were whites in home HD and KTx group, respectively. Median follow-up time was 205 days (IQR: 78-364 days) for home HD patients and 795 days (IQR: 366-1,221 days) for KTx recipients. There were 97 deaths (20%, mortality rate 253 [297-309]/1000 PY) in the home HD group, and 48 deaths (10%, 45 [34-60]/1000 PY) in the KTx group. Over 5 years of follow-up, home HD patients had almost 5-times higher mortality risk compared to KTx recipients in the entire patient population (HR: 4.74, 95%CI:3.25-6.91).

However, during the first year of therapy, while white home HD patients had higher mortality risk (HR:4.21, 95%CI:3.10-5.73) compared to their KTx counterparts, there was no significant difference in mortality risk between African American home HD and KTx patients (HR: 1.62, 95%CI:0.77-3.39). These results were consistent across different types of kidney donors.

Conclusions: Among all patients, home HD is associated with 4 times higher mortality compared to KTx recipients regardless of the type of kidney donor.

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Beyond the Bones – The Association Between Vitamin D, Graft Outcomes and Vascular Disease

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Background: Vitamin D deficiency in KTRs is an emerging theme. The purported associations between Vitamin D deficiency and various metabolic, cardiovascular and non-metabolic adverse events have not been thoroughly studied in kidney transplant recipients (KTRs).

Methods: Here, we examined the association between Vitamin D deficiency and graft loss, mortality, NODAT, cardiovascular events and development of cancers.

Results: 504 KTRs had their vitamin D checked in 2008 and were followed up for 6 years. Vitamin D deficiency was defined as a level<50nmol/L. In this population, the prevalence of vitamin D deficiency was high at 66.5% with a significantly higher prevalence in older (71.9% vs. 60.9%, P=0.006) and female recipients (male 62.1% vs. female 73.2%, P=0.006) and in relatively new transplants (recent transplants 72.3% vs. old transplants 66.6%, P=0.003). KTRs who were vitamin D deficient had significantly worse overall (77% vs. 62.9%, P=0.001), death censored graft survival (89% vs. 96%, P=0.009), development of NODAT (19.8% vs. 10%, P=0.005) and cardiovascular events (19.9% vs. 2.9%, P=0.002) when compared to those with normal levels. In a stratified analysis, this was noted to be worse in KTRs on maintenance steroids, with relatively worse baseline renal function and proteinuria, with secondary hyperparathyroidism, deceased donor transplants and earlier vs. late transplants. Although vitamin D deficiency is not associated with a higher incidence of malignancy, it is associated with higher mortality in those with cancer (33.3% vs. 12.9%, P=0.005). In a multivariate Cox model, vitamin D deficiency was associated with significantly worse overall graft (HR 2.7, P=0.001) and death censored graft survival (HR 2.4, P=0.04). NODAT (HR 2.3, P=0.03) and cardiovascular events (HR 4.0, P=0.004) independent of age, PTH levels, gender, graft number, type of transplant, time since transplantation, graft type and renal function measured by both proteinuria and eGFR.

These results were consistent across different types of kidney donors and recipients characteristics.

Conclusions: Elderly home HD patients appear to have almost 5 times higher mortality compared to KTx recipients regardless of the type of kidney donor.

Funding: Other NIH Support - R21AG047306 and R01DK95668

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Underline represents presenting author.
Conclusions: In conclusion, vitamin D deficiency which is highly prevalent in KTRs is associated with adverse outcomes. Our study stresses the need for a prospective trial of vitamin D replacement in KTRs.

Funding: Private Foundation Support

FR-PO1010

Acute Tubular Necrosis Changes in Living Kidney Donor Implant Biopsy

Associates with Higher Rejection Rates Post-Transplant


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Background: Ischemic injury may occur during organ retrieval. In deceased kidney donor transplants, delayed graft function, a form of acute tubular necrosis (ATN), associates with acute graft failure. Histological changes consistent with ATN can also be seen in implants procured with living donors (LD), however, the influence of LD-like changes at time on donation from LD on recipient graft outcomes is unclear, especially its impact on graft rejection.

Methods: We retrospectively studied all LD kidney transplants at our center from Jan 2005 to Dec 2014 who had an implant biopsy. We perform protocol biopsies at 3-6, 12 and 24 months post-transplant and for cause biopsies in all of our patients. Post-transplant biopsy results were reviewed, and patients with subclinical and clinical borderline and/or Banff scored graft rejection were captured.

Results: The study included 350 LD kidney transplant recipients, the mean age was 47.8±13.7 years (range 10-75) and 224/64% were male. The incidence of ATN in implant biopsies was 16% (n= 56). Patients with ATN had a trend toward higher risk of graft rejection in post-transplant biopsy compared with those without ATN (32.1% vs. 21.7%, p=0.09). When the study population was stratified by time from transplant to post-transplant biopsy, there was a statistically significant higher incidence of graft rejection in those biopsies performed between 1 and 24 months post-transplant (31.0% in the ATN group vs.17.8% in the non-ATN group, respectively, p=0.02). No statistical correlation was found between ATN and graft rejection after 24 months post-transplant. Importantly, implant ATN has no impact on GFR at 3, 6, 12, 24 months post-transplant.

Conclusions: Histological changes consistent with ATN in LD kidney implant biopsy are associated with higher rates of graft rejection between 1 and 24 months post-transplant. However, ATN does not affect graft function at 3, 6, 12, or 24 months.

FR-PO1011

Impact of Pre-Transplant Cardiovascular Risks on Renal Allograft Survival: A Multi-Center Prospective Study

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Background: Cardiovascular (CV) disease is a leading cause of mortality in patients with end-stage renal disease. Even after successful renal transplantation, CV risks can induce CV morbidity and mortality in renal transplant recipients. However, the impact of pre-transplant CV risks on renal allograft outcomes has not been reported.

Methods: We analyzed the graft outcomes of 2902 renal transplant recipients who were enrolled in a multi-center cohort from 1997 to 2012. We calculated pre-transplant CV risk scores by the Framingham risk model using age, sex, total cholesterol levels, smoking and a history of hypertension. Cox proportional hazard models were used to assess hazard ratios (HRs) with and without competing risks of post-transplant CV deaths, adjusting for risk factors of allograft failure including recurrence of glomerulonephritis and acute rejection.

Results: Hypertension and vascular disease (a composite of ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) were noted in 84.1% and 6.5% of the patients, respectively. During a median 6.4 years of follow-up, 122 (4.2%) patients died and 286 (9.9%) patients developed allograft failure. In multivariable-adjusted models, pre-transplant vascular disease was associated with increased risk of renal allograft failure (HR 2.43; 95% confidence interval [CI] 1.58-3.71). The HR for renal allograft failure comparing the highest with the lowest tertiles of pre-transplant CV risk scores was 1.49 (95% CI 1.11-2.00). In competing risk models, the HR for pre-transplant vascular disease was 2.01 (95% CI 1.20-3.36) and the HR for renal allograft failure comparing the highest tertiles of pre-transplant CV risk scores was 1.44 (95% CI 1.05-1.98).

Conclusions: Both pre-transplant CV risk and vascular disease are independently associated with renal allograft failure in this multi-center prospective study. Pre-transplant CV risk assessment could be useful to predict renal allograft failure.

FR-PO1012

Blood Pressure (BP) Control in Kidney Transplant Recipients: A Single Centre Experience

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Background: Cardiovascular disease is the leading cause of death among kidney transplant recipients (KTRs), however there remains uncertainty regarding optimal BP targets. Current UKRA, KDIGO and KDQI guidelines advocate BP control to 130/80 in KTRs; UKRA/KDIGO advocate tighter control (125/70) in proteinuric KTRs. We examined BP control and proteinuria in all KTRs under longterm follow up at one centre, and adherence to these recommendations.

Methods: As of 1 March 2015, 839 KTRs were attending for regular clinic review (excluding recent KTRs<1yr). We performed a retrospective database review of BP, proteinuria, renal function and antihypertensive use.

Results: The cohort was 60% male with mean allograft age 10±0.28 years. Mean decline in eGFR was 0.83ml/min/m² per year (p=0.0004). Mean SBP was 134±0.56, DBP 79±0.37. 48% had SBP<130, 62% DBP<80, 39% both. 78% received 1 antihypertensive, 42% 2-3, 4% 4-24 agents. Only 9% had PCR measured. In those with PCR>2.50, 19% had BP treated to 125/75. Dipstick proteinuria was recorded in 58% and showed a significant association with SBP (p=0.01). There were significant correlations between reducing eGFR and increasing PCR (R²=0.11, p=0.0001), and between PCR and ACE/ARB use (p=0.0002). There was no correlation between CNI level and BP (CyA p=0.88, FK506 p=0.69). There was a significant stepwise decrease in renal function (eGFR >p=0.005, eGFR p=0.01) and increase in dipstick proteinuria (p=0.03) when data were analysed in sbp groups <120, 120-140 and >140. In terms of DBP, the stepwise decrease in renal function remained (eGFR <p=0.01, eGFR p=0.0001) when data were analysed in groups<70, 70-90 and >90. DBP>90 had the most significant impact on eGFR, DBP was not associated with proteinuria.

Conclusions: The optimal BP target remains uncertain. Adherence to current guidelines is reasonable in our unit but could be improved. This study again demonstrates that SBP is the key risk factor for proteinuria, however increases in DBP >90 were most strongly associated with graft dysfunction.

FR-PO1013

Dobutamine Stress Echocardiography (DSE) Significantly Reduces the Need for Coronary Angiography in Renal Transplant Patients

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Background: There is significant controversy regarding optimal cardiac workup strategy for kidney transplantation. Some centres perform coronary angiograms (CA) in all patients whereas others have adopted a tailored approach using non-invasive techniques such as Exercise Tolerance Testing (ETT) and ischaemia assessment with cardiac imaging. This study examines the role risk stratification and DSE for cardiac workup in this patient group.

Methods: We analysed data on patients referred between 1/2012 and 31/12/2014 who were risk stratified and investigated according to the protocol (figure 1).

Results: Of 233 patients referred 92 were high risk and went on to have DSE. All other patients underwent echocardiography with/without ETT (33 ETT, 122 echocardiography and 33 CA). 16 patients had CV events, but none were peripereative. Overall event rate was 4% per year. 11 of 92 patients who had DSE had events. 11 of 33 patients who had CA had event. 28 of 92 patients had a positive DSE (i.e. suggestive of myocardial ischaemia) and of these 23 went on to CA. 6 of 28 patients with a positive DSE and 5 of 64 with a negative DSE had an event (figure 2, log rank p=0.1). 25 of 33 patients had evidence of coronary artery disease (CAD) at CA of which 13 received coronary artery stents. There was no significant difference between those with significant (>50% stenosis) CAD on CA who had events (8 of 21 patients) compared to those without significant (>50% stenosis) CAD who had events (3 of 12) (log rank p = 0.7). 6 patients with significant CAD who had PCI had events. 35 patients underwent ETT, 4 had CA following positive ETT. One patient with negative ETT had an event.

Conclusions: A careful risk stratification and using DSE decreases the need for CA and achieves very low event rates.

FR-PO1014

Levels of Indoxyl Sulfate in Kidney Transplant Patients, and the Relationship with Hard Outcomes

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Background: Kidney transplant recipients are at greater risk of cardiovascular disease (CVD). Indoxyl sulfate (IS) is a protein-bound uremic toxin that is known to be associated with the risk of CVD and mortality in both pre-dialysis and dialysis patients. Data on levels of protein-bound uremic toxins in kidney transplant patients are scarce. The objective
of the present study was to evaluate the levels of IS in kidney transplant patients and their relationship with biochemical parameters and hard outcomes (including mortality, cardiovascular (CV) events and graft loss).

Methods: In 311 consecutive kidney transplant patients, total and free IS levels were measured immediately before transplantation (T0) and then 1 month (M1) and 12 months (M12) afterwards. In a case controlled substudy (n=90), IS levels in transplant patients were compared with those in non-transplant patients with chronic kidney disease matched for age, gender and estimated glomerular filtration rate (eGFR). Over a mean ± standard deviation follow-up period of 113 ± 29 months, 55 deaths, 70 CV events and 71 graft losses were recorded.

Results: We observed a rapid, consistent, significant decrease in IS levels after kidney transplantation. Majority of IS levels were below or near the normal value at M1 and M12. We did not observe a correlation between IS levels and eGFR at M1 and M12. Total and free IS levels at M12 were significantly higher in non-transplant patients (0.34±0.23 mg/dl and 0.04±0.007 mg/dl, respectively) than in transplant patients (0.21±0.17 mg/dl and 0.001±0.01 mg/dl; p=0.003 and <0.0001 respectively), despite having similar eGFRs. Lastly, IS levels were not associated with overall mortality, CV events or graft loss at T0, M1 or M12.

Conclusions: Free and total IS levels were significantly lower in transplant recipients than in non-recipient matched for, age, gender and renal function - suggesting that kidney transplantation protects against an increase in IS levels. Importantly, serum IS levels were not associated with hard outcomes at any of the three time points.

FR-PO1015

Background: In the general population, abdominal obesity is more closely associated with metabolic and cardiovascular (CV) risk than high BMI. The ideal measure of obesity to identify risk in pediatric kidney transplant (Tx) recipients, who have impaired growth and altered body composition, has not been established. In this prospective study we compared ability of BMI, Waist Circumference (WC), and Waist-to-Height ratio (WHtR) to identify metabolic and CV risk in pediatric kidney Tx recipients.

Methods: Kidney Tx recipients 3-20 years old and 0-30 months post-Tx had WC, BMI, WHtR, blood pressure (BP), fasting lipids, leptin, HbA1c%, standard and speckle echocardiogram and carotid intima-media thickness (CIMT) measured. Patients were classified as obese or lean by 3 methods: WC (ATP cut-point male=94th%ile,females=84 th%ile), WHtR(CDC cut-point>=0.539), and BMI(>95%iles). Logistic regression determined association of metabolic and CV risk factors.

Results: The study group comprised of 33 Tx recipients, age 13.6±0.3 years. Prevalence of obesity by BMI, WC, and WHtR was 21.2%, 33.3%, and 48.5%. Prevalence of hyperglycemia/diabetes(TG) was 24.2%, high LDL 15.2%, high leptin 39.3%, high HbA1c% 12.1%, left ventricular hypertrophy(LVH) 30.3%, hypertension(HTN) 69.6%, and high CIMT48.4%. In all groups (WHr, WC, and BMI), obese children were more likely than to have HTN(OR4.5.2,2.6,6,0 1)LVH(OR5.4.7,4.8,8,8,0 0), low HDL(OR5.0,4.3,8,0 01), and low leptin(OR13.1,1.7,3,0 00). Obese children in WHr and WC groups, but not BMI group, had greater chance of high TG(OR5.4,3,2,0 01), high CIMT(OR2.0,4,5,0 05), and impaired myocardial strain(OR1.2,1.1, p<0.01). Five patients with short stature (height z>2.50) and CV risk factors (3.0 0,5 factors/patient) were not identified as obese by WC criteria(height z>0.8,0 01). Obesity were defined as WHtR (height z>2.50) and CV risk factors. WC and WHtR are more effective than BMI for detecting metabolic and CV risk amongst pediatric Tx recipients. WC may underestimate prevalence of obesity in children of short stature, and therefore WHtR may be a more sensitive method for identification of children with increased metabolic and CV risk in the kidney Tx population.

FR-PO1016

Background: Kidney transplant (KT) is the treatment of choice for end stage renal disease (ESRD). Knowledge of dialysis patients about the benefits of KT is an important determinant of their active engagement in the decision making process. We studied factors associated with patients’ knowledge about benefits of KT.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants fulfilling inclusion criteria, we randomly selected and invited 1400 to complete the questionnaire. Independent variables were demographic factors, distance to dialysis unit, and modes of education about options. In multivariable analysis, we calculated odds ratios (OR) and 95% confidence intervals (CI) for the probability of responding correctly to each of 4 questions about benefits of KT.

Results: 673 participants responded to questions about overall survival benefit of KT (correct: 32%), benefits of KT for diabetic patients (correct: 46%), for patients > 60 (correct: 29%) and for patients transplanted pre-emptively (correct: 17%). Receiving 3 or more modes of education about KT was associated with higher likelihood of correct response to questions about overall survival benefit of KT (OR:2.19;CI:1.50 to 3.20), survival benefit of KT for diabetics (OR:2.60;CI:1.39 to 3.90) and patients transplanted pre-emptively (OR:1.67;CI:1.06 to 2.64). White race was associated with higher likelihood of correct response to questions about overall survival benefit of KT (OR:1.59;CI:1.11 to 2.28) and the benefit of KT for patients > 60 (OR:1.54;CI:1.07 to 2.21). Age > 60 was associated with lower likelihood of correct response to the question about overall survival benefit of KT (OR:0.65;CI:0.45 to 0.94), benefits of KT for diabetics (OR:0.54;CI:0.38 to 0.77), and for patients > 60 (OR:0.64;CI:0.44 to 0.93). Patients on dialysis > 5 years were less likely to be aware of the benefit of KT for diabetics (OR:0.68;CI:0.48 to 0.98).

Conclusions: Dialysis patients’ knowledge about survival benefits of KT is rather limited. The most significant modifiable contributor to improvement in knowledge is diversity of modes of education about KT. Other factors include race, age and number of years on dialysis.

Funding: NIDDK Support

FR-PO1017
Pretransplant HbA1c Predicts New-Onset Diabetes After Transplantation Among Renal Transplant Recipients Jung-Im Shin, Mari Palta, Arjang Djamali, Brad C. Astor. Univ of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: New-onset diabetes after transplantation (NODAT) is a common complication among renal transplant recipients and is associated with a higher risk of cardiovascular events and poorer graft and patient survival. The association of pretransplant HbA1c with NODAT remains unclear. Identifying recipients at greatest risk of NODAT may help guide monitoring and treatment strategies to prevent or delay the onset of NODAT.

Methods: We assessed the association between pretransplant HbA1c and NODAT in 1522 non-diabetic recipients using data from the United States Renal Data System (USRDS) from 2004-2011. Cox proportional hazards models adjusted for demographics, cause of ESRD, year of transplantation, number of prior transplants, duration of pretransplant dialysis, comorbidities, lipid levels, hemoglobin level, body mass index, HCV and CMV serostatus, donor type and age, HLA mismatch, and posttransplant steroid and tacrolimus use.

Results: Median HbA1c was 5.4% and 531 (34.9%) patients had HbA1c ≥ 5.7% (i.e., prediabetes)A total of 404 (26.5%) patients developed NODAT during a median follow-up of 1.7 years. Pretransplant HbA1c was associated with the risk of NODAT in a non-linear fashion. The adjusted hazard ratio (HR) associated with 1% higher pretransplant HbA1c was 0.94 (95% confidence interval (CI): 0.62, 1.42) for HbA1c lower than 5.4% and 1.87 (95% CI: 1.30, 2.68) for HbA1c higher than 5.4%.

Conclusions: Pretransplant HbA1c is independently associated with the risk of NODAT among renal transplant recipients. A continuous relationship between pretransplant HbA1c and the risk of NODAT suggests that greater risk starts at levels below the standard threshold for prediabetes.

FR-PO1018

Background: Because mortality on the kidney transplant waitlist is high (4-6% per year), being placed on the waitlist earlier versus later has important clinical consequences. Per U.S. Organ Procurement and Transplantation Network (OPTN) rules, patients begin accruing time on the waitlist when renal function declines beyond a threshold defined as “measured (actual urinary collection) creatinine clearance level or calculated glomerular filtration rate (Cockcroft-Gault or other reliable formula) less than or equal to 20 mL/min”.

Methods: We assessed the relative performance of three commonly used kidney-function equations (Cockcroft-Gault, MDRD, and CKD-EPI). We first compared the equations mathematically to determine under what age and serum creatinine combinations each pair of equations yields discordant waitlist qualification statuses (i.e., a patient would qualify for the waitlist with one equation were used but not the other). We then applied the equations to serial creatinine measurements from three patient cohorts: one of waitlisted patients at a major U.S. academic center and two national, multicenter cohorts of CKD patients (the NIH-sponsored AASK and MDRD studies).

Key: TH = Thursday; FR = Friday; SA = Saturday; OR = Oral; PO = Poster; PUB = Publication Only Underline represents presenting author.
Results: Mathematically (assuming average weights), the Cockcroft-Gault equation almost always yields higher numeric values compared with the MDRD and CKD-EPI equations. When applied to the three actual patient cohorts, Cockcroft-Gault consistently disadvantaged patients, delaying average time to waitlist qualification by 1 to 2 years.

Conclusions: This study identified a potential source of significant inequity (on the order of 1-2 years) in wait-time accrual for kidney transplantation that stems from imprecise rules for waitlist qualification. The OPTN may need to revise the language in their kidney transplantation policies so that consistent methods to assess renal function are adopted and patients are not inadvertently disadvantaged.

Funding: NIDDK Support

FR-PO1019

New Onset Diabetes Has Unfavorable Effect on Patient but Not on Allograft Survival

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Background: New onset diabetes after transplantation (NODAT) has been linked to higher rates of graft loss and shorter patient survival. More recent awareness, improvements in care, and changes in immunosuppression may have modified this association.

Methods: Retrospective single center analysis of 1427 (age=18) first time renal transplant recipients (KTR) without pre-transplant(Txp) diabetes. Patients with <1 year of follow up and those with allograft failure in the first year post-Txp were excluded. NODAT was defined as prescription of a glucose lowering medication 1 year after Txp. Cox models adjusted for multi: potential confounders were used to examine the relationship of NODAT with allograft and patient survival.

Results: The incidence of NODAT was 16.1%. Median follow up was 5.9 years(IQR:3.5-9.2) for allograft and 6.3(IQR:3.8-9.8) for patient survival. Age, BMI, non-white race and HCV were independently associated with NODAT (all p<0.01). Compared with KTRs without DM NODAT was not associated with an increased risk of overall graft failure (aHR 1.15, CI 0.86-1.52) or death censored graft survival (DCGS) (aHR 1.12, CI 0.73-1.71) in multivar. analysis. NODAT remained borderline significant after adj. for multiple other factors for patient survival (aHR 1.39, CI 1.00-1.91 p=0.49), but not for death with functioning graft (aHR 1.34, CI 1.09-2.02). The associations between NODAT and outcomes were not detectably different over time (p=0.095 for patient survival and p=0.25 for DCGS).

Conclusions: In this cohort of KTRs NODAT had no impact on graft survival but was indep. associated with reduced overall survival.

FR-PO1020

Frequency of Hospital Readmission Post Kidney Transplantation

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Background: Early hospital readmission following kidney transplantation has been identified to be a strong predictor of adverse sequelae that can have significant clinical and economic implications. Our goal was to quantify the frequency of hospital readmissions post kidney transplantation, as well as the reasons for the rehospitalizations.

Methods: Patients who received a kidney transplant between Jan 2009 and Sept 2013 were identified from the Premier Hospital database by ICD-9-CM code. The first transplant procedure was defined as the index event. The frequency and causes for hospital readmissions were evaluated during the first 12-month after index transplant hospitalization using hospital discharge records.

Results: Of patients who received kidney transplant (n=5,402; mean age: 50.8 years) 61% were male. Most patients received transplant in urban (98%), large (≥600 beds: 61%), teaching hospitals (84%). During index transplant hospitalizations 5 deaths occurred, resulting in 5,367 evaluable patients. Among this study population, 43% had a hospital readmission for any cause during the 12 months following kidney transplant, with 41% occurring within 1 month and 67% occurring within the first 3 months. Readmissions were most frequently related to opportunistic infections (25%) including viral infections (6%), followed by renal impairment (25%), and neutropenia (4%). Among the readmissions related to viral infections, the majority were related to CMV (79%). Readmission of patients with high severity APR-DRG levels of 3 (major) and 4 (extreme) at 30% and 9%, respectively (severity of illness level rated 1-4: minor, moderate, major, and extreme).

Conclusions: Over 4 in 10 of the kidney transplant recipients in this study were rehospitalized post transplantation. A significant number of the readmissions occurred in the first month post-transplant and the majority were within the first three months; almost 4 in 10 readmissions were classified as major or extreme severity level. Among hospital readmissions, more than half of them were related to an opportunistic or viral infection, underscoring unmet needs for the prevention of these infections.

Funding: Pharmaceutical Company Support - Chimerix Inc.
**FR-PO1024**

**Associations of Serum Soluble α-Klotho, Fibroblast Growth Factor 23, and 25 (OH) Vitamin D with Kidney Function and Left Ventricular Hypertrophy in Japanese Kidney Transplant Recipients**

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**Background:** Deterioration of kidney function and left ventricular hypertrophy (LVH) is crucial for kidney transplant recipients. Any marker for predicting kidney function and LVH is needed to prevent complications.

**Methods:** This was a retrospective cohort study. Forty-seven consecutive patients were enrolled in this study at Nagoya Daini Red Cross Hospital in 2011.

**Table 1. Study population characteristics (n=47)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.8 ± 11.6</td>
</tr>
<tr>
<td>Gender</td>
<td>n=32</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>127.2 ± 11.5</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>75.0 ± 7.7</td>
</tr>
<tr>
<td>Creatine, mg/dL</td>
<td>9.4 ± 5.7</td>
</tr>
<tr>
<td>Phosphate, mg/dL</td>
<td>3.4 ± 5.4</td>
</tr>
<tr>
<td>Intact parathyroid hormone, pg/ml</td>
<td>110.0 ± 133.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>122.2 ± 6.4</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol, mg/dl</td>
<td>86.0 ± 17.3</td>
</tr>
<tr>
<td>Cr, mg/dL</td>
<td>1.3 ± 0.6</td>
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<tr>
<td>Albumin, g/dl</td>
<td>4.01 ± 0.25</td>
</tr>
<tr>
<td>Soluble α-Klotho, pg/ml</td>
<td>316.3 (142.8, 572.0)</td>
</tr>
<tr>
<td>Fibroblast growth factor 23, pg/ml</td>
<td>41.7 (64.7, 68.2)</td>
</tr>
<tr>
<td>25(OH) vitamin D, ng/ml</td>
<td>5.7 (4.2, 11.3)</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>43.9 ± 13.8</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>43.8 ± 14.3</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>105.2 ± 27.1</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>100.0 ± 24.2</td>
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<tr>
<td>Use of Cyropeptan tacrolimus</td>
<td>22 / 20</td>
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<td>Use of mycophenolate sodium</td>
<td>4 / 11</td>
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<tr>
<td>Use of ARB, n</td>
<td>33</td>
</tr>
<tr>
<td>Use of statin, n</td>
<td>25</td>
</tr>
</tbody>
</table>

Serum intact fibroblast growth factor (FGF) 23, soluble α-Klotho (sαKlotho), 25(OH) vitamin D[25(OH)D], estimated glomerular filtration (eGFR), left ventricular mass index (LVMI) and other clinical parameters after 1 year and eGFR after 3 years since kidney transplantation were measured to investigate the usefulness of these markers for predicting kidney function and LVH.

**Results:** The median serum sαKlotho, intact FGF23, 25(OH)D were 516.3 pg/ml, 58.7 pg/ml, 7.8 ng/ml, and 5.7 ng/ml, respectively. Serum sαKlotho levels were associated with difference between eGFR after 1 year and after 3 years (DeGFR) (r = 0.37, p = 0.01), but not with difference between LVMI after 1 year and after 3 years (ΔLVMI). Patients were divided into two groups based on median serum FGF23 level. Higher serum intact FGF23 levels were associated with ΔLVMI. Serum 25(OH)D levels were associated with eGFR after 1 year (r = 0.34, p < 0.05), but not with DeGFR and ΔLVMI. Multivariate regression analysis revealed that serum sKlotho was the strongest predictor of kidney function and serum intact FGF23 was that of LVMI.

**Conclusions:** Serum sαKlotho may be a good marker for kidney function and intact FGF23 for LVH in Japanese kidney transplant recipients.

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**FR-PO10123**

**Determinants of Hepcidin, the Key Regulator of Iron Homeostasis, in Renal Transplant Recipients**

Michele F. Eisengart,1 Stefan P. Berger,2 Robin P.F. Dullaart,1 Aiko P.J. De Vries,3 Stephan J.L. Bakker,1 Carlo A. Gaillard.1

**Background:** Hepcidin is synthesized in the liver and secreted into the circulation. Circulating concentrations may be influenced by body iron availability, inflammation, insulin sensitivity and tissue hypoxia reflected by erythropoietin, rather than in variation to renal clearance. The study aims at evaluating the association of donor/recipient MYH9 genotypes with circulating parameters of iron status in kidney transplant recipients.

**Methods:** Circulating concentrations of hepcidin were measured in 295 kidney recipients and their donors using a validated ELISA method. Genotyping was performed in 202 recipients and 193 donors. Mixed models were used to assess relations of SNPs and PI, RI values.

**Results:** Genotyping was performed in 295 kidney recipients and their donors, in 202 at least one US was done. In the longitudinal observation between first day and 2 years after engraftment, recipients carrying T alleles in rs5756168 showed significantly different PI indices in opposition to allele C carriers, p=0.04, for RI the differences did not reach statistical significance (p=0.14). In two-factor analyses the effects of rs5756168 different PI indexes in opposition to allele C carriers, p=0.04, for RI the differences did not reach statistical significance (p=0.14). In two-factor analyses the effects of rs5756168 different PI indexes in opposition to allele C carriers, p=0.04, for RI the differences did not reach statistical significance (p=0.14).

**Conclusions:** Identified association of transplanted kidney blood flow parameters and MYH9 polymorphism additionally confirms MYH9 effect on graft functioning shown in our previous study cited above. The study supported by grant from National Science Center NN40266840.
Circulating Inflammatory Cell Subsets Are Associated with Cardiac Function in Renal Transplant Recipients

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Background: Cardiovascular (CV) disease is a major cause of mortality and morbidity in renal transplant recipients (RTRs). Systemic and vascular inflammation is paradoxically common despite immunosuppression and is an important non-traditional CV risk factor. Monocytes are heterogeneous: the intermediate phenotype (CD14++CD16+) is particularly pro-atherogenic and pro-inflammatory compared to the classical phenotype (CD14++CD16-). Regulatory T-cells (TRegs) maintain peripheral tolerance and minimise tissue damage. This study aimed to explore the association of circulating inflammatory cell subsets with cardiac function in RTRs.

Methods: 18 stable RTRs (Mean age 55 years, 61% male) and 5 healthy controls participated. Blood monocytes and T cells were analysed by flow cytometry, and cardiac hemodynamic function measured by bioimpedance (NICOM).

Results: Circulating pro/anti-inflammatory cell subsets differed significantly in RTRs compared with whites. Closer alignment of frailty status with support for KT access may only be a marker for LGF, but also an interesting target for intervention to prevent decline with increased risk for LGF after kidney transplantation. Increased IDO activity may not only be a marker for LGF, but also an interesting target for intervention to prevent decline of renal transplant function leading to LGF.

Conclusions: ID is highly prevalent among RTR and is associated with an increased risk of mortality, independent of anemia. Since iron deficiency is a modifiable factor, correction of iron deficiency could be a target to improve survival.

Funding: NIDDK Support

Indoleamine 2,3-Dioxygenase Activity and Late Graft Failure After Kidney Transplantation

Lauren V. del Vries, 1 Claude P. Van der Ley, 2 Casper F.M. Franssen, 1 Gerjan Navis, 1 Stefan J.L. Bakker, 1 Ido Peter Kema, 1 Dept of Nephrology, UMCG, Netherlands; 1 Dept of Laboratory Medicine, UMCG, Netherlands.

Background: Long-term graft survival after kidney transplantation remains a major clinical problem. Therefore, markers that allow for early identification of patients at risk for late graft failure (LGF) are urgently needed. Indoleamine 2,3-dioxygenase (IDO) catalyzes tryptophan along the kynurenine pathway. Recent studies found IDO activity associated with occurrence of acute rejection and renal function decline shortly post-transplant. We hypothesized that IDO activity could also be a marker for LGF after kidney transplantation.

Methods: We prospectively included outpatient renal transplant recipients (RTR) with a functioning graft >1 yr, between 2001-2003. Follow-up was recorded until May 2009. Death-censored GF was defined as return to dialysis or re-transplantation. Serum kynurenine (KYN) and tryptophan (TRP) were measured with LC-MS/MS; KYN/TRP is a widely accepted measure of IDO activity.

Results: We studied 562 RTR (age 51±12 yrs, 56% men, 6.0 [2.6-11.6] yrs post-transplant). Baseline concentration of serum KYN was 1.8 [1.4-2.2] µmol/l, that of TRP was 40.0 [34.5-46.0] µmol/l, and KYN/TRP was 44.3 [35.0-57.9] µmol/mmol. In multivariable linear regression analyses, KYN/TRP was positively associated with proteinuria (β=0.17, P<0.001) and waist circumference (β=0.12, P<0.001), and inversely with eGFR (β=-0.54, P<0.001) and HDL-c (β=-0.14, P<0.001). During follow-up for 6.9 [6.1-7.4] years, 51 (9.2%) RTR developed GF. In multivariate Cox-regression analyses, KYN/TRP was positively associated with GF (age, sex, eGFR, and proteinuria adjusted HR 3.6 [95% CI 1.3-9.9], P<0.01). Further adjustment for waist circumference and HDL-c did not materially change this association (HR 3.1 [95% CI 1.3-8.9], P=0.02).

Conclusions: IDO activity, as measured by KYN/TRP, is cross-sectionally associated with eGFR, proteinuria, waist circumference, and HDL-c. Prospectively, it is associated with increased risk for LGF after kidney transplantation. Increased IDO activity may not only be a marker for LGF, but also an interesting target for intervention to prevent decline of renal transplant function leading to LGF.
Methods: A total of 2,779 adult recipients who underwent pretransplant echocardiography from 1997 to 2012 were evaluated. We divided the patients into two groups by two different categories: LVDD grade 0-1 vs. 2-3, and LA size<38 mm vs. >38 mm. Post-KT fatal/non-fatal acute coronary syndrome (ACS), graft failure (GF), and all-cause mortality was evaluated.

Results: During a mean follow-up of 4.5 years, fatal/non-fatal ACS was occurred in 49 (1.8%) patients. A total of 231 (12.4%) patients experienced GF and 116 (6.2%) died. The recipients with LVDD grade 2-3 (P=0.005) and LAE (P=0.001) showed higher occurrence of fatal/non-fatal ACS after KT. Graft failure and all-cause mortality was not different between the groups depending on both the LVVD grades and LAE. In a multivariate analysis, increased age (P<0.001), previous history of CV event (P=0.001) and LVDD of grade 2-3 (hazard ratio[HR]:2.98, 95% confidence interval[Ci]:1.535-5.787;P=0.001), and LAE (HR:1.052, 95% CI:1.006-1.101;P=0.025) were associated with ACS. However, none of LVVD grade and LAE was significantly associated with mortality and GF in a multivariate analysis.

Conclusions: In patients of KT candidate, pretransplant LVDD and LAE were independently associated with high occurrence of ACS after KT.

FR-PO1030
day-onset Risk Blood Pressure and Urinary Protein Excretion on Renal Transplant Recipients on RAAS-Blockade Laura V. de Vries,1 Linn Charlotte Dobrowolski,2 C.T.P. (Paul) Krediet,2 Frederik J. Beemelman,3 Stephan J.L. Bakker,1 Gerjan Navis,1 1Dept of Nephrology, UMCU, Netherlands; 2Renal Transplant Unit, AMC, Netherlands.

Background: In CKD patients on RAAS-blockade, it is well established that dietary sodium restriction exerts renoprotection by reduction of blood pressure (BP) and by reduction of urinary protein excretion (UPE), which is partly independent of BP. In renal transplant recipients (RTR), the effect of sodium restriction is not well-documented. We therefore studied the dietary effects of sodium restriction on BP and UPE in RTR.

Methods: We performed a randomized, cross-over trial in stable outpatient RTR with a median age of 60±9 yrs (range 41-80 yrs) and a median of 12±0.8 months post-transplantation (time from dialysis start to KTx evaluation). 30 RTR were randomized to a low-sodium diet (LS) with a sodium intake of 156±130 mmol/24h or to a regular-sodium diet (RS) (68±55 mmol/24h). We measured BP and UPE at the end of each diet period. Dietary sodium restriction was assessed by 24h urine sodium excretion.

Results: We randomized 23 RTR, of which 22 RTR (age 58±1 yrs, 50% men, eGFR 51±21 ml/min) completed the study. One patient dropped out, due to orthostatic complaints on the LS diet. Sodium intake was 156 [130-193] vs. 68 [55-86] mmol/24h on RS vs. LS diet resp. (P<0.0001). Sodium restriction significantly reduced systolic and diastolic BP. There was, however, no material change in UPE, UAE and eGFR.

Conclusions: Dietary sodium restriction effectively reduces BP in stable RTR on RAAS-blockade, but, at variance with findings in CKD, has no material effect on UPE or GF in a multivariate analysis.

FR-PO1031

Individual Blood Calcification Propensity in a Cohort of Renal Transplanted Patients Carlo M. Alfieri,1 Andreas Pasch,1 Anna Regalia,1 Maria Meneghini,1 Maria Teresa Gandolfo,1 Valentina Binda,1 Deborah Mattinzi,1 Masami Ikeda,1 Piergiorgio Messa,1 Nephrology, Dialysis and Renal Transplantation, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 1Nephrology, Hypertension and Clinical Pharmacology, Uni Hospital and Uni of Bern, Switzerland.

Background: Vascular calcifications and related cardiovascular disease have a strong impact in kidney transplanted patients (KTx). Calcification propensity (T50) is a new measure of individual blood calcification propensity. Our aim is to explore in a cohort of KTx patients1) the levels of T50 and their modifications during the 1st year of KTx and 2) the relationship between T50 and routine clinical and biochemical parameters;2) the relationship between T50 and home mineral density(BMD)and aortic calcification(ACI).

Methods: 70 KTx pts(M=38, Age:48±12 yrs).transplanted between 2005 and 2009 were recruited. Along with T50 evaluation, routine clinical and biochemical parameters and FGF-23,OPG, fetuin A and 25-(OH)-Vitamin D were tested at 1,6 and 12mth after KTx. At 1st mth, femoral Dual X-ray absorptionmetry and vertebral column X-ray for BMD(cm^2) and ACI(Kauppi) evalation were performed. T50(min.) was determined using a Nephelostar nephelometer(BMG Lacthe, Offenburg, Germany) in the laboratory of one of the authors.

Conclusions: Dietary sodium restriction effectively reduces BP in stable RTR on RAAS-blockade, but, at variance with findings in CKD, has no material effect on UPE or GF in a multivariate analysis.

FR-PO1032

Prediction of Acute Rejection in Kidney Transplant Recipients Using a Multicenter Cohort Kyoung Don Yoo,1 Junhyung Noh,2 Hajong Lee,1 Dong Ki Kim,1 Chun Soo Lim,1 Young hoon Kim,1 Yon Su Kim,1 Gunhee Kim,2 Jung Pyo Lee.1 Seoul National Univ College of Medicine; 2Seoul National Univ College of Engineering; 1Eulsan Univ College of Medicine.

Background: More than 20% of kidney transplant recipients (KTR) are likely to have rejection episode, which is associated with graft loss. However, the impact of risk factors on acute rejection had not been well clarified. Here, we aimed to build new prediction models through considering variables related to immunologic and non-immunologic factors using machine learning methods.

Methods: This multicenter cohort study included adult KTR admitted to 2 major experienced tertiary hospitals in Korea between 1997 and 2014. A total of 3,117 KTRs were enrolled. Biopsy-proven acute rejection (BARP) of these recipients was investigated by the individual learners such as decision tree, logistic regression, and ensemble learners such as random forest.

Results: We analyzed 2,045 recipients' records, with more than 50 attributes. Among them, we found that age, HLA-mismatch, CNI, and BARP incidence for building our models. In the decision tree model for the prediction of BPAR after three years of KTx, HLA DR mismatch was found to be the most important predictor. In the case of HLA DR mismatch, donor specific antibody (+) predicted in 66.6% of BPAR incidence at three year after transplantation, and also posttransplant infection episode showed significant association with BPAR. In the case of HLA full matched, old age with heavy weight recipient showed high probability of BPAR (71.4%). The final modeling represent AUC performance 0.670 (logistic regression) and 0.665 (random forest) in the BPAR prediction.

Conclusions: In this study, machine learning modeling could present an accurate and versatile tool for forecasting probability of having BPAR episode during the early years following the transplant.

FR-PO1033

Prediction of Long-Term Prognosis of the Kidney Transplantation Using Comorbidity Score Jae Yoon Park,1 Eunjin Bae,1 Sejoong Kim,1 Dong Ki Kim,1 Chun Soo Lim,1 Kwon Wook Joo,1 Yon Su Kim,1 Jung Pyo Lee.1 Seoul National Univ College of Medicine, Seoul, Korea.

Background: Comorbidity assessment is important to the informed interpretation of kidney allograft outcomes. Weights assigned to comorbidities to predict survival may vary based on the type of index disease and advances in the management of the comorbidities. We developed a modified Charlson comorbidity index (CCI) in renal allograft recipients (mCCI-KT), thereby improving risk stratification for mortality.

Methods: A total of 3,765 recipients in multicenter cohort were included to develop comorbidity score. The weights of comorbidities per the CCI were recalibrated using Cox proportional hazards model. The modified score was validated in an independent nationwide cohort (n=1,538).

Results: The Cox proportional hazards model revealed that peripheral vascular disease, mild liver disease, and diabetes with end-organ damage in the CCI significantly predicted mortality. Thus, the mCCI-KT included 3 comorbidities with recalibrated severity weights. In the validation cohort, both the CCI and the mCCI-KT were correlated with mortality. Thus, the mCCI-KT included 3 comorbidities with recalibrated severity weights. In the validation cohort, both the CCI and the mCCI-KT were correlated with mortality. The mCCI-KT stratified the risk better for mortality in renal allograft recipients compared with the CCI, suggesting that it could be a preferred index for use in clinical practice.

FR-PO1034

Patient Uncertainty Regarding Kidney Transplantation Associated with Length of Dialysis prior to Transplant Evaluation Laura J. McPherson,1 Mohua Basu,1 Stephen O. Pastan,1 Sumit Mohan,2 Rachel E. Patzer.1 Emory Univ, Atlanta, GA; 2Columbia Univ, New York, NY.

Background: End stage renal disease (ESRD) patients’ uncertainty about undergoing kidney transplantation (KTx) — i.e., decisional conflict — may be affected by cumulative time spent on dialysis prior to KTx evaluations. We aimed to investigate the association between time from dialysis start to KTx evaluations and decisional conflict.

Methods: In an ongoing clinical trial of study patients measuring the effectiveness of a shared decision tool at a single KTx center, ESRD patients were asked 10 questions assessing decisional conflict related to KTx, with possible scores ranging from 0 (none)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RS</th>
<th>LS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>140±14</td>
<td>129±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>86±8</td>
<td>79±8</td>
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<tr>
<td>Serum creatinine (µmol/l)</td>
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<tr>
<td>eGFR (ml/min*1.73)</td>
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<td>49±20</td>
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<tr>
<td>UPE (mg/24h)</td>
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<td>0.2 [0.0-0.3]</td>
<td>0.9</td>
</tr>
<tr>
<td>UACR (mg/24h)</td>
<td>29 [11-99]</td>
<td>22 [13-94]</td>
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</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
to 100 (high). Patients were dichotomized as having (score > 0) or not having (score of 0) decisional conflict. Time from dialysis start to KTx evaluation was abstracted from electronic medical records, and time on dialysis prior to evaluation was categorized as: <1 year, 1-5 year, >1 year. Logistic regression was used to assess odds ratios (ORs) for decisional conflict by time on dialysis prior to KTx evaluation.

**Results:** Of 70 surveyed patients, 64% were male, 62% were African American, and 66% had hypertension; the average age was 51 years. Patients with any decisional conflict (65%) were more likely to be male and African American in addition to having lower literacy and numeracy scores. Crude logistic regression showed that, compared to patients who had never been on dialysis prior to KTx evaluation, patients on dialysis for <1 year and >1 year evaluation were 1.4 (95% CI: 0.4, 4.9) and 2.5 (95% CI: 0.7, 9.2) times more likely to have decisional conflict, respectively.

**Conclusions:** Results suggest that longer time on dialysis prior to KTx evaluation may be associated with decisional conflict regarding KTxs. Identifying characteristics of patients with longer time on dialysis prior to KTx evaluation could help inform intervention efforts to improve patients' abilities to make decisions about treatment of their kidney disease.

**Funding:** Private Foundation Support

**FR-PO1035**

Haptoglobin and Long-Term Outcomes in Renal Transplant Recipients

Isidor Minovic, Ineke J. Riphagen, Else van den Berg, Jenny E. Kootstra.

**Ido Peter Kema,** Haptoglobin and Long-Term Outcomes in Renal Transplant Recipients

Background: Haptoglobin (Hp) is a hepatocyte-derived protein that protects against oxidative damage by binding free hemoglobin (Hb). Being an acute-phase protein, Hp is upregulated by inflammation. We hypothesized that both low and high Hp are risk factors for all-cause mortality and graft failure in renal transplant recipients (RTR).

**Methods:** Hp was measured using a turbidimetric immunoassay in a well-characterized prospective RTR cohort. Cox regression analysis was used to assess the association of Hp with endpoints.

**Results:** We included 707 RTR (57% male, age 53±13 y, eGFR 49±18 ml/min/1.73m² and 58% used a calcineurin inhibitor). Median Hp was 4.1 (IQR 1.0-8.1) g/L. Hp phenotype 1-1, 1-2, and 2-2 distribution was 18%, 50%, and 33%, resp., with Hp levels of 1.7 [1.3-2.1], 1.4 [1.1-1.8] and 1.1 [0.9-1.7] g/L resp. (P<0.001). Median 38 [32-46] minths follow-up, 81 (12%) RTR died and 45 (6%) developed graft failure. Hp showed a U-shaped association with mortality (P=0.01, fig. 1), but not with graft failure (P=0.7). Accordingly, the lowest (<0.9 g/L) and highest (>1.6 g/L) quintiles of Hp levels were associated with mortality (HR 2.65 [95% CI 1.11-6.35] and 3.10 [3.0-1.7] resp., P=0.001). Adjustment for sex, age, hsCRP, serum albumin, eGFR, BMI, Hba1c, LDH and Hp polymorphism did not materially influence the association of low Hp with mortality (HR 3.55 [1.42-8.84]). However, adjustment for hsCRP and serum albumin markedly weakened the association of high Hp with mortality (HR 2.06 [0.84-5.08]).

**Conclusions:** Low Hp is independently associated with mortality, but not graft failure, in RTR. High Hp was also associated with mortality, but this association largely depended on hsCRP and serum albumin.

**Funding:** Private Foundation Support

**FR-PO1036**

Pre-Transplantation Flow-Citometry Crossmatch Can Be a Predictor of Outcome when Donor-Specific Antibodies Are Present

Anna Rita Aguire, Patrícia Soares Souza, Gislene Oliveira Bezerra, Flavio Jota Paula, Elias David-Neto, Maria cristina R. Castro. Renal Transplant Service, Hospital das Clínicas - Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.

**Background:** Clinical relevance of pre-transplant (Tx) donor-specific-antibodies (DSA) detected by single antigen beads (SAB) when pre-Tx CDC-AHGG crossmatch (XM) is negative is still unclear. The aim of this study was to evaluate the importance of a positive flow-citometry-XM (FCXM) in patients with DSA over patient and graft survival.

**Methods:** Retrospective study, performed between Jan09 and Dec13 evaluating FCXM influence on antibody-mediated rejection (AMBR) incidence, and over graft and patient survival. Biopsies were classified according to Banfi’s09 criteria and DSA by Luminex SAB.

**Results:** From 2009-2013, 1002 kidney transplants (Tx) were performed in our center. 26125(%) were sensitized (PRA>0%) and 87.8% presented pre-Tx DSA. 60 (69%) of them had FCXM performed with serum collected before transplantation: 22 (33%) positive and 38 (64%) negative. There was no difference between the highest DSA-MFI between Tx with positive or negative FCXM [FCXM+ : 5080 (1046-15360) vs FCXM- : 3120 (397-14600)], or between the sums of all DSA-MFI of each patient between these groups [FCXM+ (247:97): (597-14600) vs FCXM- (957-15730)]. However, among patients with ABMR, FCXM+ had a significantly higher incidence of ABMR than DSA+FCXM- Tx [FCXM+ 25% vs FCXM- 90%] (p = 0.011). Patient survival did not differ between FCXM+ (82%) and FCXM- (95%) neither was affected by ABMR.

**Conclusions:** A positive pre-Tx FCXM is related to a higher incidence of ABMR in the first year after Tx and to worse graft survival, and did not influence patient survival.

**Funding:** Private Foundation Support

**FR-PO1037**

Pre-Transplant Mental Health Disorders and Non-Adherence and Post-Transplant Outcomes in Kidney Transplant Recipients

Jeytn Mucia, Franz-Marie Gurnab, Marta Novak, Joseph Kim, Olusegun Famure. Multi-Organ Transplant Program, Univ Health Network and Univ of Toronto, Toronto, ON, Canada.

**Background:** Mental health disorders (MH) and non-adherence (NA) have been associated with lower access to kidney transplantation (KT) and poorer clinical outcomes. We examined the relationship between history of MH problems, NA, and post-transplant outcomes (i.e., biopsy proven acute rejection; BPAR, death censored graft failure; DCGF; or total graft failure; TGF).

**Methods:** This was a single-centre retrospective cohort study of adult patients transplanted at our KT program from July 1, 2004 and Dec 31, 2012, and followed up until June 30, 2014. Patients with complete information about pre-transplant MH problems or NA or post-transplant history of NA in their medical record (n=9555) were included and multivariable associations between MH, NA and time to event (for BPAR, TGF and DCGF) were explored using log rank analysis and Cox proportional hazards models.

**Results:** The mean (±SD) age was 50.5 (±13.4) years, 61% of patients were male and 27% had a history of diabetes. Twenty-two percent had a positive history of MH problems and 11% had a history of NA. Fifteen percent of the patients had BPAR, 5,6% had DCGF and 13% had TGF (death or DCGF). Participants with a history of pre-transplant NA but not with history of MH had higher risk for BPAR (log rank test p = 0.049 and p=0.46 for NA and MH, respectively). This difference, however, was not significant after adjusting for socio-demographic characteristics, donor type and HLA mismatch: adjusted HR (95% CI) 1.36 (0.84-2.23) and 1.16 (0.77-1.75) for Na and MH, respectively. Neither the history of pre-transplant MH nor pre-transplant NA was associated with DCGF or TGF. These results remained qualitatively unchanged after multivariable adjustment: adjusted HR (95% CI) 1.81(0.96-3.42) and 0.99 (0.58-1.70) for Na and MH, respectively.

**Conclusions:** A history of pre-transplant mental health disorders or non-adherence are not associated with poor post-transplant outcome in a select group of patients who are cleared for transplantation. Post-transplant patients with such problems should have equal access to kidney transplantation compared to patients with no MH problems.

**Funding:** Government Support - Non-U.S.

**FR-PO1038**

HLA Profile and Short and Long Term Outcomes in African American Donors and Recipients

Rabi Yacoub, Girish N. Nadkarni, John C. He, Paolo Cravedi, Rebecca L. Kent, Ioannis Konstantinidis, Karen Lok yee Keung, Sander Florman, Peter S. Heeger, Barbara T. Murphy, Madhav C. Menon. Mount Sinai, NY.

**Background:** We have previously reported the apparent greater impact of HLA-matching over both allograft and recipient ABO status, in African American (AA) recipients and AA-donor organs in deceased donor kidney transplantation (DDKT).

**Methods:** We utilized data from the UNOS database (1995 – 2012), and analyzed 10 year death censored graft survival (DCGS), 1 year clinical acute rejection (1y-AR), and delayed graft function (DGF) using Cox-regression and logistic regression in a combined multivariable model including HLA-matching and mismatching adjusted for key covariates. We performed sensitivity analysis using a subgroup of DDKT patients after 2003 with less betweentool HLA nomenclature and implementing bootstrap sampling.

**Results:** We had complete data (outcomes and predictors) for 96236 recipients (Age 49.23±15.13, 60.4% male). AA-recipients constituted 30.2% while AA-donor organs were utilized 13.1% of DDKT (n=29071&12575, respectively). Similar to the whole UNOS cohort, among AA-recipients both HLA-matching and mismatching individually had significant stepwise association with all outcomes (10-yr DCGS, 1y-AR & DGF). However, distinct from the whole cohort, we identified that when added in a combined model along with other covariates and adjusted for each other, HLA-matching and mismatching had equal effects on each of the three examined outcomes. Among AA-donors, neither HLA-A
Below-average physical QOL at 12-months was observed in 23% of patients and was associated with pre-transplant BMI (OR 1.12 per 1 kg/m² increase, CI 1.02-1.23, p<0.02) and a pre-transplant SPBB score < 12 (OR 3.05, CI 1.17-7.97, p=0.02). In contrast, pre-transplant diabetes, dialysis, maintenance steroids and 12-month eGFR were not associated with physical QOL.

Conclusions: Decreased pre-transplant physical function predicts impaired physical QOL one year after kidney transplant. Further studies are needed to determine whether physical rehabilitation interventions can improve post-transplant QOL.

FR-PO1041

Ist Report of Korean Organ Transplantation Registry (KOTRY) Tai Yeon Koo,1 Hye Jin Lim1, Kyungok Min,2 Hyunjin Ryu,2 Jong Cheol Jeong,3 Jae Seok Yang,2 Myoung Soo Kim,2 Jae-Joong Kim,2 Curie Ahn,1 Kotry Study Group.1 Transplantation Center, Seoul National Univ Hospital; 2Dept of Nephrology, Ajou Univ School of Medicine; 3Dept of Surgery, Yonsei Univ College of Medicine; 4Devision of Cardiology, Asan Medical Center; 5Korean Organ Transplantation Registry, Republic of Korea.

Background: The Korean Organ Transplantation Registry (KOTRY) were launched in 2014 to construct the nationwide transplant database system which encompasses outcomes of various transplanted organs by support of the Korea Centers for Disease Control and Prevention.

Methods: In 2014, kidney, liver and heart transplant cohorts were established with participation of 29/58 centers for kidney, 13/35 centers for liver, and 4/8 centers for heart, covering more than 80% of total cases. Lung and pancreas transplant cohorts are also in progress since 2015. A web-based database system and attached biobank system have been developed. Annual data report and related information of database development process are available at http://www.kotry.org. From July 2014 to December 2014, 419 transplants in kidney transplantation (KT), 430 in liver transplantation, and 77 in heart transplantation were registered.

Results: Among 419 KT, deceased donor (DD) was performed in 156 patients (37.2%). Mean age was 47.7±11.2 and 56.8% of transplants were males. Diabetic recipients were 23.2%, and 5.8% of transplants were older than 65 years. Their original kidney disease was most often chronic glomerulonephritis (39.6%), followed by diabetic nephropathy (18.6%). Among DD, deceased donor transplantation was performed in 21.7% of living donor KT. Mean age of donors was 45.3±13.2 and 59.9% were males. Among DD, expanded-criteria donor was 23.7%. Mean serum creatinine of living donor before and after KT were 0.81±0.18mg/dl and 1.16±0.27mg/dl, respectively.

Conclusions: The KOTRY is expected to provide infrastructures for research in the field of KT and invaluable data for the Asian organ transplantation field.

Funding: Government Support - Non-U.S.
FR-PO1044

Comorbidity Burden of Kidney Transplant Recipients Predicts Emergency Usage Despite increased Family Physician Visits

Hatem A. Alnasser, Sita Gourishankar, Kevin C. Wen. ¹Univ of Alberta, Canada; ²King Fahad Specialist Hospital, Saudi Arabia.

Results: Of 354 maintenance RTRs (mean age: 54.3 ± 11 years), 60.5% were male and 39.5% were female. The mean number of comorbidities (mean ± SD: 3.4 ± 1.9) was significantly higher in female recipients (4.0 ± 2.0) compared to male recipients (3.0 ± 1.6). The most common comorbidities were hypertension (47%), diabetes mellitus (35%), and coronary artery disease (20%).

Methods: We performed a retrospective study of 354 maintenance RTRs attending a single center renal transplant clinic between 1 Jan 2007 and 31 Dec 2012. Comorbidities were defined using a modified Charlson Comorbidity Index and the number of medications prescribed to treat these conditions was recorded. The primary outcome was the number of emergency department visits (EDVs) per year, defined as an in-person encounter within 72 hours of a patient’s kidney transplant. The secondary outcomes were the number of inpatient hospitalizations and the number of emergency admissions per year.

Results: The mean number of EDVs per patient was 1.4 ± 1.5, 1.2 ± 1.3, and 1.0 ± 1.3 for patients with 0–2, 3–4, and 5 or more comorbidities, respectively. In multivariate analysis, a greater number of comorbidities was associated with a higher number of EDVs (OR = 1.35, p=0.001). Similarly, a greater number of medications was associated with a higher number of EDVs (OR = 1.001, p<0.001). The number of inpatient hospitalizations and emergency admissions per year also increased with an increasing number of comorbidities.

Conclusions: Comorbidity burden of kidney transplant recipients is a significant predictor of emergency usage. This study highlights the importance of comprehensive management of comorbidities in order to reduce emergency visits and improve health outcomes in kidney transplant recipients.

Funding: Government Support - Non-U.S.

FR-PO1045

Stroke Predictors and Outcome in Renal Transplant Recipients

Mark Duncan Findlay. ¹,² Peter C. Thomson, ²Patrick B. Mark. ¹Glasgow Renal and Transplant Unit, Glasgow, United Kingdom; ²Glasgow Renal and Transplant Unit, Glasgow, United Kingdom.

Background: End-stage renal disease is associated with a high incidence of cerebrovascular disease. Conventional risk factors do not always apply and established preventative strategies may be ineffective. The incidence, predictors & outcomes following stroke in those with a functioning renal transplant is not well described.

Methods: All adult patients with a renal transplant attending Glasgow Renal and Transplant Unit between 1st Jan 2007 and 31st Dec 2012 were identified using the electronic patient record. Clinical, demographic & laboratory data were collected including presence of diabetes, cardio- or cerebrovascular disease (CeVD), atrial fibrillation, deprivation, serum renal and bone chemistry and use of immunosuppressants. Stroke was identified via discharge codes, cerebral imaging or death certification. Independent predictors of stroke were identified via multivariable regression analysis. Fatality & causes of death are presented.

Results: 636 patients were identified, mean age 58 years (SD 12.9). 60.5% were male and 9.1% had AF. During follow-up 7.1% received a transplant as first RRT modality. 23 patients experienced a stroke during 3455 patient years of follow-up. 83.3% were ischemic. Stroke incidence was 6.9/1000 patient years for all stroke and 3.76/1000 patient years for first stroke. A stepwise backward regression revealed predictors of stroke as older age (HR 1.05, p=0.025) and previous CeVD (HR 18.16, p=0.001). Significant independent predictors for first stroke were age, diabetes and AF (p=0.005). There were no cases of SAH in PCKD. AF associated with time to stroke (p=0.003), but there was no detectable benefit from use of warfarin. 134 died during follow-up. 62.5% deaths followed stroke with 7, 28 and 365 day fatality of 20.8, 25 and 45.8%. Cardiovascular (75%) or malignancy (13%) were the cause of death in most cases.

Conclusions: Renal transplant recipients have a high incidence of stroke and poor outcome following stroke. Risk factors include prior CeVD, age, diabetes and AF. Although AF associated with time to stroke, the role of warfarin in prevention is poorly defined, requiring further study.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
FR-PO1046
Factors Influencing Racial Disparities in Renal Transplantation Outcomes
Sumit Mohan, Barry I. Freedman, William Mark Brown, Stephen O. Pastan, Ajay K. Israni, David P. Schlaff, Robert S. Gaston, R. Bray, Amber M. Reeves-Daniel, Bruce A. Julian, Jasmin Divers, Coffee Hill, Wake Forest School of Medicine, Emory Univ, Univ of Minnesota, Minneapolis Medical Research Foundation, Univ of Alabama at Birmingham.

**Background:** Kidney transplants from African American (AA) deceased donors have worse outcomes than kidneys procured from donors of other ethnic groups; deceased donor kidney transplants (DDKTs) engrafted into AAs fare worse than kidneys placed into recipients of other ethnic groups. The role of biological and environmental factors in these disparities remains unclear. We sought to identify factors contributing to these ethnic differences in AA and European American (EA) recipients of kidneys from AA and EA donors, in a study using donor-matched design to eliminate donor-specific confounding effects.

**Methods:** We compared allograft survival of DDKTs in 4 types of donorrecipient pairs (TDRP) (AA-AA, EA-AA, EA-AA, and EA-EA). Models were fitted using a mixed effect Cox model with particular focus on effect modifiers of the TDRP association with allograft survival.

**Results:** We identified 669 AA and 3,383 EA donors resulting in 669 AA-AA, 669 AA/EA, 3,383 EA-AA and 3,383 EA/EA DDKTs. In agreement with previously reported trends, AA donors were more likely to be younger, male, hypertensive, and with higher serum creatinine, while EA recipients were more likely to be employed (46% vs. 37% and 33%) and less likely to experience delayed allograft function (DGF) (19% vs. 28% and 23%). Adjusted analyses controlling for donor and recipient characteristics identified strong interaction effects between the TDRP and incidence of DGF (P<0.009) and between the TDRP and employment status (P=0.04). Observed hazard ratios varied from 0.9 for an employed (EA/EA) pair without DGF to 4.3 for an unemployed (AA/AA) pair with DGF.

**Conclusions:** Ethnic differences in employment status and incidence of DGF were the strongest effect modifiers of the association between the TDRP and allograft survival for DDKTs. These differences partially explained the observed racial disparity in outcomes for DDKTs.

**Funding:** Other NIH Support - NIH RO1 DK070941 (BF), NIH RO1 DK084149 (BF), NIH RO1 MD090655 (JD, BIF), NIH/NIAD Genomics of Transplantation S1U1-AI070119 (AKI)

FR-PO1047
Renal Transplantation in Bardet-Biedl Syndrome
Robert M. Haws, Aditya Joshi, Siddharth A. Shah, Omar M.A.A. Alkandari, Martin A. Turman.

1Dept of Pediatrics, Marshfield Clinic, Marshfield, WI; 2Dept of Pediatrics, Univ of Oklahoma Health Science Center, Oklahoma City, OK; 3Dept of Pediatric Nephrology, Univ of Louisville, Louisville, KY; 4Dept of Pediatrics, Mubarak Al-Kabir Hospital & Hamid Al-Essa Transplant Center, Safat, Kuwait.

**Background:** Bardet-Biedl syndrome (BBS) is a rare, multisystemic genetic disorder frequently associated with chronic kidney disease (CKD). Data regarding renal transplantation (RT) in BBS is lacking and reports tend to highlight complications. We report RT outcomes in the largest BBS cohort examined to date.

**Methods:** An international BBS registry was interrogated to identify individuals that had undergone RT and capture age, gender, body mass index (BMI), transplant and patient survival, donor source, and comorbidities.

**Results:** RT was performed in 19/171 (11%) registry subjects (mean age 9 y; range 2-25 y). RT patients were younger (9 vs. 17.9 y, p<0.05) and more likely to be female (82% vs. 50%). Deceased donors provided 12/21 kidneys; one patient received a combined liver/renal transplant. Two patients that underwent RT in the 1980s and died at <10 y of age were excluded from further analysis. Patient and kidney survival is shown.

**Conclusions:** Outcomes following RT in patients with BBS is favorable. Female predominance raises questions regarding gender as a potential modifying factor impacting CKD prevalence.

**Funding:** Private Foundation Support

FR-PO1048
Kidney Transplant Recipient Hospital Readmission: Examination of Discharge-Level Factors
Michelle L. Lubetzky, Maria Ajaimy, Layla Kamal, Graciela De Boccardo, Enver Akalin.

1Department of Medicine, Transplantation, Montefiore, Bronx, NY.

**Background:** Early rehospitalization after kidney transplantation (KTxs) is common and is considered a quality metric. Few studies have examined preventability or discharge factors associated with early rehospitalization.

**Methods:** We performed a single-center, retrospective cohort study between 2011-2015 of adult KTx recipients. The primary outcome was at least one readmission within 30 days after discharge. Secondary outcomes were reason for readmission, potential for process improvement to reduce readmission, and all-cause graft failure.

**Results:** Of 462 KTx, 31.4% were readmitted within 30 days of discharge. The reason for discharge was surgical in 20.1%. Of those with non-surgical reasons, 21.7% were from infection, 20.9% graft dysfunction, 21.7% gastrointestinal, 21.7% metabolic, and 13.9% other. Readmission was significantly associated with all-cause graft failure (p=0.006). The assessment of preventability showed that the reason for readmission was present at the time of discharge in 17.7%, additional hospital resources may have abrogated the readmission in 15.8%, and 12.4% could have been managed as outpatient. On univariate analysis, risk factors for rehospitalization were: presence of comorbidities (p=0.03), complication during hospitalization (p<0.001), discharge electrolyte abnormalities (p=0.001) and kidney function at discharge (p=0.003). Table 1. On multivariate analysis, the presence of 3 comorbidities pre-KTx (OR 2.01 95% CI 1.84-3.86), electrolyte abnormalities at discharge (OR 1.77 CI 1.17-2.69), delayed graft function (OR 1.65 95% CI 1.27-2.17), and post KTx complications (OR 1.79 CI 1.11-2.71) were associated with increased risk of readmission.

**Table 1:** Comparisons of Patients Requiring Rehospitalization versus No Readmission

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<th>Readmission No</th>
<th>Readmission Yes</th>
<th>p-value</th>
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<td>188 (90%)</td>
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<tr>
<td>Recipient Race</td>
<td>Black</td>
<td>31 (16.1%)</td>
<td>35 (24.4%)</td>
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<tr>
<td></td>
<td>Hispanic</td>
<td>13 (6.9%)</td>
<td>16 (11.4%)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>45 (23.5%)</td>
<td>13 (9.0%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>23 (12.5%)</td>
<td>24 (16.7%)</td>
</tr>
<tr>
<td>Any Recipient Comorbidities</td>
<td>217 (56.5%)</td>
<td>119 (74.7%)</td>
<td>0.0044</td>
</tr>
<tr>
<td>Recipient BMI &gt; 35 kg/m²</td>
<td>32 (16.1%)</td>
<td>13 (8.6%)</td>
<td>0.4634</td>
</tr>
<tr>
<td>Recipient Diabetes mellitus</td>
<td>137 (46.2%)</td>
<td>41 (27.9%)</td>
<td>0.0105</td>
</tr>
<tr>
<td>Recipient Prior solid Organ Transplant</td>
<td>32 (16.1%)</td>
<td>17 (11.4%)</td>
<td>0.5797</td>
</tr>
<tr>
<td>Recipient Cardiac Comorbidity</td>
<td>89 (26%)</td>
<td>41 (28%)</td>
<td>0.9045</td>
</tr>
<tr>
<td>Recipient Pneumocystis</td>
<td>35 (17%)</td>
<td>20 (13.3%)</td>
<td>0.1612</td>
</tr>
<tr>
<td>Recipient HIV, HCV, or HBV</td>
<td>32 (16%)</td>
<td>24 (16.7%)</td>
<td>0.8836</td>
</tr>
<tr>
<td>Recipient pre-transplant albumin &lt; 3.5 g/L</td>
<td>10 (4.9%)</td>
<td>7 (5%)</td>
<td>0.3982</td>
</tr>
<tr>
<td>Recipient pre-transplant hemoglobin &lt; 12 g/dL</td>
<td>49 (25.5%)</td>
<td>27 (18.4%)</td>
<td>0.1687</td>
</tr>
<tr>
<td>Recipient time to 1st disch</td>
<td>Low &lt; 483</td>
<td>122 (82.9%)</td>
<td>87 (62%)</td>
</tr>
<tr>
<td></td>
<td>Medium 483-1579</td>
<td>130 (41.2%)</td>
<td>40 (26.4%)</td>
</tr>
<tr>
<td></td>
<td>High &gt; 1579</td>
<td>65 (45.3%)</td>
<td>28 (18.9%)</td>
</tr>
<tr>
<td>Recipient, all disch</td>
<td>160 (50.5%)</td>
<td>71 (42%)</td>
<td>0.1040</td>
</tr>
<tr>
<td>Recipient, standard criteria donor</td>
<td>182 (87.5%)</td>
<td>87 (60%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Recipient, deceased criteria donor</td>
<td>36 (17.5%)</td>
<td>27 (18.2%)</td>
<td>0.6885</td>
</tr>
<tr>
<td>Recipient using donor</td>
<td>29 (17.5%)</td>
<td>18 (12.3%)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization complication</td>
<td>159 (52.6%)</td>
<td>49 (67.6%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Hospitalization, length of stay &gt; 7 days</td>
<td>65 (45.3%)</td>
<td>34 (22.8%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Hospitalization, intensive care unit location</td>
<td>34 (17.5%)</td>
<td>24 (16.3%)</td>
<td>0.7135</td>
</tr>
<tr>
<td>Hospitalization surgical or radiologic intervention</td>
<td>23 (7.5%)</td>
<td>20 (13.4%)</td>
<td>0.2046</td>
</tr>
</tbody>
</table>

**Conclusions:** Early readmission is associated with worse graft survival. Many readmissions may be preventable and review of process improvement may reduce early readmission after KTx.

Thrombosis and infection resulted in graft loss in the first year in 1 patient with 2 kidneys. One patient died awaiting a second RT. Acute reversible rejection in the first year was seen in 1/17 kidneys. Diabetes, hypertension, and obesity were present in 18%, 71%, and 88% of subjects, respectively. Malignancy was not observed (mean follow-up 9.8 y; range 1-21 y). BMI was increased compared to age-matched BBS patients without RT (42.2 v. 35.2, p<0.05).

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

Underline represents presenting author.

609A
FR-PO1049

Kidney Transplant Outcomes for Patients with Amyloidosis – A United Network for Organ Sharing Database Analysis

Ali Khalil, Tim E. Taber, Muhammad Ahmad Mujtaba, Muhammad S. Yaqub, Asif A. Sharfuddin. Medicine/Neph, Indiana Univ, Indianapolis, IN.

Background: Outcomes of patients with Amyloidosis who receive a kidney transplant have not been extensively studied. We examined UNOS database for outcomes of such recipients.

Methods: UNOS database was queried for recipients with code “3016” which corresponds to “Amyloidosis”. Duration of study period was Nov 1987 to Dec 2014.

Results: A total of 625 recipients were identified as in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at time of transplant (yrs) SD</td>
<td>54.8±11.1</td>
</tr>
<tr>
<td>Mean Donor Age</td>
<td>40±15.1</td>
</tr>
<tr>
<td>Median Time On Wait List (days/ range)</td>
<td>2610-2706</td>
</tr>
<tr>
<td>Caucasian/African American/Hispanic/Other (%)</td>
<td>80.5/7.2/9.1/3.2</td>
</tr>
<tr>
<td>Deceased/Living (%)</td>
<td>56.5/43.5</td>
</tr>
<tr>
<td>M/F (%)</td>
<td>62.4/37.6</td>
</tr>
<tr>
<td>On Dialysis at time of transplant (%)</td>
<td>80.2</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>25.7±4.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6.3</td>
</tr>
<tr>
<td>Repeat Kidney Transplant (%)</td>
<td>3.8</td>
</tr>
<tr>
<td>PRA &gt;80 (%)</td>
<td>3.6</td>
</tr>
<tr>
<td>Zero Mismatch (%)</td>
<td>8.6</td>
</tr>
<tr>
<td>Blood Type A/AB/O (%)</td>
<td>40.7/5.3/12.5/41.6</td>
</tr>
<tr>
<td>ECD Donor/DCD (%)</td>
<td>9.6/29</td>
</tr>
<tr>
<td>Multi-Organ Transplant (%)</td>
<td>6.6</td>
</tr>
<tr>
<td>- Heart(n)</td>
<td>- 21</td>
</tr>
<tr>
<td>- Liver(n)</td>
<td>- 23</td>
</tr>
<tr>
<td>- Pancreas(n)</td>
<td>- 2</td>
</tr>
<tr>
<td>Delayed Graft Function (%)</td>
<td>14.6</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL) at discharge (SD)</td>
<td>2.3±2.1</td>
</tr>
<tr>
<td>Treated for Rejection within 6mo (%)</td>
<td>11.2</td>
</tr>
<tr>
<td>Treated for Rejection within 1yr (%)</td>
<td>12.8</td>
</tr>
<tr>
<td>Death With Functioning Graft (%)</td>
<td>28.3</td>
</tr>
<tr>
<td>Unadjusted 1 yr/3yr/5yr/10 yr Graft Survival (%)</td>
<td>87.5/79.3/71.2/58.2</td>
</tr>
<tr>
<td>Actual Patient Survival 1yr/3yr/5yr/10 yr</td>
<td>91.8/83.0/75.8/61.2</td>
</tr>
</tbody>
</table>

After excluding multi-organ transplants, the 1 year unadjusted graft survival was 88.6% and the 1 year patient survival was 92.1%. Kaplan Meier Survival Curves are in the Figure.

FR-PO1050

Early Experience with the New Kidney Allocation System


Background: On December 3, 2014, major changes to deceased donor kidney allocation were implemented under the new Kidney Allocation System (KAS).

Methods: Using national registry data, we compared changes in rate of DDKT among adult kidney-only waitlist registrants 1/2011-3/2015 pre vs post-KAS via Poisson regression, adjusting for age, sex, race, ABO blood type, calendar year, calculated panel reactive antibody (CPRA), and wait time. We compared donor service area-level geographic disparity pre vs post-KAS using multilevel Poisson regression and median incidence ratio (MIRR). We also compared CPRA of DDKT recipients pre vs post-KAS, and incidence of delayed graft function (DGf).

Results: Pre-KAS, access to DDKT was poorer for women (IRR=0.92, African-Americans (AAs) (IRR=0.88, Hispanics (IRR=0.79), all p<0.01). Access was best for patients of ABO type AB (IRR vs O=2.29, p=0.01) and worst for ABO type B (IRR vs O=2.29, p=0.01). KAS was associated with no change in overall DDKT access (p=0.7), but with improved access for AAs (IRR=1.16, interaction p<0.001) and patients of ABO type AB (IRR=1.29, interaction p<0.001). Geographic disparity declined post-KAS (MIRR=1.76 pre-KAS, 1.64 post-KAS). Median CPRA at transplant was 0 both pre and post-KAS; the proportion of recipients with CPRA 80-99 decreased from 13.6% to 10.1% (p<0.001), but the proportion with CPRA=99 rose from 1.6% to 14.0% (p<0.001, Figure 1).

Conclusions: After recent changes to kidney allocation, DDKT access improved for AA patients and geographic disparity declined. Women and Hispanic patients are still disadvantaged, and disparity by ABO type worsened. The proportion of recipients with CPRA=99 rose dramatically. Increase in DGF may suggest risk of poorer long-term outcomes.

Funding: NIDDK Support

FR-PO1051

Kidney Transplantation Tourism: High Risk and Bad Outcome for the Recipients

Amjad E. Elagroudy. Internal Medicine Dept, College of Medicine and Medical Sciences, Arabian Gulf Univ, Manama, Bahrain.

Background: While the ethical aspects of transplant tourism have received much attention recently, less has been written about the medical safety of this practice. We retrospectively evaluated the outcomes of patients who purchased organs internationally and presented to our center for follow-up care.

Methods: We report the outcome parameters of 270 local recipients of unrelated kidney (URT) vendor transplants presenting to our institute between 1986 and 2014. Their outcome was compared with 123 recipients of living-related donor transplants matched for age, gender and transplant duration done in our center as controls (RT).

Results: Age of unrelated recipients was 42.6±13.4 years with Male % of 68. The country of transplant was mainly in Philippines (n=35), Pakistan (n=36), India (n=57), Iran (n=40) and Egypt (n=25). Comparison of commercial recipients with controls showed high co morbidities (P=0.01) with hepatitis-C (n=2 vs. 0) and hepatitis-B (n=2 vs. 0) and cytomegalovirus (n=4 vs. 1). Donor age was 25.9±3.8 vs. 34.6±8.6 years (P=0.0001) and 90.4% were male. Biologic agents induction in 74 (27.4%) vs. 123 (100%) (P=0.0001), acute rejections in 65 (24.1%) vs. 26 (21.1%) (P=0.7), while recurrent rejection in 13 (4.8%) vs.1 (0.8%) (P=0.04), surgical complications including lymphocele 16 (5.9%) vs. 0 (0%) (P=0.0001), ureretal obstruction 7 (2.6%) vs. 0 (0%) (P=0.007), hematoma 4 (1.5%) vs.1 (1.1%) (P=0.06) and recurrent urinary tract infection 18 (9.9%) vs.6 (6.8%) (P=0.3). Overall 1- and 10-year for graft survival was 91% and 22% vs. 98% and 44% and for patient survival 96% vs. 70% vs. 98% and 78% in URT and RT, respectively (P=0.001).

Conclusions: Although 1 year graft and patient survival of kidney transplants in recipients with Amyloidosis is inferior to standard outcomes, long-term outcomes are not remarkably different. Careful selection of this population can lead to satisfactory outcomes. To our knowledge this is the first and largest report on the outcomes of these patients from the US national database.
Conclusions: Although recent developments increased success in renal transplantation, receiving a kidney from a paid living donor at a commercial transplant center still carries greater risks for the recipient.

Methods: We analyzed 93 patients who received a 2nd transplant at The Royal London Hospital between November 1994 and January 2015. 59 patients did not receive primary transplant nephrectomy (TNx) and had failed allograft in situ at the time of second graft (group A) whilst 34 patients underwent TNx prior to second graft (group B). 2nd transplant survival was the primary end point. Sensitization, waiting time for 2nd graft, graft function and rejections were second end points.

Results: Group A patients had significant longer graft survival than group B (100.6 months vs 40.2 months, p<0.001). Waiting time from primary graft loss to second graft in group A was shorter than group B (36.7 months vs 59.1 months, p=0.013). In total, 33 patients had pre-formed anti-HLA antibodies (low titre). Group B had significantly higher rate of pre-formed anti-HLA antibodies than group A (50.0% vs 29.3%, p=0.047). The rate of HLA class I in group B was also significantly higher than that in group A (47.1% vs 25.7%, p=0.038). Group B had numerically higher rate of acute rejection than group A (32.4% vs 15.3%, p=0.033). GFR between both groups did not differ until 3 years post-transplant. In group A, 2nd graft survival rates at 6month, 1.3 and 5 years were 94.9%, 93.0%, 87.0% and 82.3%, and were significantly better group B (73.3%, 70.0%, 60.6% and 46.8%, p<0.001). On multivariate analysis, waiting time for second transplant, TNx, second transplant donor age and delayed graft function were independently associated with second graft survival. TNxs had highest hazard ratio (2.83, 95% CI 1.22-6.67, p=0.015).

Conclusions: Prior TNx is associated with inferior 2nd renal graft survival in this observational study and calls for an urgent randomized control trial.

FR-PO1053

Induction Agent Use, Mortality and Acute Rejection in Older KT Recipients


Background: Induction agents are commonly used as an initial intensive immunosuppression after kidney transplantation (KT) to prevent acute organ rejection; this presentation is the first to label. Little is known about induction agent use in older KT recipients.

Methods: Data on 19,546 older KT recipients (2005-2013) was ascertained from the Scientific Registry of Transplant Recipients. Induction agents were classified as thymoglobulin/ATG, IL-2, or other induction agents. The risk of mortality was estimated using a proportional hazards Cox regression model (hazard ratio (HR)) adjusting for all confounding KT factors (age, sex, race, BMI, peak PRA, history of diabetes, years on dialysis) and KT factors (HCV, HLA mismatches, cold ischemia time, donor type, donor age, and donor sex). The relative risk (RR) of 1 year acute rejection was estimated using modified Poisson regression adjusting for all recipient and KT factors.

Results: The mean age was 69 (SD-3.8 years), 36% female, 19% black and 27% live donor recipients. There is an increasing utilization by year of induction agents, with 84% use in older recipients. Compared to those who did not receive induction, the risk of mortality for older recipients was decreased for those who received thymoglobulin/ATG (HR=0.86, 95%CI:0.79-0.94), IL-2 induction agents (HR=0.89, 95%CI:0.81-0.97), and other induction agents (HR=0.85, 95%CI:0.75-0.97). Additionally, compared to those who did not receive induction, the risk of 1 year rejection for older recipients was increased for those who received IL-2 induction agents (HR=1.36, 95%CI:1.15-1.61), as well as other induction agents (HR=1.27, 95%CI:1.03-1.57) but not thymoglobulin/ATG (HR=1.06, 95%CI:0.90-1.25).

Conclusions: For older KT recipients, there is an increasing trend in the use of induction agents and a decreased risk of mortality regardless of the type of induction agent used. However, there is little evidence for a protective effect of induction agent use for 1 year acute rejection.

Funding: Other NIH Support - NIA, Private Foundation Support

FR-PO1054


Background: The aging immune system has fewer naïve T cells, more memory T cells, and less T cell receptor variability. Older transplant patients tend to have more comorbidities and less functional reserve. This combination makes them more difficult to immunosuppress with higher risk of infection, and potentially increased mortality from rejection treatment.

Methods: In order to determine the impact of rejection treatment on outcomes in our transplant recipients >70 years of age, we reviewed the outcomes of recipients transplanted at our center from 1/2009-12/2013. Induction regimens varied; maintenance immunosuppression consisted of tacrolimus, mycophenolate, and rapid steroid withdrawal.

Results: During this time period, we transplanted 110 over 70 years of age. Of these, 27 patients had rejection – 24 ACR, 1 combined AMR/ACR, 1 AMR. Followed by ACR (see table). 11 of these patients received Tcell depleting agents, the rest received IV steroids +/- IVIg. There was no difference in age, race, donor type, prior transplant, or induction therapy between the two groups. Mean creatinine was higher in the rejection group. Treatment aimed to stabilize functions - the rate of decline in estimated GFR after rejection treatment was no different between groups. Within 6 months of rejection treatment, there were 12 infectious complications, only 3 of which required hospitalization (urosepsis-2, CMV-1). There were no differences in rates of BK viiremia, CMV viiremia, graft survival, or mortality. 7 of the 27 patients died at some point after rejection, only one was related to infection >1 year later and not related to treatment.

Conclusions: Among our >70 patients, rejection treatment appeared well tolerated with few complications requiring hospitalizations and no treatment related mortalities. In addition, it appeared that treatment stabilized function in the majority of patients.

FR-PO1055

Mortality After Kidney Allograft Failure and Return to Dialysis

Anupriya Brar, Edem Nguannon Timpo, Rahul M. Jindal, Nabil Sunrami, Faridah Moos, Ambera C. Hargraves, Andrew DeMarco, Edem Nguannon Timpo, Rahul M. Jindal, Nabil Sunrami, Faridah Moos, Ambera C. Hargraves, Andrew DeMarco.

Background: Our hypothesis was that kidney allograft failure (KAF) and return to dialysis (RTD) results in greater mortality versus patients with end-stage renal disease (ESRD). We also sought to identify variables associated with mortality after KAF.

Methods: We used an incident cohort of patients from the United States Renal Data System who initiated any form of dialysis between Jan 2003 and Dec 2008 after KAF. We followed patients until retransplantation, death or Sept 2009. Multivariable Cox analysis was used for statistical associations.

Results: 7,156 patients were followed for a mean of 30.8±22.6 months. 3,622 (50.6%) patients were lost to follow up. Main causes of death were cardiovascular (37.0%), infection, 1.54%, other 16.4% and metabolic/endocrine (7.9%) causes. Predictors of all-cause mortality included age at KAF (hazard ratio (HR)= 1.03, 95% confidence interval (CI) 1.03-1.04), diabetes (DM) as cause of kidney failure (HR=1.52, CI 1.36-1.68), congestive heart failure (CHF) (HR= 1.19, CI 1.04-1.36), peripheral arterial disease [PAD] (HR= 1.23, CI 1.04-1.55), stroke (HR= 1.27, CI 1.12-1.43), and female sex (HR=1.17, CI 1.09-1.25).

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

Underline represents presenting author.

61A
The ideal intravenous (IV) fluid for kidney transplantation (KTx) has not been defined, despite the common use of normal saline (NS) in the perioperative period. The high chloride content of NS is associated with an increased risk of hyperchloraeic metabolic acidosis, which may increase the risk of hyperkalemia and delayed graft function (DGF). Balanced electrolyte solutions (BESS) have a lower chloride content, which may decrease this risk and avoid the need for dialysis due to hyperkalemia. Randomised controlled trials (RCTs) have used biochemical outcomes to compare fluids and have been underpowered to address patient-centred outcomes such as DGF. We systematically reviewed the effect of BES versus NS on DGF, hyperkalemia and acid-base status in KTx recipients.

Methods: We searched the Cochrane Renal Group’s Specialised Register to 24th March 2015. We included RCTs of KTx recipients that compared perioperative IV lower-chloride solutions to NS. Two independent investigators assessed studies for eligibility and risk of bias. Data were extracted using standardised forms and pooled according to a published protocol.

Results: Six studies (477 participants) were included in the review. All participants were adult KTx recipients and 70% received live-donor KTx. The overall risk of bias was low for selection bias and unclear for remaining domains. There was no difference in the risk of DGF (RR 1.03, 95%CI 0.62–1.70, P=0.91) or hyperkalemia (RR 0.48, 95%CI 0.04–6.10, P=0.57) for participants who received BES compared to NS. Compared to NS, BES were associated with a higher blood pH (mean difference pH 0.07, 95%CI 0.05–0.09, P<0.00001), higher serum bicarbonate (mean difference HCO₃⁻ 3.04mmEq/L, 95%CI 2.13–3.94mmEq/L, P<0.00001) and lower serum chloride (mean difference chloride -9.93mmol/L, 95%CI -19.96–0.11mmol/L, P<0.05).

Conclusions: Intraoperative balanced electrolyte solutions are associated with less hyperchloraeic metabolic acidosis compared to normal saline. However, these data do not support their use to reduce clinical events.
FR-PO1060

Outcomes of Kidney Transplant Recipients from Donation After Circulatory Death Donors without Pre-Agonal Heparin Administration

Layla Kamal, Joel Lindower, Maria Ajaimy, Michelle L. Lubetzky, Graciela De Boccardo, Enver Akalin, Liis K. Kayler.
Montefiore-Einstein Center for Transplantation.

Background: Protocols of organ donation after circulatory death (DCD) are considerably varied. Heparin administration during the pre-agonal phase has been recommended to improve organ perfusion and prevent blood clots; however some protocols avoid heparin before verification of death based on legal or professional concerns. We assessed outcomes of kidney transplant recipients who received DCD kidneys recovered with and without heparin.

Methods: We retrospectively evaluated recipients of kidney transplants between 2013 and 2014 from controlled DCD donors who received (n=23) or did not receive (n=29) pre-agonal heparin.

Results: All kidneys underwent machine perfusion. No DCD donors had a similar kidney donor profile index but were more likely to have mild histologic changes, elevated terminal creatinine perfusion resistant index, and to be imported from non-local donor service areas compared to the Heparin donors. Recipients of No Heparin kidneys were more likely to be female, sensitized, prior solid organ recipients, and to receive thymoglobulin induction but were less likely to have diabetes. None of these differences reached statistical significance. Post-transplantation, 1 patient died early due to a cardiac event (no Heparin group). Graft failure occurred in 2 patients in the no Heparin group (one each of sepsis/ intraparenchymal venous thrombosis and chronic histologic changes suggestive of donor disease) and 1 patient in the Heparin group (renal artery thrombosis). Between group differences were small in terms of delayed graft function, 6-month acute rejection, and estimated GFR at 3, 6, and 12 months.

Conclusions: Our findings suggest that DCD kidneys recovered without pre-agonal heparin are not at increased risk for primary non-function or thrombosis.

FR-PO1061

Effects of Dopamine Donor Pretreatment on Graft Function After Kidney Transplantation: Five-Year Follow-Up of a Randomized Controlled Trial

Urs Brech, Bernhard K. Krämer, Peter Schneulle. V. Medical Clinic, Univ Medical Center Mannheim, Mannheim, Germany; Nephrology, Center for Renal Diseases, Weinheim, Germany.

Background: For the study group: A previous multicenter randomized controlled trial reported reduced dialysis requirements after kidney transplant with dopamine donor pretreatment. Data on long-term outcomes are needed.

Methods: We calculated five-year graft survival from follow-ups at 60 European centers. We analyzed intention-to-treat and on-study medication and proteinuria prevalence estimates as tertiles of dopamine exposure because infusion times varied by treatment arm (range 0-1,929 min). Recipients with functioning grafts at three months were analyzed separately to differentiate early events from long-term consequences of the trial intervention. Statistical analyses were performed by multiple logistic regression and Cox regression using SAS. Results were considered significant if p < 0.05.

Results: 234 children (61% male) with an age of 2.5 ± 2.4 years (range 0.02-21.2 years) were included in the study, 128 (55%) from the dopamine and 106 (45%) from the saline group. At the end of the five-year follow-up, 223 recipients (95%) were alive. Graft survival rates at five years were 98.4% and no allograft was lost due to thrombotic complications. The causes of death were acute respiratory distress syndrome (1), cancer (1), and trauma (1). The overall death censored graft survival was 83.3 ± 8.0% (HR 0.84, 95%CI 0.54-1.29; p = 0.42) in the dopamine group compared to 92.7 ± 5.0% (HR 0.25, 95%CI 0.03-0.23; p < 0.001) in the saline group. The incidence of eGFR at 3, 6, and 12 months.

Conclusions: Dopamine administered for >270 min provided a long-term graft survival advantage independent of early events after Transplantation.

FR-PO1062

Does Calcineurin Inhibitor Timing Matter? Single Center Experience with En-Bloc Kidney Transplantation

Maya Campana, Oksana A. Kucher, Sanjeev Akkina, Ignatius Yun-Sang Tang. Pharmacy Practice, Univ of Illinois at Chicago; Medicine, Nephrology, Univ of Illinois at Chicago.

Background: En-bloc kidney transplantation (KTx) has excellent outcomes. To minimize vascular complications and nephrotoxicity, calcineurin inhibitor (CNI) therapy is often delayed. The purpose of our study is to investigate the impact of CNI initiation timing on 1-year graft outcomes.

Methods: This is a single-center, retrospective review of adult en-bloc KTx between 2001 and 2013. Timing of CNI initiation was decided by the operating surgeon. Patients were divided into two groups, those that received CNI therapy early (<48 hours) or delayed (>48 hours) posttransplant. The primary objective was to compare one year estimated glomerular filtration rate (eGFR) between the groups. Secondary outcomes included graft and patient survival, CNI levels, incidence of delayed graft function (DGF), rejection and graft failure rates.

Results: Twenty-one en-bloc KTx recipients were included in the analysis. Ten patients received CNI therapy within 48 postoperative hours (Early CNI Group). There was no difference in age, race, gender, PRA, cause of ESRD or BMI between the groups. Only 50% of Early CNI patients received lymphocyte depleting therapy vs. 100% in the Delayed CNI group (p = ns). In the Early CNI Group, 3 patients were on anticoagulants; all other patients received tacrolimus and mycophenolate maintenance. There was no difference in eGFR between groups at one year or at any other time points. Comparable therapeutic tacrolimus trough was observed at 5, 10 and 30 days posttransplant. There was no difference in DGF or graft failure incidence. In the delayed CNI group, one patient died of sepsis at 6 months.

Conclusions: Timing of CNI initiation had no impact on one year graft function and patient survival.

FR-PO1063

Reduction of Pediatric Renal Transplantation Vascular Thrombosis Rates Utilizing Low Dose Heparin Infusion


Background: Pediatric renal allograft thrombosis rates are 4-10% and often result in allograft loss. Thrombotic risk factors are smaller native vessel size, deceased donor source, and time between donor and recipient death. In our pediatric program from 1971 – 1992, 5 of 69 consecutive renal transplants (7.2%) were lost to vascular thrombosis. This study assesses if low dose continuous heparin infusion reduces the risk and outcome of thrombosis in pediatric renal transplants.

Methods: Over 22 years (1993-2015), 44 of 100 consecutive children post renal transplant received low dose continuous heparin (10 units/kg/hour) for 1 week for thrombotic risk: 1) age < 6yr (n=24); 2) laboratory profile of hypercoagulability (n=10); 3) oliguric/nadir creatinine (n=2); 4) high risk: 5) patient history of access thrombosis or vasculitis (n=1). Renal scans were obtained on days 1, 3, 5 and when clinical deterioration occurred.

Results: Only 2 thrombotic events were noted which did not cause graft loss: 1) 24RD transplant- venous thrombosis immediately post-op with successful thrombectomy at 2hr and allograft recovery; 2) 17yr DD double renal artery allograft arterial thrombosis of smaller inferior renal artery on day 10 (heparin stopped day 7). One patient on heparin infusion required laparotomy 3hrs after surgery for thrombosis external to the anastomosis. One patient not on heparin also required laparotomy in the first 24hrs post-op for hemoptysis evacuation. One patient in each group had primary non-function/surgical loss with removal of the kidney within the first 3 days post transplant. Graft survival at 1yr was 96% and no allograft was lost due to thrombotic complications.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

613A
FR-PO1064

The Influence of Induction Immunosuppressive Therapies and Diabetes on Graft Loss After Kidney Transplant

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Background: Induction therapy plays a significant role to reduce the rate of acute rejection in kidney transplant (KT). Understanding differences in outcomes associated with various induction agents may lead to improvements in KT care. Our objectives were to examine the influence of various induction therapies and diabetes on graft and patient survival after KT.

Methods: We used the 2000-2013 United Network for Organ Sharing (UNOS) data to evaluate the effectiveness of induction therapies and diabetes on graft and patient survival after KT. The patients were divided into four groups based on induction therapy: Basiliximab (n=24,484), alemtuzumab (n=3,321), rabbit anti-thymocyte globulin (n=ATG) (n=54,974) and daclizumab (n=13,358). Also the patients were divided into four groups based on diabetic status: non-diabetic (n=192,333), type1 diabetes (n=11,863), type 2 diabetes (n=45,543) and new onset of diabetes (n=10,509). The main outcome were the risk of graft loss and death at 1.3, 5.10 years. Cox proportional hazards model was used to estimate the hazard ratios.

Results: Graft loss was significantly higher in alemtuzumab group (HR=1.171; P<0.002) and rabbit anti-thymocyte globulin group (HR=1.109; P<0.0001) versus basiliximab group. Daclizumab group showed significantly lower risk for graft loss (HR=0.902; P<0.001) than basiliximab group. Death was significantly higher in rabbit anti-thymocyte globulin group (HR=1.075; P<0.0001) versus basiliximab group. Daclizumab group showed significantly lower risk for death (HR=0.850; P<0.0001) than basiliximab group. Graft loss was significantly higher in type 2 diabetes (HR=1.451; P<0.0001).

Conclusions: Induction immunosuppressive therapies and diabetic status play significant role in long-term graft and patient survival. Basiliximab and daclizumab as IL-2 RA receptor antagonists have better long-term graft and patient survival outcomes.

FR-PO1065

Doc-Induction Type Influence Outcomes in Kidney Transplant Recipients at Different Phases of Hepatitis B Infection

Khalil K. Sureshkar, Richard I. Marcus, Bhuyna Chopra. Nephrology and Hypertension, Allegheny General Hospital, Pittsburgh, PA.

Background: Host response to hepatitis B virus (HBV) infection is variable with some patients progressing to chronic liver disease. Immunosuppression associated with kidney transplantation in such patients may increase the risk of disease progression. We aimed to analyze the impact of potent depleting vs. non-depleting antibody induction on the outcomes in kidney transplant recipients (KTRs) at different serological stages of HBV infection.

Methods: Using UNOS database, we identified adult KTRs from 2001 to 2011 who at the time of transplantation were in one of the 3 serological stages of HBV infection: HBsAg+/HBcAb- (early infection), HBsAg+/HBcAb+ (inactive carrier or immune tolerant), or HBsAg+/HBcAb+ (clearing infection) sero-status. These findings support a practice of choosing induction type based on the immunological risk in such recipients rather than the serological status following HBV infection.

FR-PO1066

Health Economic Analysis of Rabbit Antithymocyte Globulin (Thymoglobulin) versus Basiliximab (Simulect) in Renal Transplantation – A German perspective

Friedrich Thaiss, 1 Thomas Benzing, 2 John Reitan, 3 Thomas Paivanas, 4 Meghan E. Gallagher, 5 Michael Sean Wiesener, 6 Nikolai Zink, 6

1 Univ. Hospital, Nephrology, Hamburg, Germany; 2 Univ. Hospital, Nephrology, Cologne, Germany; 3 RfM Group, Crown Point; 4 TAP & A, Annandale; 5 Sanofi, Cambridge; 6 Univ. Hospital, Nephrology, Erlangen-Nuernberg, Germany.

Background: Kidney transplantation is now accepted as a proven therapeutic modality prompting a greater need to understand the cost-effectiveness of different treatment approaches.

Methods: The primary objective of this study was to quantify the economic consequences of acute rejection and adverse events in patients undergoing cadaveric kidney transplantation and receiving ATG (Thymoglobulin - Thymo) compared with those receiving basiliximab (Simulet - Sim). Health economic data were collected according to reimbursement calculations from 3 German sites in an existing database (Brennan et al NEJM, 2006).

Results: Based on the clinical data from the Brennai trial, the study quantified current cost and changes in treatment patterns. Results demonstrate that at 12 months the cost of the Thymo-regimen is €5,753 more than that of the Sim-regimen. However, costs of delayed graft function, nonfatal graft failure events and post-graft failure dialysis are lower among Thymo treated patients. Thymo treated patients incurred higher graft maintenance costs, consistent with their longer graft survival. In total the associated cost-offset from less rejection events with Thymo offset the added cost from drug treatment and therefore Thymo is a more cost-efficient resource vs Sim due to cost avoidance. To further evaluate differences between the two groups we considered quality-adjusted life year differences. The Thymo cohort is projected to enjoy 405,714 QALY after 1 year. After a decade, the Thymo cohort is projected to cost 332,232 Euros less than the Simulet cohort while enjoying 10.8 more QALYs.

Conclusions: This analysis was intended to provide information that should be considered when weighing the costs and benefits of two immunosuppressive regimens and to investigate if treatment changes might result in more cost-effective care.

Funding: Pharmaceutical Company Support - Sanofi and RfM
FR-PO1068
Thymoglobulin Induction Therapy; Results for 5 Years – Improving the Survival of Renal Allograft and Patient
Virginia Barra Pedroza, Benjamin Gómez-Navarro. Nephrology and Transplantation, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, Mexico.

Background: The factor that impacts the survival of renal allograft is the presence of acute rejection. In our city, using Thymoglobulin has offered to patients at high immunological risk, and through the years has sought to reduce adverse events use. The objective is to evaluate the frequency of acute rejection during the last 5 years in patients receiving Thymoglobulin induction.

Methods: An ambispective cohort, patients transplanted in UMAE HE-CMNO, Jalisco, Mexico is included in the period June 2010 to June 2014 who received induction therapy with Thymoglobulin. Was recorded the frequency of acute rejection, the frequency of infections, use of Filgrastim(G-CSF), graft loss and death at 12 months of transplantation.

Results: A 370 patients were included, which received initial doses of Thymoglobulin 0.6mg/kg-1.5mg/kg. In 2013, by multivariable analysis Thymoglobulin dose was that associated with a lower incidence of acute rejection was analyzed and found that 1mg/kg for 4 days (cumulative dose 4mg/kg) is a protective factor for the occurrence of acute rejection (IC 95‰ 0.11-0.60, OR 3,7, p<0.001), for this reason almost patients received this dose. In 2010, the rate of rejection was 10‰ and actually is 7.8‰ (p=0.05;).

Infections disease was reduced about 30‰. Currently few patients use of r-g-CSF because leukopenia-neutropenia, lost the renal graft or die during the first year.

Conclusions: Interestingly, in our hospital, we observed a lower rate of acute rejection and improved patient survival and allograft. Apparently finding the right dose in our patients has allowed thymoglobulin induction is safe and minor complications.

FR-PO1069
Randomized Trial of Tacrolimus/Everolimus versus Tacrolimus/Enteric-Coated Mycophenolate Sodium to Prevent Biopsy-Proven Acute Rejection and Chronic Allograft Injury in Adult, Primary Kidney Transplantation
Giselle Coated Mycophenolate Sodium to Prevent Biopsy-Proven Acute Rejection
Randomized Trial of Tacrolimus/Everolimus versus Tacrolimus/Enteric-Coated Mycophenolate Sodium and steroids. Primary endpoint was change in eGFR (MDM4) from RND to M12. Main secondary endpoint a composite efficacy of treated biopsy-proven acute rejection (IBPR, Banff ≥II), graft loss, or death and safety.

Results: At M12, the clinical benefit observed in eGFR did not achieve statistical significance (1.70, 95% CI -0.53, 3.95; p=0.134) whilst eGFR at M24 for EVR was significantly better (p<0.006). The composite efficacy endpoint was comparable at M12 & M24. Overall acute rejection rates were very low with more iBPVR in EVR, but mild in severity (Banff IIA & IB). In both the groups, number of patients with de novo DSA at M12 or M24 was low and unrelated to outcomes. At M24, rate of CAN (IF/TA) was significantly higher in the CNI versus EVR (35.1 vs 26.7%, p=0.029).

Conclusions: Early conversion to EVR at 3 months vs continued CNIs better preserved renal function with comparable overall efficacy and safety up to 2-years.

Table: Outcomes at M12 and M24

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FR-PO1070
Early Conversion to Everolimus in De Novo Renal Transplant Recipients: 24-Month Results from the ELEVATE Study
Johan W. De Fijter, Hallvard Holdaas, Patricia M. Lopez, Cesar Escrig, Zailong Wang, Josep M. Cruzado, Markus van der Giet. For the ELEVATE Study.

Background: Long-term therapy with calcineurin inhibitors (CNIs) is associated with nephrotoxicity i.e., glomerulosclerosis and interstitial fibrosis (IF). We present the 24 month results from the ELEVATE study (NCT01114529), which compared an early conversion to everolimus (EVR) vs standard CNI in renal transplant recipients (RTxR).

Methods: ELEVATE, a 24M, multicenter, open-label, randomized, de novo RTxRs 10–14 weeks post-Tx to convert from CNI to EVR (n=360; C, 6–10 ng/mL) or standard CNI (n=357; C, TAC 5–10 ng/mL, CSA 100–250 ng/mL); all received enteric-coated mycophenolate sodium and steroids. Primary endpoint was change in eGFR (MDM4) from RND to M12. Main secondary endpoint a composite efficacy of treated biopsy-proven acute rejection (IBPR, Banff ≥II), graft loss, or death and safety.

Results: At M12, the clinical benefit observed in eGFR did not achieve statistical significance (1.70, 95% CI -0.53, 3.95; p=0.134) whilst eGFR at M24 for EVR was significantly better (p<0.006). The composite efficacy endpoint was comparable at M12 & M24. Overall acute rejection rates were very low with more iBPVR in EVR, but mild in severity (Banff IIA & IB). In both the groups, number of patients with de novo DSA at M12 or M24 was low and unrelated to outcomes. At M24, rate of CAN (IF/TA) was significantly higher in the CNI versus EVR (35.1 vs 26.7%, p=0.029).

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FR-PO1071
Early Conversion from Cyclosporine to Everolimus Following Living-Donor Kidney Transplantation: Outcomes at Five Years Post-Transplant in the Randomized ZEUS Trial: A Post-Hoc Analysis
Ingeborg A. Hauser,1 Frank Lehner,1 Wolfgang Arns,1 Clemens Butke,1 Ute Eisenberger,2 Rudolf P. Wuthrich,2 Petra Reineck,1 Rolf A. Stahl,1 Anja Susanne Mühlfeld,1 Heiner H. Wolters,1 Barbara M. Suwelack,1 Katharina M. Heller,1 Martina Porstner,1 Oliver Witzke,1 Claudia Sommerer,1 2ZEUS Study Group, Germany; 2ZEUS Study Group, Switzerland; 3Novartis Pharma, Germany.

Background: To study renal function and patient outcome after 5 years in living-donation subgroup of kidney de novo transplant recipients after conversion to an everolimus (EVR) based regimen and withdrawal of calcineurin inhibitor therapy.

Methods: Post hoc subgroup analysis from the prospective, open-label, controlled, multi-center study ZEUS. 300 renal transplant (Tx) patients were randomized at month (mo) 4.5 post Tx to either receive EVR plus enteric coated-mycophenolate sodium (EC-MPS) or cyclosporine (CsA) plus EC-MPS regimen. Of these 80 living donation recipients (EVR group n=42; CsA group n=38). Patients could enter an observational follow-up (FU) period where outcome on patients’ safety and efficacy was recorded until mo 60 post Tx.

Results: Adjusted eGFR (Nankivil) in living-donation subgroup at mo 60 was 67.2 (95% CI [62.5, 71.9]) mL/min/1.73m2 in EVR vs 60.8 (95% CI [56.0, 65.6]) mL/min/1.73m2 in CsA patients, resulting in a difference of +6.4mL/min/1.73m2 in favor of EVR patients (p=0.031, ANCOVA). Unadjusted mean eGFR after 5 years was 69.5 mL/min for EVR vs 66.0 mL/min for CsA (p=0.006, Wilcoxon). BPVRs during FU since mo12 occurred in 4 patients of the EVR and 3 of the CsA group, all BANFF grade IA except one BANFF grade IIa among EVR patients. From randomization to mo 60 one death occurred in CsA living-donor recipients, two in the EVR living-donation subgroup; one graft loss occurred in the EVR, none in the CsA group. Overall safety profile was similar between both treatment groups.

Conclusions: The presented analysis shows that EVR-based regimen with early elimination of CNI therapy in living-donor kidney transplant recipients is associated with a significant benefit on renal function maintained over 5 years post Tx without compromising safety and efficacy.

Funding: Pharmaceutical Company Support - Novartis Pharma GmbH
FR-PO1072


Background: Tacrolimus (TAC) and Sirolimus (SRL) are commonly used immunosuppressive drugs in kidney transplantation. SRL has been shown to induce the expansion of regulatory T cells in post-transplant recipients converted from TAC to SRL.

Methods: This study included 84 renal transplant recipients from a randomized trial of SRL conversion (n=55) or TAC maintenance (n=29). The conversion started at 12 months post-transplant. PBMC were collected at 0(baseline), 6, 12, 24, 36 and 48 months post-randomization. T cell subpopulations were analyzed by flow cytometry.

Results: Absolute frequencies of CD4+Foxp3+ T cells were similar in both groups (0.63±0.06%; SRL) VS 0.66±0.12% (TAC) % of Lymphocytes, p=0.79). SRL conversion led to a significant increase in CD4+Foxp3+ T cells at 6, 12 and 24 months post conversion with highest frequencies observed at 12 months post conversion (2.23±0.23% (SRL) VS 0.08±0.12% (TAC) %, p<0.01). However, we observed a decline of CD4+Foxp3+ T cells started at 24 months and the differences were no longer significant compared to the TAC group at 36 and 48 months post-conversion (1.41±0.60% (SRL) VS 1.07±0.44% (TAC) %, p=0.23).

Conclusions:Switching from TAC to SRL results in an expansion of CD4+Foxp3+ T cells which peaked at 12 months post-conversion but no significant frequency differences were observed at 48 months follow-up and we observed more percentage of T cells that co-expressed IFN-γ and RORgt which are Th1 and Th17 markers respectively.

FR-PO1073

Pulmonary Complications in Kidney Transplant Recipients: Role of Everolimus Giannhi Cappelli, Andrea Solazzo, Fabio Nava, Decenzo M. Bonuichi. Nephrology Dialysis & Renal Transplant Unit, Univ Hospital of Modena, Modena, Italy.

Background: Kidney transplant recipients are at higher risk to develop pulmonary side-effects, which are frequently drug related and a relationship with cyclosporine (CyA). Everolimus (EVL) and Cyclosporine (CyA) are commonly used immunosuppressive agents in kidney transplantation. SRL has been shown to induce the expansion of regulatory T cells in post-transplant recipients converted from CyA to SRL.

Methods: We performed a translational study. First we analyzed the in vivo pulmonary pro-fibrotic potential of Everolimus (EVE) by computing a pulmonary fibrosis index score (PFIS), obtained by using several computerized tomography, hemogasanalysis and spirometric parameters, in 13 RT patients in EVE treatment and 13 patients treated with CyA (CyA group). Subsequently, we carried out an in vitro study in which we assessed whether EVE at low- (5, 10 nM) or high-dosage (50 nM, 500 nM e 5 μM) was able to induce EM in bronchial epithelial cells (Nuli-1) and human type II pneumocyte-derived A549 cells. Additionally, microarray analysis was performed to identify biomarkers in each cell line.

Results: In the in vivo part of the study, we found that the PFIS was higher in EVE-treated patients compared to those treated with ADV (mean±SD 2.58±1.83 versus 1.21±1.25). This effect was positively correlated to the trough levels (TL) in EVE-treated patients (R2=0.35). The higher PFIS score was measured in patient of the EVE group that reached a TL>5. Interestingly, in vitro, only very high doses of EVE were able to up-regulate alpha-SMA, Fibronectin and Vimentin in gene and protein levels and A549. No effects were seen in Nuli-1. Interestingly, microarray analysis confirmed the above-mentioned results.

Conclusions: All together, our data suggested that only very high doses of EVE may induce pulmonary fibrosis and that this effect could be mediated by EM in pneumocyte cells.

FR-PO1075

Efficacy and Safety of Three Different Treatment Regimen in De Novo Renal Transplant Patients: 48 Months Follow-Up Results of the HERAKLES Trial Wolfgang Arms, Volker Klicem, Claudia Sommerer, Johannes Jacobi, Bruno Vogt, Ingeborg A. Hauser, Petra Reinkic, RolflA. Stahl, Thomas Rath, Martina Porstner, Martin G. Zeier, Frank Lehner, Klemens Budde, Oliver Witzke. HERAKLES Study Group, Germany; HERAKLES Study Group, Switzerland; Novartis Pharma, Germany.

Background: To compare safety and efficacy of 3 different immunosuppressive regimen at month (mo) 48 after kidney transplantation (KTx).

Methods: 802 patients (pts) were included in this 1 year, prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to mo 60 post Tx. After induction therapy all pts received cyclosporine A (CSA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 mo post Tx, 499 pts were randomized 1:1:1 to either a) Everolimus (EVR) 5-160mg (81pts) and CyA (100-180mg/ml) EC-MPS (n=166) (5 nM, 500 nM e 5 μM), b) to a calcineurin inhibitor (CNI)-free regimen with Everolimus (EVR) (5-10mg/ml) + EC-MPS (n=171) or c) to a CNI-reduced regimen with ERV (3-8mg/ml) + reduced CSA (50-75mg/ml; n=162). All pts continued on steroids. At time of mo 48 FU Interims-analysis of data were available from 110(73%) STD, 117(79%) CNI-free and 111(76%) CNI-low treated pts of the FU ITT population.

Results: From randomization to mo 48 BPAR was reported in 19/151(13%) STD, 24/149(16%) CNI-free and in 23/147 (16%) CNI-reduced pts (ITT; p=ns). 5 deaths (3%) occurred in STD, 3(2%) in CNI-free and 6(4%) in the CNI-reduced group. 96% graft losses were observed in the STD, 6(4%) in the CNI-free and 2(1%) in the CNI-reduced group. Composite failure (BPAR, death, graft loss, loss to FU) occurred in 32(21%) STD, 36(24%) CNI-free and in 39(27%) CNI-reduced treated pts. Premature discontinuation due to AEs was reported for 5(3%) of STD, 5(3%) of CNI-free and 11(15%) of CNI-reduced patients (safety-population) since mo 12 to 48. cGFR (Nankivell, LOCF) was significantly improved by +8.6ml/min in favor of the CNI-free regimen at mo 48 (ITT=p<0.02).

Conclusions: Mo48 results from HERAKLES show that immunosuppressive regimen using EVR with reduced-dose or without CNI-exposure reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized immunosuppression to minimize CNI-exposure.

Funding: Pharmaceutical Company Support - Novartis Pharma

FR-PO1076

SparTacus: Multicentre, Prospective Randomised Study Comparing Tacrolimus Hexal® versus Prograf® Based Regimen in De Novo Renal Transplant Recipients Wolfgang Arms, Thomas Rath, Lars C. Rump, Klemens Budde, Daniel Baumer, Peter Schenker. 1Spartacus Study Group; 1Novartis Pharma Germany.

Background: In a transplant (Tx) setting, studies evaluating pharmacokinetic (PK) parameters and therapeutic equivalence of generic tacrolimus vs the reference drug are lacking. SparTacus (NCT01649427) study was designed to compare PK profile of tacrolimus hexal® with prograf® in renal Tx recipients (RTx).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: In this prospective, two-phase open-label study, 76 de novo RTxR were randomized to receive tacrolimus hexal® (n = 35) or prograf® (n = 41), both in combination with entero-derived mycophenolate sodium + corticosteroids + basiliximab induction therapy. Starting dose of tacrolimus was 0.15 mg/kg/day, adjusted to target trough levels (C0) of 8–12 ng/ml from Tx to month (M) 1; 5–10 ng/ml up to M3; and 5–8 ng/ml up to M6. Primary objective of the study in phase 1 was to demonstrate comparability of Tacrolimus hexal® vs prograf®. Here we present the PK results of the first month.

Results: At M1, the dose-normalised tacrolimus 12-h-AUC (h/10^3XL) was comparable between tac. hexal® vs prograf® (2.02 ± 2.0 vs. 2.02 ± 2.0; difference, 0.0 ± 0.0; 90% CI: 0.0, 0.0; p = 0.998). C0 for tac. hexal® vs prograf® was 12.2 ± 1.7 vs. 12.2 ± 1.7 (90% CI: -0.134, 0.377; p = 0.581), C0 at day 11, respectively. Of 76 patients, 40 (PK-Set 40 pts.) to date completed 6-M treatment; tac. hexal®, n = 19; prograf®, n = 21. At M6, tacrolimus hexal® vs prograf® had a comparable incidence of composite events (ITT, n = 77; 5.7% vs 9.8%, p = 0.681) and its individual components (BFAR [5.7% vs 7.3%], graft loss [0.0% vs 2.4%], death [0.0% vs 2.4%]). Incidence adverse events (AES, SAE) were comparable (AES: 97.1% vs 100%; serious AES: 37.1% and 42.1%).

Conclusions: Tacrolimus hexal® has a PK profile similar to that of prograf®, with comparable efficacy and safety in de novo RTxR.

Funding: Pharmaceutical Company Support - Novartis Pharma Germany

FR-PO1079

Intensified Dosing of Mycophenolate Mofetil Is Associated with Slower Progression of Chronic Renal Allograft Injury – Results from a Randomized Controlled Trial

Mladen Knotek,1 Miha Arni,2 Jadranka Buturovic,1 Danica Galesic Ljubanovic,1 Nika Jogić,2 1Dept of Medicine, Renal Div, Univ of Zagreb Medical School, Merkur Univ Hospital, Zagreb, Croatia; 2Dept of Nephrology, Univ Medical Centre Ljubljana, Ljubljana, Slovenia; 1Inst of Pathology, Univ of Ljubljana Medical Faculty, Ljubljana, Slovenia; 2Dept of Pathology, Dubrava Univ Hospital, Univ of Zagreb Medical School, Zagreb, Croatia; 3Univ of Zagreb School of Medicine, Dubrava Univ Hospital.

Background: Intestinal fibrosis (ci) is a major histological predictor of long-term graft outcome. This randomized controlled trial (NCT01860183) was designed to evaluate the effect of intensified mycophenolate mofetil (MMF) dosing on progression of ci during the first year post kidney transplantation (KT).

Methods: Immunologically low-risk KT recipients were randomized on MMF 3g/d or 2g/d during the first year post KT. Immunosuppression consisted of basiliximab induction, with tacrolimus, MMF ± steroids. Protocol biopsies were performed at implantation, and at 1 and 3 months post KT and at the 12th month post KT. Progression of ci (Di) was calculated as ci12-ci0. MMF dose was calculated as an average dose at 1, 3, 6 and 12 months. Difference in Di with respect to MMF dose was analyzed in an ITT population using one-way ANOVA.

Results: Here we report interim results from patients who completed 12 months follow-up by June 1st 2015. Patient and KT data are similar in MMF 3g and MMF 2g group, except for average MMF dose, which was higher in the 3g group (2697 ± 321.6 vs. 1745.5 ± 359.0 g, p < 0.001). In an overall study population ci progressed during first 12 months post KT from 0.45 ± 0.51 (ci0) to 1.41 ± 0.87 (ci12) (p < 0.001). Di was lower in the MMF 3 g group (0.60 ± 0.74) as compared with MMF 2g group (1.36 ± 0.93; p = 0.01). Serum creatinine at 1 year was similar in both MMF groups (116.5 ± 25.0 vs. 115.1 ± 33.7; p = 0.899). Incidence of acute rejection was similar and no significant differences were seen in common adverse events between both groups.

Conclusions: Intensified dosing of MMF (3g daily) during the first posttransplant year in a tacrolimus-based regimen may be associated with slower progression of chronic allograft injury.

Funding: Government Support - Non-U.S.

FR-PO1080

Safe Conversion from Tacrolimus to Belatacept in Kidney Transplant Recipients with Allograft Dysfunction

Anil Reham, Dhiren Kumar, Hasan Fattah, Anne L. King, Pamela Kimball, Ankur Atal Gupta, Gaurav Gupta. Virginia Commonwealth Univ, Richmond, VA.

Background: Belatacept might be an alternative to Calcineurin Inhibitors (CNI) to avoid short and long-term nephrotoxicity. Prior data on low immunologic risk de-novo kidney transplant recipients (KTxP) with stable graft function switched from a CNI to belatacept demonstrated improved renal function. There is minimal data on the use of belatacept for sensitized patients and those with impaired graft function [estimated glomerular filtration rate (GFR) <50].

Methods: EBV seropositive patients were converted to belatacept from tacrolimus for biopsy proven presumed acute CNI toxicity and/or interstitial fibrosis/tubular atrophy. Belatacept was initiated based upon prior published protocol (Grinyo et al., Transpl Int. 2012 Oct). Mycophenolate dose was increased from baseline dose of 1-2g/d to a dose of 2-3g/d to minimize risk of rejection.

Results: Seventeen (mean age: 46±10 years) patients were switched from tac to belatacept at a median of 4 months post-KTxP. A majority were African-American (13/17; 76%) and received deceased donor KTxP (76%). Seven patients (41%) were sensitized (median PRA: 31%; range 5-99%). Renal function improved significantly from a peak mean GFR of 28.1±12 ml/min/1.73m^2 to an GFR of 42±11±12 ml/min/1.73m^2 (p<0.001) at a median follow-up of 15 (range-7-30) months post-conversion. Surveillance biopsies performed in 7/17 patients did not show rejection or worsening of chronicity. No evidence of delayed donor specific antibody (DSA) was noted in 1617 (94%) patients. One patient with pre-existing DSA and stable creatinine had rising DSA after a viral infection. A biopsy showed subclinical antibody-mediated rejection. There were no cases of BK viremia, CMV disease or malignancies.

Conclusions: In this study first on KTxP patients with significantly reduced GFR we report remarkable improvement in renal function in patients converted from tacrolimus to belatacept with acute CNI toxicity and chronic allograft fibrosis without a significant concurrent increase in risk of rejection, worsening chronicity and DSA. Further studies with protocol biopsies are needed to ensure safety and wider applicability of this approach.
FR-PO1081

Infusion of Belatacept in Kidney Transplant Recipients

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Background: Belatacept (bela) is an IV administered selective T-cell co-stimulation blocker approved for preventing organ rejection in EBV-positive adult kidney transplant recipients. The logistics of IV maintenance therapy are challenging for some pts/caregivers; the safety of home infusion has not been well described. Phase 2/3 study participants have received bela home infusion under certain circumstances. Here, we compare the safety of bela infused in the home vs a facility.

Methods: Pts in the 008 (BENEFIT/NCT002556570), 027 (BENEFIT-EXT/NCT00114777), 010 (NCT00402168), and 034 (NCT00455010) studies were eligible to receive bela home infusion if the site sought IRB approval and if the pt lived ≥2 hrs from the site and had been exposed to bela for ≥28 wks in 008 or 027, >16 wks in 010, or >6 wks in 034. 008 and 027 compared bela with CsA regimens with basiliximab induction. In 010, pts receiving a stable CNI regimen were switched to a bela regimen. 034 compared bela with tacrolimus steroid-sparing regimens under thymoglobulin induction. Rate and time to pre-specified peri-infusional AEs and peri-infusional serious AEs were recorded in pts who received bela in the home (N=66) or in a facility (N=672).

Results: Pts administered bela in the home received a median of 32.5 (range, 1–61) infusions. No pre-specified or serious peri-infusional AE was reported, including in the 034 study.

Conclusions: No pt (irrespective of steroid use) receiving home infusion of bela had a pre-specified or serious peri-infusional AE. These data suggest that bela was safely administered in the home.

FR-PO1082

Optimizing the Immunosuppression Regimen with Belatacept

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Background: Belatacept with basiliximub induction plus maintenance MMF/corticosteroids is associated with a higher 3-year eGFR compared to cyclosporine but a higher 1-year incidence of acute rejection. In an attempt to optimize the belatacept immunosuppression regimen we investigated the safety and efficacy of a novel combination utilizing belatacept with rATG induction (3 mg/kg) and maintenance everolimus+corticosteroids.

Methods: Retrospective single center analysis of the first 33 patients to receive our belatacept regimen compared to a historical control group of 66 patients matched for donor type, KDPI, ESRD cause, CIT, and corticosteroid protocol who met our belatacept criteria (EBV seropositive and low immunologic risk [first transplant, no DSA ≥500 MFI, cPRA ≤30%]) but received basiliximub induction with maintenance tacrolimus/MMF+corticosteroids. We compared the 6-month eGFR and the rates of rejection and infection between the groups.

Results: Demographic and transplant characteristics were similar. Mean tacrolimus trough (SD) at months 3 and 6 were 8.7 (2.5) and 8.4 (2.8), respectively. Mean everolimus trough (SD) at months 3 and 6 were 5.5 (2.6) and 5.3 (2.6), respectively. Eleven patients didn’t tolerate everolimus and were placed on MME. Rejection occurred in 3 patients (1 of each: type 1a, type 1b and type 2b) and 1 belatacept patient (type 2a) (P=0.07). The belatacept rejections occurred in patients who didn’t tolerate everolimus and occurred after everolimus was discontinued. By month 6 two grafts were lost in the tacrolimus group with a 100% patient survival for both groups. eGFR at month 6 for belatacept and tacrolimus treated patients was 61.9 (15.3) and 60.1 (21.2), respectively (P=0.51). The incidence of CMV infection, BK viremia, and UTI was similar between the groups.

Conclusions: The findings suggest that a belatacept regimen with limited T cell depletion and an mTORi can maximize efficacy and maintain safety. These results of a synergistic effect of costimulation blockade and mTOR inhibition are consistent with experimental studies and phase 2 data. A larger prospective trial is warranted to fully evaluate this approach.

Funding: Pharmaceutical Company Support - BMS

FR-PO1083

A Change in Insulin Sensitivity and Lipid Profile in Renal Transplant Recipients Converted from Cyclosporine or Standard Release Tacrolimus to Once-Daily Prolonged Release Tacrolimus

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Background: New-onset diabetes after transplantation may be associated with the use of tacrolimus (Tac) causing impaired insulin release or reduced insulin sensitivity. And, dyslipidemia commonly occurred after transplantation. Such effects in insulin sensitivity and lipid profile have not been studied in renal transplant recipients receiving traditional twice-daily tacrolimus (TacBID) or cyclosporine and then compared to the new once-daily prolonged release formulation of tacrolimus (TacOD).

Methods: We performed an observational prospective study of 15 stable non-diabetic renal transplant recipients on change in insulin sensitivity and lipid profile in renal transplant recipients converted from cyclosporine or standard release tacrolimus to once-daily prolonged release tacrolimus. We evaluated the level of HbA1c,total cholesterol, HDL, LDL, TG, apolipoprotein A1, apolipoprotein B, serum creatinine, fasting plasma glucose, fasting insulin and HOMA-β at base line, two and four months. To analyze differences in parameter, we performed a t-test in both groups (cyclosporine to TacOD conversion group/ TacBID to TacOD conversion group), and GLM-repeated measures ANOVA. HOMA-β = (360 x Fasting insulin)/(Fasting glucose-63) HOMA-RI (insulin resistance) = (Fasting glucose x Fasting insulin)/405.

Results: At baseline, parameters were not different in both groups (cyclosporine to TacOD conversion group/TacBID to TacOD conversion group). In GLM-repeated measures ANOVA, the result did not showed and any change in insulin sensitivity and lipid profile and revision at baseline, two and four months.

Conclusions: Conversion from standard TacBID or cyclosporine to TacOD is safe. In spite of a reduced Tac exposure, there was no change in insulin sensitivity and lipid profile in renal transplant recipients.

FR-PO1084

Tacrolimus Dose Requirement Based on the CYP3A5 Genotype in Renal Transplant Patients

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Background: Tacrolimus and ciclosporin A (CsA)are widely used to protect graft function after renal transplantation. The aim of the present study is to determine whether CYP3A5*1 and CYP3A5*2 genotype is a predictive index of tacrolimus dose requirement, and evaluate the selection accordance of tacrolimus or CsA treatment.

Methods: We tested archival peripheral blood of 218 kidney recipients for CYP3A5 genotyping with PCR-SSP. The doses and blood concentrations of tacrolimus and CsA for recipients were measured at day7, 1st month , 3rd month,6th month and 12th month after renal transplantation, as well as hepatic and renal function. In addition, we also observed the incidence of acute rejection happening on these participants.

Results: 123 patients took tacrolimus treatment and 95 patients took CsA treatment after renal transplantation.In tacrolimus treatment group, genotype CYP3A5*5G was associated with low tacrolimus dose-adjusted concentration after transplantation, showing lower acute rejection rate compared to CYP3A5*AA/AG group but with no significant different (P=0.154).In CsA treatment group, there was no significant difference in acute rejection rates between CYP3A5*AA/AG and CYP3A5*GG(P=0.494) with no different in dose-adjusted concentration as well. For CYP3A5*GG patients, tacrolimus treatment cause lower acute rejection rate than CsA treatment (P=0.030), taking shorter time to get a stable immune situation than CsA treatment. For CYP3A5*AA/AG patients, tacrolimus treatment cause similar acute rejection rate with CsA treatment (P~0.982), but took longer time to get a stable immune situation than CsA treatment. What’s more, tacrolimus treatment costs much than CsA treatment.

Conclusions: These results indicate that CYP3A5*5A/AG carriers need higher tacrolimus dose than CYP3A5*GG homozygote to achieve the target blood concentration. And, CsA carriers preferred to tacrolimus treatment and CYP3A5*5A/AG carriers preferred to CsA treatment depended on the incomes. CYP3A5 genotyping is a new approach for detecting tacrolimus dose requirement and a predictive index for the tacrolimus or CsA treatment selection in the kidney recipients.
FR-PO1085
Intratpanel Tacrolimus Level Variability in Pediatric Kidney Recipients
Predicts Allograft Loss After Transfer to Adult Care
Hilda E. Fernandez,1 Sandra Amaral,2 Amanda A. Shaw,1 Roy D. Bloom,3 Alden Michael Doyle,1 Sumit Mohan,1 Susan L. Furth,2 Columbia Univ; CHOP; PENN; Hahnemann Univ.

Background: Allograft loss is especially common in 17-24 year olds and is associated with non-adherence around the time that transplant care is transferred from the pediatric to adult setting. We explored whether coefficient of variation of tacrolimus (CV TAC) levels post-transfer, as a marker of non-adherence, was associated with allograft loss in a cohort of pediatric kidney recipients transferring to adult transplant centers.

Methods: Retrospective cohort of transplant recipients at Children’s Hospital of Philadelphia transplanted 1999 to 2011 who transferred care to University of Pennsylvania or Hahnemann University Hospital, identified by chart review. CV TAC was calculated as SD divided by mean TAC over 12 mos. Date of transfer was defined as the last Pediatric visit. We compared pre-transfer TAC CV in those that subsequently lost their graft to those that did not.

Results: 24 of 65 subjects had sufficient data for analysis. Median age at transplant was 15.9y (8.5-18.9). The cohort was primarily male (66%), White (77%), had CUKAT (8%), and 46% had LRKT. Median age at transfer was 20y (17.4-22.1). Four patients had allograft loss within 365 days post-transfer. Pre-transfer CV TAC for subjects with allograft loss post-transfer (n=4) was significantly higher as compared to subjects without allograft loss (n=20) (49.4% vs 26.2%, p = 0.0275).

Conclusions: CV TAC may aid in identifying patients at risk for allograft loss post-transfer. Future analysis will investigate the effect of race, age at transfer, rejection, de novo DNA pre-transfer that may also help predict adolescent kidney transplant recipients at risk for allograft loss following transfer to adult transplant centers.

Funding: Other NIH Support - NIH Kidney Disease Epidemiology T32 Minority Supplement

FR-PO1086
High Tacrolimus Level Variability in the Early Post-Transplant Period Is Associated with Reduced Patients and Graft Survival After Kidney Transplantation
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Background: The effect of Tacrolimus levels variability in the early period after kidney transplantation is not properly understood. We sought to evaluate whether increased drug level variability is associated with reduced graft survival and evaluated the relative effect of exposure to high and low drug levels.

Methods: We screened the Rabin Medical Center registry database for adult patients from 2001 to 2013 that were treated with tacrolimus, mycophenolate mofetil and corticosteroids and had at least 6 values of drug level during the first six months after the transplantation. Variability was defined as the time average of the absolute value of the difference from the mean and this value was divided by the mean to get the variability index. Univariate and multivariate Cox proportional hazard model was used with the combination of death and graft failure as composite outcome.

Results: We identified 803 patients who met the inclusion criteria, ninety eight (12.2%) of them reached the end point during median follow up time of 3.7 years (range 0.5 to 12.9 years). The increased variability index was associated with increased hazard of death or graft failure by univariate (Hazard Ratio (HR) 1.029 per %, 95% Confidence Interval (CI) 1.006-1.052, p=0.013) and multivariate models (HR 1.036 per %, 95% CI 1.01-1.062, p=0.006). Variability was still significantly associated with reduced graft survival after introducing acute rejection into the model (HR 1.038 per %, 95% CI 1.008-1.056, p=0.006) by introducing exposure to levels above 15 ng/ml into the model didn’t change the association between variability index and the composite outcome while introducing exposure to levels below 5 ng/ml eliminated the association and made it non-significant (p=0.18).

Conclusions: High variability index in the first six month after kidney transplantation is associated with increased mortality and graft loss. This association is, probably, mediated by exposure to low drug levels.

FR-PO1087
Decision Tree Analysis of Renal Transplantation Recipients Outcomes: A Single Center Data Mining
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Background: Results from former literature on factors influencing renal transplant outcomes are quite confusion and few include factors influencing outcomes of rejection cases. This study was intended to get the factors in order and to provide reliable predictive models for clinical practice with decision tree analysis, and attempted to discuss about decision tree integrated with renal transplant database, predict the model development and to serve personal medical care in big data era.

Methods: Renal transplant recipients registering between May 1988 and April 2014 in Kidney Center of the First Affiliated Hospital of Zhejiang University were included. Living state, not registred by chart review. CART was evaluated by decision tree.

Results: Totally 3921 cases were included. The loss-to-follow rate is 9.7%. With survival rate as the object, we got the most important factor, steroids (P<0.01). Patients in the following factor combination showed the highest survival rate: steroids, mycophenolate mofetil (MMF), stenting, warm ischemic time (WIT) ≤6.5min, cold ischemic time (CIT) £300min, and aspartate aminotransferase (AST) 6 months post operation£34UL (survival rate 95%, no rejection cases). Patients had the lowest acute rejection rate when in the factor combination: steroids, antihuman thymocyte globulin or basiliximab induction, no blood transfusion history and female (0%, 83). Patients with acute rejection were regarded as a new database. The patients who took steroids and received stents shows similar outcomes with patients who had no rejection. Important factors that could be intervened for long-term outcomes included stenting, statins, steroids, etc.

Conclusions: Decision tree analysis is an outstanding choice for risk stratification, prognosis prediction and dynamic follow-up. Immunosuppression therapy was regarded as the most important factor for renal transplant recipients' survival, rejection and other outcomes. Factors should be considered in combination for each specific patient.

FR-PO1088
Comparison of Clinical Outcome Between ABO Incompatible and Compatible Spousal Donor Kidney Transplantations
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Background: Spousal donor is an important source to overcome shortage of living donor in kidney transplantations (KTs). We aimed to compare the clinical outcomes in ABO incompatible KT (ABOi-KT) to those of ABO compatible KT (ABOc-KT) from spousal donors.

Methods: We analyzed 580 KT cases from spousal donors among 3043 living donors KT cases registered in the Korean Organ Transplantation Registry. Clinical outcome between ABOi-KT and ABOc-KT were compared by episodes of acute rejection (AR), graft function, grafts and patients survival rates.

Results: The proportion of spousal donors in ABOc-KT was higher than that of ABOi-KT (40.9% vs. 21.4%, P<0.001). The biopsy proven AR-free survival rate in ABOi-KT was comparable to ABOc-KT (79.7% vs. 82.3%, P=0.188). The renal allograft function showed no difference until 16 months after KT. The 3-year graft survival (92.5% vs. 95.7%), and patient survival (96.4% vs. 98.5%) were not significantly different between ABOc-KT and ABOi-KT groups (P=0.05, respectively). Multivariate analysis revealed that ABOc-KT from spousal donors did not affect the graft, patient survival and BPAR-free survival rate.

Conclusions: The results of our study show that the ABOc-KT donor is an important source of living donor, and can be a good alternative of overcoming donor organ shortage.

FR-PO1089
3-Year Outcomes After ABO Incompatible Kidney Transplantation without Steroids

Background: Early steroid withdrawal paired antibody induction therapy provides comparable outcomes to steroid maintenance patients. However, ABOc transplantation is considered higher immunologic risk, and it unclear if a steroid free regimen is appropriate for this population.

Methods: We performed 40 ABOc transplants with pre-transplant plasmapheresis (PP) with IVIG to an isohemagglutinin titer 1:16 and 2 post-tpx PP/IVIG treatments, immunosuppression with tacrolimus, mycophenolate, and intraoperative rituximab (375mg/ 125mg). Prior to 2008, patients received an IL-2 receptor blocker, and prednisone tapered to 5 mg by 6 months. After 2008, induction included Thymoglobulin® (6 mg/kg in 4 divided doses) and steroid withdrawal by postop day #3. Patients underwent protocol biopsies at predefined intervals. We compared outcomes at 3 years between those who had and had not received maintenance steroids.

Results: 24 patients received maintenance steroids and 16 underwent rapid steroid withdrawal. There were no differences in sex, starting isohemagglutinin titer, or blood group mismatch between the groups. Antibody mediated rejection was more common in the steroid maintenance group (41% vs 31%) as was cellular rejection (50% vs 47%), though not significantly different. At 3 years, renal function was similar between those with and without steroids- eGFR 46±25 cc/min vs 52±15 cc/min, respectively. Approximately 50% of patients underwent protocol biopsy at 3 years. There were no differences in the degrees of interstitial fibrosis, glomerulosclerosis, or transplant glomerulopathy between groups. Graft survival, patient survival, and infectious complications were also similar.

Conclusions: Even in higher immunologic risk ABOc transplant recipients, rapid steroid withdrawal appears to provide similar medium term results as steroid maintenance therapy without the longterm side effects.
FR-PO1090

Three Year Outcome of a Pioneer ABOi Renal Transplant Programme in Malaysia
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Background: ABO incompatible (ABOi) renal transplantation increases organ donor pool and is an option for patients with no blood group compatible donors. We report here results of a pioneer ABOi renal transplant programme in Malaysia which was first established in Prince Court Medical Centre in 2011.

Methods: Ten patients entered into our ABOi programme between July 2011 and December 2013. Data were analyzed to determine the number of therapeutic plasma exchange (TPE) and/or immunoadsorption (IA) with Glycosorb columns to achieve target pre transplant ABO antibody titres of < 1:16 and ABO titres post transplant. Graft function and rejection rates together with graft and patient survival at 3 years were also determined.

Results: Median baseline ABO titres was 1:128 and all patients achieved target pre transplant ABO titres of < 1:16 after a median of 4 TPE and/or IA. Median follow up was 32 months with all patients maintaining ABO titres of < 1:16 at follow up with no protocol post transplant TPE/IA. There was 1 case (10%) of acute cellular rejection at one year which was reversed with steroids but none had antibody mediated rejection. Patient and graft survival was 100% at 3 years with current median serum creatinine 108μmol/L.

Conclusions: The results of our pioneer ABOi renal transplant programme with graft and patient survival of 100% at 3 years is extremely encouraging and suggest that graft and patient outcome is similar to ABO compatible renal transplants. The use of ABO incompatible donors may effectively increase organ donor pools especially in countries where both cadaver and living related kidney transplant rates remain poor. Our results also suggest that national ABOi renal transplant programmes may be effectively introduced and led by a private medical centre to complement and support more established renal transplant programmes in government institutions which are now beginning to perform their own ABOi renal transplants in light of our success.

Funding: Clinical Revenue Support

FR-PO1091

Improved Graft Outcome After Blood Transfusion: Still in Effect?
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Background: Blood transfusions can lead to sensitisation in potential transplant patients. We previously quantified the risk of sensitisation from transfusion per se by looking at a cohort of male patients on the transplant waiting list and ascertaining the transfusion history from electronic records and questionnaires. Prior to standard triple immunosuppression, transfusions were associated with overall better graft outcome possibly by a tolerogenic effect or by selecting non-sensitisers. The majority of patients who were transfused do not become sensitised, we wanted to characterise graft outcome in this group.

Methods: We obtained graft outcome information on the original cohort of patients. Data was collected prospectively as part of routine surveillance.

Results: 100 out of the initial 126 male patients were transplanted. 10 were excluded from further analysis due to death or graft loss in the immediate post-transplant period. 11 of remaining 90 patients were DSA prior to transplantation, 8 also had a history of previous blood transfusion. 4 of the 8 patients with a previous blood transfusion and DSA had a rejection episode (2 AMR and 2 ACR). Of the remaining 79 patients who were DSA negative prior to transplantation, 26 had a previous transfusion (TR+ DSA-) and 53 did not have a history of transfusion (TR- DSA-). Comparison between the two groups is shown in (table 1).

Conclusions: Lack of sensitisation with a history of leuco-depleted transfusion is associated with a lower risk of rejection post-transplantation. This suggest that previous mechanisms of transfusion tolerance or “non-sensitisers” are still relevant in the modern immunosuppression era.

FR-PO1092

Geriatric Renal Transplantation in Deceased Donor Showed Compatible Clinical Outcomes to Younger Recipients
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Background: According to USRDS annual report, while 50.3% of patients who start hemodialysis were aged over 65 years, only 19.3% of patients who underwent renal transplantation was aged over 65 years. Elderly ESRD patients still are not underwent renal transplantation as much as younger recipients. There were many previous studies about geriatric renal transplantation outcome in white, however data in Asain were limited. The aim of this study is analysis of geriatric kidney transplantation outcome in Korea.

Methods: From May 1993 to December 2013, kidney transplantations performed in Asan medical center were retrospectively reviewed. Recipients younger than 20 years and who underwent other organ transplantation were excluded. Binary logistic regression was used for evaluating risk factors of graft failure before half-life. Half-life of kidney allograft was defined as 10 years according to previous study.

Results: Regardless of donor type, there is no statistically significant difference in death censored graft survival between geriatric population and younger recipients.

Conclusions: Geriatric renal transplantation can be encouraged in Asain ESRD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

620A
FR-PO1093
Long-Term Survival and the Associated Risk Factors for Death in Patients (pts) with Kidney Transplantation (Tx) Tanja Abeling,1 Irina Scheffner,1 Verena Broecker,2 Michael Mengel,1 Hermann G. Hailer,3 Anke Schwarzer,2 Wilfried Gwinner,1 1Hanover Medical School, Germany; 2Cambridge Univ, United Kingdom; 3Univ of Alberta, Canada.

Background: Deaths over a period of up to 10 years (yrs) and the related risk factors were studied in Tx pts with protocol biopsies (Bx) (total observation: 4805 patient-yrs). 

Methods: 892 pts with kidney Tx in 2000-2007 were included. Protocol Bx were taken at 6 weeks, 3 and 6 months post-Tx (n=2251). 862 Bx for cause were taken in the 1st year and 262 thereafter. Lost-to-follow up was negligible (n=15). All acute rejections and clinical borderline cases in protocol Bx were treated.

Results: Patient and graft survival was 80% at 5yrs and 68% at 10yrs. Patient survival was 92% at 5 yrs and 82% at 10 yrs. 99 deaths occurred, related to infection (24%), cardiovascular disease (15%), malignancy (16%), other specified causes (8%). Deaths were less in living donor or kidney/pancreas Tx and more frequent for extended donor criteria-Tx. A three-level multivariate Cox regression model was created in a stepwise fashion, using significantly different variables from the pre-Tx, peri-operative, and long-term post-Tx period between survivors and deceased pts. Pre-Tx variables in the final model included recipient age, HLA-DR mismatches, diabetes, coronary heart disease, heart failure, and peripheral arterial disease. A significant peri-operative variable was cold ischemia time. In the long-term course, variables for death included increased loss of graft function, urinary tract infection, and higher PTH levels. Compared to the survivors, deceased pts received more therapies for rejection seen in protocol Bx (0.30 vs. 0.43 per patient) and in Bx for cause (0.29 vs. 0.34 per patient), however, this was not a significant factor in the final model. Also, the proportion of anti-rejection treatments was not higher in pts who died from infections, compared to pts dying from other causes. Concordance of the final model was 0.79; 200-fold bootstrapping confirmed its applicability.

Conclusions: Based on these results a tool is presented that readily allows risk calculation and stratification of individual pts, as a pre-requisite for individualized and optimal pre- and post-Tx care.

Funding: Government Support - Non-U.S.

FR-PO1094
Causes of Death-Censored Kidney Allograft Failure: A Matched Case-Control Study of 340 Kidney Allograft Recipients Mohamad M. Alkald,1 Jim Kim,1 Choli Hartono,1 Thangamani Muthukumar,1 Meredith J. Aull.1 1Medicine, Well Cornell Medical College, New York, NY; Surgery, Well Cornell Medical College, New York, NY.

Background: Causes of kidney allograft failure in the current era of immunosuppression have not been clearly defined.

Methods: We did a matched case-control study of death-censored allograft failure among the 1672 adult kidney transplants at our center between 11/2001 and 12/2011. The cases and controls were matched 1:1 for age, donor type and year of transplant. We reviewed the charts and used the last available biopsy diagnosis for each case to determine the cause of death. Concordance of the final model was 92% at 5 yrs and 82% at 10 yrs. 99 deaths occurred, relating to infection (24%), cardiovascular disease (15%), malignancy (16%), other specified causes (8%). Deaths were less in living donor or kidney/pancreas Tx and more frequent for extended donor criteria-Tx. A three-level multivariate Cox regression model was created in a stepwise fashion, using significantly different variables from the pre-Tx, peri-operative, and long-term post-Tx period between survivors and deceased pts. Pre-Tx variables in the final model included recipient age, HLA-DR mismatches, diabetes, coronary heart disease, heart failure, and peripheral arterial disease. A significant peri-operative variable was cold ischemia time. In the long-term course, variables for death included increased loss of graft function, urinary tract infection, and higher PTH levels. Compared to the survivors, deceased pts received more therapies for rejection seen in protocol Bx (0.30 vs. 0.43 per patient) and in Bx for cause (0.29 vs. 0.34 per patient), however, this was not a significant factor in the final model. Also, the proportion of anti-rejection treatments was not higher in pts who died from infections, compared to pts dying from other causes. Concordance of the final model was 0.79; 200-fold bootstrapping confirmed its applicability.

Conclusions: Based on these results a tool is presented that readily allows risk calculation and stratification of individual pts, as a pre-requisite for individualized and optimal pre- and post-Tx care.

Funding: Government Support - Non-U.S.

FR-PO1095
Effect of Simultaneous Native Nephrectomy on the Outcome of Kidney Transplant Recipients with Autosomal Dominant Polycystic Kidney Disease Jeong Ho Kim, Bum Soon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim, Byung ha Chung. Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea.

Background: End stage renal disease (ESRD) patients with autosomal dominant polycystic kidney disease (ADPKD) required native nephrectomy because of limited space for renal allograft. However, the appropriate timing for nephrectomy and also its effect on allograft patient survival has not been fully investigated.

Methods: We retrospectively analyzed 41 kidney transplant recipients with ADPKD in whom transplantation was done either simultaneously, after or without native nephrectomy at Seoul St. Mary’s hospital between January 1987 and February 2014. We divided patients into 2 groups; simultaneous nephrectomy group (group A, n=13), after or without nephrectomy group (group B, n=28) and compared the perioperative outcome, post-transplant complications, allograft survival rate.

Results: There was no significant difference in the proportion of anti-rejection treatments (0.29 vs. 0.34 per patient), however, this was not a significant factor in the final model. The mean operative time was significantly longer in group A than group B (6.48 ± 1.84 vs. 5.27±0.84 hours, P = 0.048). The mean intraoperative blood transfusions was also significantly more needed in group A than B (3.66±3.43 vs. 0.75±0.26 units; P = .018). However, there were no differences in the incidence of acute rejection and other complications such as post-operative bleeding, infectious complication between the two groups (P > .05). The graft survival rate also did not differ between the two groups (P > .05).

Conclusions: Our study suggests that the complication rates were acceptable and there was no significant impact on graft survival rate when native nephrectomy was done during kidney transplantation in ADPKD patients with ESRD. Therefore, if native nephrectomy is needed in ADPKD for kidney transplantation it can be done safely during transplantation.

FR-PO1096
Predictors of Renal Function Change After Kidney Transplantation Yoshifumi Hamasaki,1 Kent Doi,2 Akihiko Matsumoto,2 Daigoro Hirohama,1 Nobuhioko Sato,1 Daiculture Katagiri,1 Rei Ishikshi,1 Wako Kawarazaki,1 Eisei Noiri,1 Masaomi Nangaku.1 1Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; 2Emergency and Critical Care Medicine, The Univ of Tokyo, Tokyo, Japan; 3Urology, The Univ of Tokyo, Tokyo, Japan.

Background: Several perioperative factors including histological findings of allograft biopsy are known to be associated with graft function during the early post-transplantation (KT). Urinary L-type fatty acid binding protein (u-L-FABP) was reported to be correlated with serum creatinine, serum cystatin C, and estimated glomerular filtration rate (eGFR) in a cross sectional study evaluating post-KT patients. It is unclear what factors in post-KT period predict the longitudinal change of renal function.

Methods: The data from post-KT patients followed at The University of Tokyo Hospital were collected retrospectively. Patients followed-up less than 6 months after KT were excluded. To identify predictors of the longitudinal change of renal function, we analyzed data including clinical parameters measured at each outpatient visit. The primary outcome was determined as the change of eGFR during 6 months period.

Results: 32 post-KT recipients were analyzed in this study. Age and eGFR at baseline of these patients were 51.3 ± 12.7 years old and 41.2 ± 16.1 ml/min/1.73m² (mean ± SD), respectively. The duration from KT to collection of clinical parameters was 6.8 ± 7.3 years (mean ± SD). Changes of eGFR were evaluated 6 months after. When patients were divided into two groups with (N = 15) and without (N = 17) eGFR decline after 6 months, u-L-FABP and urinaly and protein were significantly higher in the eGFR decline group (u-L-FABP, 11.6 ± 5.1 vs 5.1 mg/ml, and urinary protein; 272.7 ± 97.2 vs 97.2 mg/gCr, respectively). On ROC analysis, u-L-FABP and urinary protein predicted eGFR decline after 6 months (AUC [95%CI] = 0.78 [0.60-0.96] and 0.70 [0.51-0.89], respectively). On multiple regression analysis, u-L-FABP and urinary protein were significantly correlated with the absolute and relative eGFR changes during 6 months observation period.

Conclusions: u-L-FABP and urinary protein measured at outpatient clinic can predict the change of renal function of post-KT patients.

FR-PO1097
Plasma Proenkephalin and Poor Long-Term Outcome in Renal Transplant Recipients Lyanne M. Kienek,1 Joachim Struck,1 Michel M. Joosten,1 Rudolf A. de Boer,1 Oliver Hartmann,2 Stephan J.L. Bakker,1 1Nephrology, UMC Groningen, Netherlands; 2Sphingotec GmbH, Germany; 3Cardiology, UMC Groningen, Netherlands.

Background: Enkephalins are well-known endogenous opioid peptides. Recent evidence indicates that they are not only involved in regulation of pain, but also in homeostasis of the immune system and the circulation. Proenkephalin (pro-ENK) is stable in plasma and has been established as reliable surrogate marker for unstable enkephalins. Recent studies found associations of pro-ENK with acute kidney injury and prognosis after myocardial infarction. We aimed to investigate whether pro-ENK could be linked to chronic kidney injury and poor long-term outcome in renal transplant recipients (RTR).

Methods: We included 664 RTR who were 8.1 ± 7.6 years after transplantation. Plasma levels of pro-ENK were measured with a double monoclonal sandwich immunoassay.

Results: Mean age was 53±13 years, 56% was male, estimated glomerular filtration rate (eGFR) 49 ml/min/1.73m² (interquartile range [IQR]: 37-64 ml/min/1.73m²) and
urinary albumin excretion (UAER) 40 mg/24h (IQR: 10-196 mg/24h). Median pro-ENK was 110 pmol/L. Pro-ENK was correlated with both eGFR (r = 0.73, P < 0.001) and UAER (r = 0.35, P < 0.001). During a median follow-up of 3.1 years (IQR: 2.7-3.9 years), 45 RTR developed graft failure and 76 died. Pro-ENK was both associated with increased risk of graft failure (hazard ratio per standard deviation increment of the log of pro-ENK: 2.25, 95% confidence interval, 1.69-4.5) and all-cause mortality (1.83; 1.24-2.69), independent of age, sex, eGFR, and UAER. These associations remained materially unchanged after additional adjustment for body mass index, alcohol consumption, smoking, systolic blood pressure, antihypertensive drug use, use of calcium channel inhibitors, and high-density lipoprotein.

Conclusions: High concentrations of pro-ENK are linked to chronic kidney injury as reflected by correlations with eGFR and UAER. In addition, pro-ENK was independently associated with increased risk of graft failure and mortality in RTR. Pro-ENK is an interesting new biomarker which may aid in early identification of RTR at risk for large graft failure and premature mortality.

Funding: Private Foundation Support

FR-PO1100
Pre-Kidney Transplant Left Ventricle Ejection Fraction, Long-Term Allograft Function, and Survival

Adults with ESRD were recruited from the renal transplant waiting list. The studies concerned the association between post-transplant serum albumin concentration and post-transplant outcomes in kidney transplant recipients (KTRs) and allograft survival. Methods: To evaluate the impact of serum albumin level on graft and patient survival, we performed a retrospective multi-center cohort study in Seoul National University Hospital, Asan Medical Center, and Kangdong Sacred Heart Hospital. A total of 2815 KTRs who underwent renal transplantation from Jan 1997 to Jan 2012 were classified into two groups according to the level of serum albumin at 1 year after transplantation (higher albumin group, ≥4.0 g/dL, n=1978 vs. lower albumin group, <4.0 g/dL, n=837). The Cox proportional hazard model was adjusted with age and gender of recipient, donor type, age of donor, diabetes mellitus, and estimated glomerular filtration rate (eGFR) at 1 year after transplantation. Results: The mean age of the recipients was 41.7±11.3 (range, 18-73) years, and 59.1% were male. The rate of graft failure was higher in lower albumin group compared to higher albumin group (Hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.367-2.477, P<0.001), even though eGFR at 1 year after transplantation was not different between the two groups (61.7±19.8 vs. 62.1±15.8 mL/min, P=0.615). Both all-cause mortality and non-cardiovascular mortality rates were higher in lower albumin group (HR 2.227, 95% CI 1.258-3.943, P=0.006, and HR 2.784, 95% CI 1.254-6.179, P=0.012, respectively). Every 1.0 g/dL higher serum albumin concentration was associated with 69.2% lower all-cause mortality (HR 0.308, 95% CI 0.196-0.483, P<0.001). Conclusions: Serum albumin level at 1 year after transplantation is a prognostic factor for graft failure and patients’ mortality in KTRs. Therefore, evaluation and management for hypoalbuminemia should be considered to improve outcomes in KTRs.

FR-PO1101
Progression of Coronary Artery Calcification in Renal Transplant Recipients – A Follow-Up Of 7 Years

Sibel Gulcicek, Nurhan Seyahi. Dept of Internal Medicine, Div of Nephrology, Istanbul Univ, Cerrahpasa Medical Faculty, Istanbul, Turkey.

Background: In the general population coronary artery calcification (CAC) and its progression is associated with cardiovascular and all cause mortality. We conducted a study to determine the progression of CAC in renal transplant recipients; we also examined the factors associated with progression and the impact of the analytic methods used to determine CAC progression. Methods: We used multi-detector computed tomography to examine CAC in 113 prevalent renal transplant recipients, who did not have a documented cardiovascular disease. After CAC scoring was performed and changes in CAC scores were evaluated in each patient individually, to calculate the incidence of CAC progression. Univariate and Multivariate logistic regression analysis was used to evaluate the determinants of CAC progression.

Results: Baseline CAC prevalence was 34.5% and the mean CAC score was 47.08 ± 135.25. At follow-up scan that was performed after an average of 6.9 ± 0.5 years, CAC prevalence increased to 47.6% and the mean CAC score to 140.18 ± 332.11. Progression of individual CAC score was found between 32.7 and 34.5 %, depending on the method used to define progression (Hokanson and Sevrukov). In patients with baseline CAC, median annualized rate of CAC progression was 13.8. Based on univariate analysis, age, presence of baseline CAC, high baseline CAC score, high body mass index were significantly associated with CAC progression defined according to both the Hokanson and Sevrukov methods. Moreover, HDL cholesterol level was significantly associated with CAC progression when progression was defined according to Hokanson’s method and donor type, high triglyceride levels and systolic blood pressure were significantly associated with CAC progression according to Sevrukov’s method.Based on multivariate analysis baseline CAC and high triglyceride were the independent determinants of CAC progression.
Conclusions: Progression of CAC is the usual evolution pattern of CAC in renal transplant recipients. Besides baseline CAC, high triglyceride level were also associated with progression of CAC.

Funding: Clinical Revenue Support

FR-PO1102


Background: Although the risk for morbidity and mortality has been studied in subjects with renal transplantation (RTxs), a few study has investigated the role of adiponectin (ADPN) for cardiovascular disease (CVD) in RTxs recipients.

Methods: We studied 57 adult RTxs subjects (39 males, 18 females; 10 cadaveric donors) with at least three years of allograft survival (median 251 months). We examined clinical backgrounds such as treated drugs, blood pressure (BP, mmHg), body mass index (BMI), and blood chemistry including cholesterol (total, LDL-C, HDL-C), glucose, glycated hemoglobin (HbA1c), and serum high- and low-molecular-weight (HMW-LMW) ADPN fractions with regard to the associations of the visceral and subcutaneous fat areas on CT scan. We also analyzed the associations of CVD and post-transplant diabetes mellitus (PTDM) with ADPN fractions and the fat areas.

Results: The visceral fat area was inversely correlated with serum HMW- and LMW-ADPN levels (r=-0.400, p=0.002 and r=-0.296, p=0.025, respectively). Furthermore, the visceral fat area was inversely correlated with the HMW ratio and positively with the LMW-ADPN ratio (r=-0.444, p=0.001 and r=0.467, p=0.001, respectively), but no significant correlation was noted between the subcutaneous fat area and the ADPN ratio. On multiple regression analysis, eGFR and visceral area were significant reducing factors of ADPN HMW levels, and the alteration of eGFR was identified as an increasing factor of HMW-ADPN levels. Patients with CVD had higher visceral fat area (p=0.004), lower HMW-ADPN ratio (p=0.022) and higher LMW-ADPN ratio (p=0.049), but not in the subcutaneous fat area. On multiple logistic analysis, the higher HMW-ADPN ratio and statin treatment were identified as reducing factors of the development of CVD, but the LDL-C level was an aggravating factor. Moreover, the higher LMW-ADPN ratio and the visceral fat area were aggravating factors of PTDM.

Conclusions: Even in Japanese renal transplant recipients, visceral fat area and ADPN fractions were significant factors for the development of both CVD and PTDM.

Funding: Government Support - Non-U.S.

FR-PO1103


Background: Post transplant outcomes, in obese chronic kidney disease (CKD) patients having bariatric surgery (BS) as a bridge to renal transplantation, have not been widely reported.

Methods: The database at our center of renal transplant recipients having BS prior to transplant from was reviewed. Control group: all obese renal transplant recipients not having BS with body mass index (BMI) greater than 37 at time of transplant. BMI, patient and graft survival, time on wait-list, acute rejections and infections requiring hospitalization were compared between both groups. Immunosuppressant drug levels were assessed in both groups.

Results: 11 patients had BS prior to transplant. There were 25 obese controls. Median follow up post transplant was 12 months (range 2 to 39 months) in BS group versus 63 months (range 48 to 75 months) in the controls. There were no deaths in the BS group but 5 deaths among controls, of which 4 had functioning grafts at time of death. No significant difference in patient survival was found (P = 0.18). There were 2 graft losses in the BS group versus 6 in the controls (P = 0.77). 4 of which were due to death with functioning grafts. Death-censored graft survival was borderline worse in the BS group (P = 0.05). Rejections were more frequent in the BS group. 4/11 patients had acute rejections in the BS group versus 3/25 in the control group (P = 0.01). Tacrolimus levels were at target in cases seen in Biopsy. Bespect in 1 patient who was non-adherent. Tacrolimus levels were lower in cases of rejection seen in the controls. There were no significant differences in time on waitlist, BMI prior to BS or mean eGFR at 6 months (60.6 in BS and 64.8 mL/ min/1.73 m2 in controls). However, the rate of infections was significantly higher in the BS group, 9/11 versus 10/25 in the control group (P = 0.02).

Conclusions: Despite possible increased transplant candidacy in obese CKD patients having BS, higher rejection rates and inferior death-censored graft survival compared to matched controls seen in this study suggest that vigilance is mandatory. Further investigation is required.

FR-PO1104

Association Between Serum Magnesium Level and the Risk of New-Onset Diabetes After Renal Transplantation in Korea Hoon Yu, Hyungjin Cho, Eunhye Shin, Su-Kil Park. Div of Nephrology, Asan Medical Center; Univ of Ulsan College of Medicine.

Background: New onset diabetes mellitus after transplantation (NODAT) is a serious complication following renal transplantation. Association between serum magnesium level and new-onset diabetes after renal transplantation is controversial. The aim of this study was to identify the association between serum magnesium level and the development of NODAT in Korea.

Methods: The recipients who underwent living donor kidney transplantation between January 2009 and April 2012 were reviewed. Diagnosis of NODAT is defined by American diabetes association criteria. Serum magnesium level were measured at pretransplant, 3 days, 7 days and 3 months posttransplant. Univariated and logistic regression analysis were performed to examine the association between serum magnesium level and NODAT at 1 year posttransplant.

Results: Total 419 patients were enrolled. NODAT was diagnosed in 85(20%) patients. Mean magnesium level at 3 and 7 days after transplantation was significantly lower in patients who diagnosed with NODAT. On logistic regression analysis, Age >40, Obesity, pretransplant glucose were associated with NODAT. However, there is no a association between serum magnesium and NODAT.

Table 1. Risk factors of new-onset diabetes - univariate analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Non-NODAT</th>
<th>NODAT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>334 (86)</td>
<td>85 (20)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>40.8±10.5</td>
<td>47.8±10.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, male (%)</td>
<td>117 (53)</td>
<td>53 (62)</td>
<td>0.143</td>
</tr>
<tr>
<td>Family history of Diabetes (%)</td>
<td>50 (15)</td>
<td>21 (24.7)</td>
<td>0.036</td>
</tr>
<tr>
<td>Tacrolimus (%)</td>
<td>230 (68.9)</td>
<td>59 (69.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cyclosporine (%)</td>
<td>104 (31.1)</td>
<td>26 (30.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Mycophenolate mofetil (%)</td>
<td>273 (81.7)</td>
<td>64 (75.5)</td>
<td>0.181</td>
</tr>
<tr>
<td>Azathioprine (%)</td>
<td>30 (9.0)</td>
<td>11 (12.9)</td>
<td>0.306</td>
</tr>
<tr>
<td>Corticosteroids (%)</td>
<td>315 (94.3)</td>
<td>83 (97.6)</td>
<td>0.273</td>
</tr>
<tr>
<td>Impaired fasting glucose, pretransplant</td>
<td>12 (3.6)</td>
<td>11 (12.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Glucose, pretransplant</td>
<td>88.7±10.4</td>
<td>96.7±13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity, pretransplant</td>
<td>51 (15.3)</td>
<td>35 (41.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mg, pretransplant</td>
<td>2.17±0.35</td>
<td>2.22±0.34</td>
<td>0.201</td>
</tr>
<tr>
<td>Mg, 3 days</td>
<td>1.77±0.20</td>
<td>1.83±0.23</td>
<td>0.026</td>
</tr>
<tr>
<td>Mg, 7 days</td>
<td>1.77±0.20</td>
<td>1.82±0.23</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Conclusions: A lower magnesium level at posttransplant may be associated with NODAT after renal transplantation in Korea.

FR-PO1105

Is NODAT Really Associated with Acute Rejection in Kidney Only Transplantation? Rosa M. Montero, Florence R. Delaney, Manohursingh Ranglal, Paula Mobillo, Syed K. Hasan, Param Shivshahry, Maria P. Hernandez-Fuentes. 1-3 Nephrology & Transplantation, Guy’s & St Thomas’ NHS Foundation Trust, London, United Kingdom; 2NHR Comprehensive Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital, London, United Kingdom; 3MRC Centre for Transplantation, DTMB, King’s College, London, United Kingdom; 4King’s Clinical Trials Unit, Biostatistics Dept, King’s College, London, United Kingdom; 5Nephrology & Transplantation, King’s College Hospital NHS Foundation Trust, London, United Kingdom; 6Nephrology & Transplantation, East Kent Hospitals Univ NHS Foundation Trust, London, United Kingdom.

Background: Previous reports suggest an association with New Onset Diabetes After Transplantation (NODAT) and rejection however it is unclear whether this effect is secondary to hyperglycaemia or a result of previous episodes of treated rejection. This observational study aims to determine the association between acute rejection(AR) and NODAT.

Methods: 381 renal transplant recipients (RTRs) from the KALIBRE study were analyzed. Clinical details and laboratory results were collected in this cohort from 2010-2014. Episodes of AR were identified by renal transplant biopsies;Banff 2009 Categories 2&4 and 3 that were treatment responsive. NODAT was defined as HbA1C>6.5% 3months post renal transplantation. Cox’s regression proportional hazards was used for survival analysis. diabetes associated 381 RTRs (39female, 64%white, 39%non-white, Age at transplant range:17-75). 47 patients were diagnosed with NODAT (13.1%) and 93 (24.4%) with AR. 17/47 (36.2%) patients with NODAT had AR. Rejection free survival in NODAT group was significantly lower than patients without NODAT (p=0.036 HR 1.75). Mean tacrolimus

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

Underline represents presenting author.

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levels between rejectors and non-rejectors were not significantly different (10.1 and 10.3 ng/mL, respectively). T1DM and T2DM combined did not increase the rates of rejection in the cohort.

Conclusions: An association between NODAT and AR has been observed that was independent of tacrolimus levels. RTRs with diabetes mellitus did not have the same effect on AR rates suggesting a different underlying mechanism specific to NODAT rather than just hyperglycaemia.

**Funding:** Other NIH Support

1. Guy’s  & St Thomas’ Charity, Grant number R090782 Title: Clinical Validation of non-invasive peripheral biomarkers to predict and diagnose rejection following renal transplantation.

2. National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London

3. GSTT Kidney Patient Association

4. Quest Diagnostics

5. GSTT Kidney Patient Association

**Conclusions:** Secondary hyperparathyroidism associated with ESRD improves after kidney transplantation (KT) in most patients. However, in some patients, high PTH persists post-KT to cause a tertiary hyperparathyroidism (THPT) state, leading to hypercalcaemia and worsening post-transplant bone disease. New calcimimetic drugs are often delayed by insurance post-KT leaving few options for physicians.

Methods: In this retrospective study, we identified kidney transplant recipients between 2008 and 2013 who underwent parathyroidectomy (PTx) for THPT.

Results: We identified 26 (2.5%) patients who underwent PTx, 10 of 101 patients who underwent KT at our center. Pre-surgery mean calcium andPTH levels were 10.4±1.3 mg/dL and 508±404 pg/mL respectively. Post-KT, median time to PTx was 482 days (Q1,Q3: 275,999); 65% underwent PTx greater than one-year post-KT. PTx indications included persistent hypercalcaemia despite medical therapy (62%) and worsening osteoporosis (42%). Sestamibi scan showed hyperplasia and adenoma in 50% and 34% respectively. However, surgical pathology showed hypercellular parathyroid tissue in 25/26 (96%) patients. Predictive value of the Sestamibi scan was poor (Cohen’s kappa index 0.1). PTx complications included hypercalcaemia (19%), transient renal failure (12%), and temporary nerve paresis (4%). There was no deleterious effect on long-term allograft function after PTx compared with baseline values, serum creatinine was identical at 1 month (1.3±0.5 vs. 1.3±0.6, P=0.34), and PTx complications included hypercalcaemia (19%), transient renal failure (12%), and temporary nerve paresis (4%). There was no deleterious effect on long-term allograft function after PTx.

Conclusions: In one of the largest case series, we have shown that (a) Parathyroidectomy is required for tertiary hyperparathyroidism to treat hypercalcaemia refractory to medical therapy and worsening osteoporosis (b) Sestamibi scan is inaccurate in differentiating between hyperplasia and adenoma and (c) Parathyroidectomy is well tolerated with no long-term deleterious effect on allograft function.

FR-PO1108

**Parathyroidectomy for Tertiary Hyperparathyroidism in Kidney Transplant Recipients** Brian M. Zwecker, 1 Zahra Deen, 1 Sreedhar A. Mandalayam, 1 Luan D. Truong, 2 A. Osama Gaber, 2 Emad H. Asham, 2 Dana M. Hong, 2 Venkat Ramanathan. 1 Nephrology, Baylor College of Medicine; 2 Transplant, Houston Methodist Hospital.

**Background:** Hyperparathyroidism is a common complication following kidney transplantation (KT) and is associated with increased mortality. PTx is used when medical therapy fails.

**Methods:** We identified kidney transplant recipients who underwent PTx from 2008 to 2013 who underwent parathyroidectomy (PTx). PTx indications included persistent hypercalcaemia despite medical therapy (62%) and worsening osteoporosis (42%). Sestamibi scan showed hyperplasia and adenoma in 50% and 34% respectively. However, surgical pathology showed hypercellular parathyroid tissue in 25/26 (96%) patients. Predictive value of the Sestamibi scan was poor (Cohen’s kappa index 0.1). PTx complications included hypercalcaemia (19%), transient renal failure (12%), and temporary nerve paresis (4%). There was no deleterious effect on long-term allograft function after PTx compared with baseline values, serum creatinine was identical at 1 month (1.3±0.5 vs. 1.3±0.6, P=0.34), and PTx complications included hypercalcaemia (19%), transient renal failure (12%), and temporary nerve paresis (4%). There was no deleterious effect on long-term allograft function after PTx.

**Conclusions:** In one of the largest case series, we have shown that (a) Parathyroidectomy is required for tertiary hyperparathyroidism to treat hypercalcaemia refractory to medical therapy and worsening osteoporosis (b) Sestamibi scan is inaccurate in differentiating between hyperplasia and adenoma and (c) Parathyroidectomy is well tolerated with no long-term deleterious effect on allograft function.

FR-PO110

**Insulin Resistance: Is It a Risk Factor for Left Ventricular Hypertrophy in Pediatric Renal Transplant Recipients?** Jale Sezer, Nur Canpolat, Gulseren Pehlivan, Salim Caliskan. Pediatric Nephrology, Istanbul Univ Cerrahpasa Faculty of Medicine, Istanbul, Turkey.

**Background:** Renal transplantation reverses uremia-related risk factors for cardiovascular disease; however, immunosuppressive therapy causes metabolic abnormalities such as insulin resistance, hyperglycemia and dyslipidemia. The aim of the present study was to evaluate the effects of these metabolic abnormalities as a risk factor for left ventricular hypertrophy in pediatric renal transplant recipients.

**Methods:** This is a retrospective study involving 31 renal transplanted children and adolescents (19 male; age 4-20 years) and 19 healthy controls. Anthropometric indices, office blood pressure (BP) and laboratory measurements and also left ventricular mass index (LVMI) at the same time were recorded from the patients’ files. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Insulin resistance was defined as a HOMA-IR ≥ 2.5. Dyslipidemia was defined as HDL-C<40 mg/dL, and/or LDL-C>130 mg/dL, and/or TG>150 mg/dL.

**Results:** Age at transplantation was 12.4±4.4 years with a median follow-up of 27 months. One patient received pre-emptive transplantation, 25 were on PD and 5 on HD before transplantation; 25 patients received a kidney from a living donor. Triple immunosuppressive therapy was used in all patients, except two who were not using steroids at time of the enrolment. Patients had significantly higher BMI-SDS, fasting glucose, fasting insulin, HOMA-IR and TG as well as lower HDL-C levels than controls (p<0.05 for all). Nine patients (29%) had insulin resistance; 11 (42%) were dyslipidemic; and 15 (50%) were hypertensive. LVMI was significantly higher in the patients than the controls (40.0±9.1 vs. 25.8±5.71; p<0.001); left ventricular hypertrophy was noted in 11 patients (48%); LVMI was correlated only with indexed diastolic BP (r=0.433, p=0.039), however, not with any of the lipid parameters or HOMA-IR. HOMA-IR was correlated with only BMI (r=-0.381, p=0.035). There was no association between HOMA-IR and steroid doses.

**Conclusions:** Although insulin resistance and dyslipidemia are prevalent in pediatric renal transplant recipients, hypertension appears to be the main risk factor for left ventricular hypertrophy.

FR-PO107

**Mediterranean Type Diet Is Associated with Low Risk of New-Onset Diabetes and Mortality After Renal Transplantation** Marvse Ostik,1 Eva Corpeleijn,1 Gerjan Navis,1 Charlotte A. Keyzer,1 Sabita Soedamah-muthu,2 Else van den Berg,1 Daan Kromhout,1,2 Stephan J.L. Bakker.1 1Univ of Groningen; 2Univ of Wageningen, Netherlands.

**Background:** The incidence of new-onset diabetes after transplantation (NODAT) and cardiovascular events leading to premature mortality is high in renal transplant recipients (RTR). We hypothesized that a Mediterranean type diet protects against development of NODAT and premature mortality in RTR.

**Methods:** In a prospective cohort study consisting of 707 adult stable RTR with a median follow-up of 3.8 years (interquartile range [IQR], 3.0-4.6 years) from baseline, 28 (6%) developed NODAT and 52 (11%) patients died. RTR with ≥ 5 points were both significantly associated with a lower risk of developing NODAT (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.20-0.94; P=0.04) and mortality (HR, 0.54; 95% CI, 0.31-0.94, P=0.03), both adjusted for age and sex. The results of multivariable analyses, in which we adjusted for potential confounders including total energy intake, physical activity and smoking status, did not materially change the results of the analyses adjusted for age and sex.

**Conclusions:** Dietary habits that resemble the Mediterranean type diet may protect against NODAT and mortality after kidney transplantation. More attention should be directed to the nutritional habits of renal transplant recipients.
Intra-Abdominal Hypertension and Renal Dysfunction in Pregnancy

Wongmarn Kittanamongkolchai,1 Elliott G. Richards,2 Mari Charisse B. Trinidad,3 Wendy White,2 Vesna D. Garovic,1 Nephrology, Mayo Clinic, Rochester, MN; 4Maternal Fetal Medicine, Mayo Clinic, Rochester, MN.

Introduction: The effects of high intra-abdominal pressure (IAP) on renal function have been known for over a century. However, the diagnosis of peripartum intra-abdominal hypertension (IAH)/abdominal compartment syndrome (ACS) is challenging due to the lack of specific symptoms. Cases of IAP in pregnancy without ACS have been reported.

Case Description: A 32 year old obese primigravida with a twin pregnancy at 33 weeks gestation was admitted for intractable nausea and vomiting. She was oliguric and unresponsive to IV fluid. Her blood pressure was normal. Cr increased from a baseline of 0.8 mg/dL to 1.7 mg/dL. A FeNa obtained after fluid resuscitation was 0.02%. Renal ultrasound showed patent renal vessels and no hydronephrosis. A diuretic was given with slight improvement in urine output. IAP measured by an intravesical catheter was 35 mmHg, and abdominal perfusion pressure (APP) (difference between mean arterial pressure and IAP) was 46 mmHg (normal ≥ 50-60 mmHg). She was suspected to have IAH/ACS and was closely monitored. 2 days later, she developed hypertension, an increase in liver transaminases, and proteinuria. The decision was made to deliver with delivery due to severe preeclampsia. IAP measured immediately after C-section decreased to 18 mmHg, and it was 7 mmHg prior to delivery. Urine output increased to 2.5 L per day and Cr declined to 0.7 mg/dL after delivery.

Discussion: Animal and human studies indicate that oliguria and acute kidney injury are frequent consequences of IAH/ACS, and can be present at relatively low levels of IAP. In our case, the IAP of 35 mmHg was quite extreme compared to IAP of 4-28 mmHg observed in cohort studies of peripartum patients. We suspected that obesity and twin pregnancy contributed to the extreme IAH. Her APP was significantly low and restoration of renal function was readily observed after reduction of IAP. Our case may support the theory that IAH/ACS is underdiagnosed and underappreciated. Recent reports from IAH/ACS is probably underrecognized as IAH is not routinely measured. Further study is needed to elucidate the impact of IAH in pregnancy.

SA-PO002 Diabetes, Deafness and Renal Disease – A Case Report

Ioliada Godinho, Joana Gameiro, Noélia Lopez Santos, Sofia C.A. Jorge, Fernando Abreu, Estela Nogueira, Maria Alice Fortes, Jose António Lopes, Patricio Aguiar, Dolores López Præsa, António Gomes da costa. Hospital Santa Maria, Lisbon, Portugal.

Introduction: Deafness and kidney disease as well as diabetes and kidney disease are associations of which the Nephrologist is well aware. However, the concomitance of the three is not as usual, neither is a family history of these diseases.

Case Description: This is the case of a 78 year old woman with non-nephrotic proteinuria, no haematuria, normal renal function, slowly progressive bilateral sensorineural hearing loss and recently diagnosed diabetes and maculopathy and a maternal family history of deafness, diabetes and renal disease. The patient progressed with increasing proteinuria despite antiproteinuric measures and a renal biopsy was performed, revealing Focal and Segmental Glomerulosclerosis (FSGS). Alport syndrome and Fabry disease investigation was negative. Facing the personal and maternal family history, the mitochondrial mutation m3243A>G was pursued and identified in heteroplasmia and maternally inheritance. Mitochondrial Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Diabetic Mitochondrial Diabetic Diabetic Diabetic Disease (MIDD) with renal involvement as FSGS. The renal biopsy ultrastructural study is ongoing. While waiting the etiologic investigation because of symptomatic nephropathy the patient was started on prednisolone 1mg/kg/d with no antiproteinuric response and with side effects causing her to interrupt this medication.

Discussion: Mitochondrial diseases constitute a group of rare diseases in which renal involvement is uncommon, although possible. This is the case with MIDD, in which patients present with non-insulin dependent diabetes and sensorineural hearing loss, which may be accompanied by other manifestations as cardiomyopathies or maculopathy. Renal involvement is possible, mostly as tubulointerstitial nephritis or less frequently presenting as glomerulopathy, namely FSGS. In this type of FSGS, the proteinuria is usually non-nephrotic, with scarce response to antiproteinuric measures, and slow progression to chronic kidney disease. The association of FSGS with mitochondrial diseases is not well known to the nephrologic community. Its timely diagnosis is particularly important to avoid exposure to ineffective and toxic immunosuppression.

SA-PO003 Chronic Inflammatory Demyelinating Polyneuropathy Associated with Advanced Focal Segmental Glomerular Sclerosis Albert Ndzonga,1 Rada Petrinjac-Nmeadic,2 Lelka K. George,3 Elvia Gospamanova.1 Nephrology, UTHSC, Memphis, TN; 2Neurology, Tri-State Neurology, PLLC, Memphis, TN.

Introduction: Chronic demyelinating polyneuropathy (CDP) is rarely reported in patients with nephrotic syndrome (NS). CDP tends to manifest concomitantly with NS. We report a case of CDP developing at a time of focal segmental glomerular sclerosis (FSGS) progression to ESRD and mimicking uremic neuropathy.

Case Description: A 23-year-old female with NS was admitted to our hospital for proven dry 1y collapsing FSGS and serum creatinine (SCr) 1mg/dL was initiated on oral prednisone and lisinopril. He was lost to follow up and returned 1.5 years later complaining on burning pain and numbness in both feet in 4 weeks. Physical exam was normal except for unsteady gait, inability to perform tandem gait, decreased sensation from feet to upper legs, depressed Achilles and ankle flexor reflexes. Laboratory tests showed Scr 44mg/dL, hyperkalemia, metabolic acidosis, normocytic anemia, and normal creatinine phosphokinase. A diagnosis of ESRD due to progression of untreated FSGS was made and dialysis was started. CT head and MRI spine were normal. Cerebrospinal fluid had protein of 74 mg/dL. Serum creatinine (SCr) was 1mg/dL. Electromyography (EMG) showed absent compound muscle action potential (CMAP) and F-waves in both peroneal and tibial nerves, active denervation in tibialis anterior, gastrocnemius and extensor digitorum brevis muscles, and prolonged distal latencies and reduced motor action velocity with normal amplitude of CMAP on both arms. Sensory nerves action potentials on sural and peroneal nerves were absent with prolongation of peak latencies on other nerves. The constellation of clinical, EMG and normal inflammatory, infectious and autoimmune laboratory markers was consistent with diagnosis of CIDP. Plasmapheresis was performed with partial improvement of neurological symptoms and was followed by intravenous immunoglobulin infusions as a maintenance therapy.

Discussion: CIDP should be considered in patients presenting with peripheral neuropathy and history of FSGS. Correct diagnosis of CIDP is critical as untreated CIDP leads to inability to walk. Autoimmune mechanisms may be responsible for CIDP and glomerular damage in FSGS but remain to be proven.

SA-PO004 Alloimmune Membranous Nephropathy in Fabry Disease Zuhair T. Lathara,1 Josephine E. Ambruits1 Department of Coe et al. Medicine, Medical College of Wisconsin, Milwaukee, WI; 2Pathology, Nephropath, Little Rock, AR.

Introduction: Use of enzyme replacement therapies may cause allo-reactivity that causes illness superimposed on the primary disease.

Case Description: A 20 year old male with Fabry disease developed proteinuria. He has the 3.1 kb alu-alu deletion including exon 2. His most recent agalsidase serum enzyme activity was low at 0.8 mg/hour/ml (normal 6.2 to 18.6). He has chronic arthralgia and progressive hearing loss. He has had a stroke secondary to right hemisphere infarction. His last agalsidase level was 7.32 mg. He has hypertension, with 2 blockers. His urine protein creatinine ratio was 2.0 mg/mmol. He had a 1 gram of protein per gram of urine creatinine. His proteinuria had ranged from 1.3 to 2.9 gram/gram over the preceding four months. Serological testing showed a negative RPR, negative tests for hepatitis B and C, and an antibody 1 of 1640 titer. A kidney biopsy showed Fabry disease and superimposed membranous nephropathy. Lisinopril 2.5 mg/day was started. Rheumatological evaluation showed no evidence of lupus erythematosus. The most recent protein to creatinine ratio was 0.71 gram/gram, with a serum creatinine of 0.8 mg/dL.

His kidney biopsy stained positive for anti-agsalsidase, but normal control kidney did not. He had anti-agalsidase antibodies in his serum that did not block agalsidase activity. Immunofluorescence for the phospholipase A2 receptor (PLA2r) was negative within the glomeruli and his serum did not have antibodies to PLA2r.

Discussion: Enzyme replacement therapies may lead to allo-reactivity. Membranous nephropathy has been described in three such patients but not in Fabry disease. Its occurrence may change the therapy of the primary disease and force specific treatment of the nephritis superimposed on the primary disease. Funding: Veterans Administration Support, Clinical Revenue Support

SA-PO005 Silicone Implant Associated Acute Kidney Injury in a Male Transgender Patient

Frank J. O Brien, Brian Y. Young. Div of Nephrology, Santa Clara Valley Medical Center, San Jose, CA.

Introduction: Obstructive kidney disease secondary to nephrolithiasis is a well-described cause of acute kidney injury. Stone formation is often due to dietary or metabolic factors, often no predisposing factors are found. We describe a rare case of obstructive acute kidney injury associated with hypercalcuria and hypercalciemia in a 32-year-old transgender patient. Patient was found to have granulomatous disease associated with silicone implants.

Case Description: 32-year-old male to female transgender patient presented to our institution with fatigue. Routine labs showed creatinine 11 mg/dL, BUN 140 mg/dL, K 7 mmol/L. She was emergently dialyzed, and imaging showed obstructing ureteric calculi, requiring bilateral stent insertion. Patient had a history of silicone implants in hips, buttocks and thigh 5 years previous. These were inserted by a non health care professional. There was no history of calcium stone production or hormonal therapy use. Diagnostic work up for nephrolithiasis revealed; 24 hour urinary calcium 866 mg/24 hours, serum calcium 12.5 mg/dL, phosphorus 4.2 mg/dL. Other 24-h calcium and 24-h CMAP on both limbs were normal. ACE level was 216 units/L. CXR was normal. PTH and malignancy work up was negative. CT abdomen revealed subcutaneous edema in lower back/gluteal area, around the sites of previous silicone implants, and inguinal lymphadenopathy. Subsequent galium scan showed tracer uptake around inguinal area, buttock and hips, consistent with granulomatous activity around silicone implants. Excisional lymph node biopsy revealed foreign body type giant cells consistent with granulomatous disease. Empty vacuoles were noted within the giant cell cytoplasm consistent with silicone induced granulomas. Hypercalcemia was managed with both calcitonin and total parenteral fluids and definitive therapy with prednisone was commenced when diagnosis was made.

Discussion: Hypercalcemia due to silicone implant associated granulomatous disease is a rare, but important presentation. Our patient developed symptoms years after initial implant insertion. With the growing prevalence of cosmetic surgery, particularly in the transgender community, physicians need to be increasingly aware of the associated long term complications.
**SA-PO006**

Isolated Diplopia Caused by Calcineurin Inhibitor Therapy in a Patient with Idiopathic Membranous Nephropathy  
Nader S. Bahri, Ashwani K. Gupta.  
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**Introduction:** Neurotoxicity is a common side effect of treatment with calcineurin inhibitors. Tremors are frequently reported as the most common manifestation. Variable presentations can include headaches, seizures, visual hallucinations or blindness. Six nerve palsy has been reported in previous cases of bone marrow and cardiac transplant patients receiving calcineurin inhibitors. In many of these previously reported cases, the drug was administered intravenously and very high drug levels were found.

**Case Description:** 42-year-old Caucasian female with biopsy proven idiopathic membranous nephropathy (IMGN) who was being treated with tacrolimus and prednisone for nephrotic syndrome. Her tacrolimus levels were maintained between 6.8-9.8 ng/mL. Her urine protein/creatinine ratio of 8 gm/gm was successfully reduced to less than 1 gm/gm. She continued to be in complete remission but after 3 months of therapy she presented with diplopia. The diplopia was binocular and vertical. The patient was seen for an ophthalmologic evaluation. Her visual acuity was 20/20. Pupils were equal and reactive to light and accommodation. No nystagmus was observed. Visual fields and color vision was also normal in both eyes. Assay for Acetyl-choline receptor antibody was negative.

The patient remained compliant with her medications despite the side effects. At this time she was switched to low dose Cyclosporin (CyA) in anticipation that similar side effects may not be observed. Though CyA levels were 44 ng/mL and 59 ng/mL on two occasions but her symptoms did not resolve. A consultation with neuro-ophtalmology was sought and the patient was instructed to discontinue CyA. The symptoms completely resolved 4 days after stopping CyA.

**Discussion:** This is the first reported case of isolated diplopia secondary to calcineurin inhibitors in low doses for treatment of IMGN. Monitoring of serum concentrations of these drugs has not been correlated with toxicity. The mean duration to onset of symptoms in these previous reports is 2-3 weeks and the symptoms completely resolved in all of these cases within a week of discontinuation of the drug.

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

**Underline represents presenting author.**

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**SA-PO008**

A Case of Minimal Change Disease After the Administration of Anti-RANKL Monoclonal Antibody  
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**Introduction:** Receptor activator of nuclear factor kappa B (RANK)-RANK ligand (RANKL) has emerged as an important regulator of bone mineral density and microstructure. In addition to bone, recent studies have revealed that RANKL may contribute to the podocyte survival signal after its injury. Here we report a case that RANKL inhibition might contribute to the onset of nephrotic syndrome.

**Case Description:** A 59-year-old male without any episodes of proteinuria was given denosumab, a fully human monoclonal antibody to RANKL, to treat osteoporosis. Two weeks after its administration, he showed bilateral peritidal edema. Laboratory tests revealed that he had microscopic hematuria, severe proteinuria (15g/gCr), hypoproteinemia (4g/dL) and hypoalbuminemia (1g/dL). The proteinuria selectivity index was below 0.1, indicating that he had selective proteinuria. Based on the results, he was diagnosed to have nephrotic syndrome. Renal biopsy showed minor glomerular abnormality with less tubulointerstitial damage, indicating minimal change disease (MCD). Taken altogether, glucocorticoid therapy of prednisolone 50 mg/day had started. After four weeks of treatment, the level of urinary protein was still high (4.1g/gCr), but it decreased gradually to the range of partial remission (1.2g/gCr) with another 8 weeks treatment of prednisolone.

**Discussion:** This may be a rare case to report the association of RANKL inhibition with MCD. The responsiveness to glucocorticoid therapy was not good enough to promptly induce complete remission, suggesting that podocyte injury due to RANKL inhibition could be responsible at least in part in MCD in this case.

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**SA-PO009**

Eculizumab in Management of Thrombotic Lesions in Kidney Allograft of Patient with Anti-Phospholipid Syndrome  
Anju Yadav, Ravi Sunderkrishnan, Andres Rodrigo Caero.  
Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.

**Introduction:** Thrombotic microangiopathy (TMA) is one of the hallmarks of anti-phospholipid syndrome (APS). Eculizumab is a humanized anti-C5 monoclonal antibody which has been used in atypical hemolytic uremic syndrome. Recently, there have been reports of use of Eculizumab in transplant patients with APSL TMA.

**Case Description:** We present a case of a 58 year old Caucasian man with history of systemic lupus erythematosus, APSL on warfarin, hypertension, rheumatoid arthritis, transient ischemic attack, coronary artery disease with triple vessel bypass, chronic kidney disease stage 5 for which he received pre-emptive living unrelated kidney transplant. After an uneventful post-transplant course, he was discharged on warfarin. He presented to the hospital 4 days later, with acute renal failure, pain over the graft and sub-therapeutic INR. A perinichreatic collection was drained. Cytomegalovirus and BK polyoma viremia were ruled out. Transplant kidney biopsy, revealed TMA with segmental necrosis and small vessel fibrin thrombi and no acute rejection. High dose steroids along with aggressive anticoagulation was received two sessions of plasmapheresis. After meningococcal meningitis immunization, Eculizumab 900mg/week was started. After 4 doses, Eculizumab was changed to 1200mg/two weeks. Creatinine trended down from 7.3 to 3.0 mg/dl and dialysis was stopped after 7 sessions. He was positive for IgG anticardiolipin, beta-2 glycoprotein, and lupus anticoagulant and was started on daily aspirin and warfarin with INR goal of 2.5-3.5.

**Discussion:** Treatment with Eculizumab and plasmapheresis resulted in a relatively rapid and dramatic improvement of graft function in our patient and should be considered in difficult to manage TMA/APS in transplant patients. Its use permits a safer approach of controlling the complement final common pathway.

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**SA-PO010**

Transient Gestational Diabetes Insipidus in a Patient with Pre-Eclampsia  
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Dept of Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA.

**Introduction:** Diabetes insipidus (DI) is manifestation of post pituitary insufficiency characterized by polyuria and polydipsia. DI can be neurohypophyseal, nephrogenic, polydipsia related or gestational (GDI). L-deamino-8-d-arginine vasopressin (DDAVP) is a vasopressin analogue which had higher and prolonged anti-diuretic activity with no effects on smooth muscle. An increase in urine osmolality by at least 50% following administration of DDAVP is diagnostic of disorder.

**Case Description:** We present a case of a 22-year-old African American primigravida woman with no past medical history, in 32nd week of pregnancy, admitted with pre-eclampsia with no liver injury. On admission, blood pressures were between 140-165/60-70 mmHg. After an uneventful delivery she had urine output ranging 6-9 liters along with polydipsia. Both of these were present all through out her third trimester. On exam there was no evidence of volume overload or dehydration. Labs were sodium 137mEq/L, Potassium 2.8mEq/L, Ab 3.0mg/dl, TSH 4.16, urea nitrogen <0.3, creatinine 0.4, serum osmolality 284, urine osmolality 141, spot urine protein/creatinine ratio of 0.8. With one dose of 5mcg subcutaneous DDAVP improved diuresis and urine osmolality to 358 within 24hrs. Oral DDAVP

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

Underline represents presenting author.
SA-PO011

Introduction: The dangers of baclofen toxicity in patients with advanced kidney disease and in particular patients on dialysis remain underappreciated by many physicians.

Case Description: We present a case of a 64 year old male who developed an uncommon case of altered mental status during his hospitalization. His medical history included ESRD for which he was receiving in-center hemodialysis, diabetes and hypertension. He initially presented to the hospital with complaints of shortness of breath and hiccups. His shortness of breath was attributed to volume overload and resolved with two consecutive days of dialysis with fluid removal. For his intractable hiccups, he was started on baclofen. During his hospitalization, he became lethargic and was unable to move his lower extremities. Laboratory data including serum sodium, potassium, glucose, calcium, BUN, phosphorus, liver function tests, troponins, inr work up and ammonia levels were unremarkable. Neuroimaging, including CT head and brain MRI, were unchanged from previous studies and revealed moderate diffuse cerebral atrophy. An EEG was also performed and did not suggest signs of epileptic activity. Further investigation revealed that he had received a total of 20 mg of baclofen over 2 days. After other etiologies were ruled out, we determined that he may have suffered from baclofen induced encephalopathy. His baclofen was stopped and he was prescribed daily sessions of hemodialysis for three days with the intent of clearing baclofen. He was dialyzed for 4 hours during each dialysis session with a high flux dialyzer. After his first session of dialysis, the patient was more alert and would follow simple commands. At 3 days, the patient’s mental status returned to baseline and he was able to move his extremities.

Discussion: Although the kinetics of baclofen elimination during hemodialysis are not well understood, this case demonstrates the resolution of baclofen induced encephalopathy with frequent and consecutive dialysis. Furthermore, we hope this case raises awareness among physicians of the toxic effects that baclofen can cause in dialysis patients.

SA-PO012

Introduction: Urea cycle disorders (UCDs) are rare pediatric diseases but partial enzyme deficiency can persist throughout adulthood. Little has been published about the role of hemodialysis in addressing the acute complications of UCDs in adulthood. Catabolic states are well known trigger factors for the life-threatening acute hyperammonemia.

Case Description: We are reporting a 32 year old male patient with history of partial ornithine transcarbamylase deficiency diagnosed at age of 6 months. He presented with altered mental status due to acute hyperammonemia (100mg/dl). He was treated with a pre-specified protocol (infusion of Na Phenylacetate/benzoate and Arginine HCl, fasting for 36 hours along with intravenous administration of lipids and glucose followed by protein restricted diet of 35 grams per day and Na phenyl butyrate & L-citrulline). This was consistent with Pauci-Immune Glomerulonephritis or ANCA negative vasculitis.

Discussion: This was consistent with Pauci-Immune Glomerulonephritis or ANCA negative vasculitis. It can lead to TMA causing multi-organ failure and the potential for death if not managed in time. Pregnancy can cause aHUS in any trimester. One should maintain a low suspicion for aHUS in a pregnant patient with prompt initiation of eculizumab to prevent negative outcomes.

SA-PO013

Introduction: Atypical Hemolytic Uremic syndrome (aHUS) is known to cause acute thrombotic microangiopathy (TMA) in pregnancy with adverse maternal and fetal outcomes. A French study showed that aHUS usually occurs postpartum when activity of placentally derived factor E selectin is low and deposition of IgM is high. We present a case of a young lady early in pregnancy with severe thrombocytopenia and acute renal failure suspicious for TTP, but later diagnosed with aHUS, which improved with eculizumab.

A 30 year old G1P5A5LS 10 weeks pregnant with a past medical history of 5 first trimester miscarriages presented with vomiting, vomiitng and watery diarrhea whose labs show a hemoglobin (Hgb) 7.8 g/dl, platelet (PLT) count 15K/ul, BUN 65 mg/dl and serum creatinine 2.44 mg/dl along with a LDH of 1,847 U/L, haptoglobin <8 mg/ml, and albumin 3.2 g/dl. Liver function tests (LFTs) and coagulation studies were normal. She was suspected to have TTP and transferred to our tertiary medical center. Urinalysis revealed 3+ protein and 3+ blood. Blood smear showed schistocytes. A diagnosis of TMA was made and plasmapheresis was started. Serologies for lupus and anti-phospholipid antibody syndrome were negative and LFTs remained normal, ruling out HELLP. The ADAMS-13 activity level was not to be 129%. Renal function declined requiring the initiation of hemodialysis(HD). On the basis of ongoing hemolytic anemia with thrombocytopenia, renal failure and a negative ADAMS-13, she was started on Eculizumab. After 2 doses, her renal function and urine output improved and HD was stopped. At discharge, her Hgb was 8.5 g/dl, PLT 150 K/uL, and BUN/creatinine 23/1.84 with the plan to receive monthly eculizumab infusions.

Discussion: aHUS is caused by activation of the complement system due to a genetic deficiency of its regulatory proteins, specifically complement factor H, factor I, and membrane cofactor protein. It can lead to TMA causing multi-organ failure and the potential for death if not managed in time. Pregnancy can cause aHUS in any trimester. One should maintain a low suspicion for aHUS in a pregnant patient with prompt initiation of eculizumab to prevent negative outcomes.

SA-PO014
I've Got a Fever and the Only Prescription Is More Colchicine: Familial Mediterranean Fever Related Pauci-IgM Glomerulonephritis Ashvin Bang, Anam Khan, Celia A. Peña, Rajeev Raghavan. Nephrology, Baylor College of Medicine, Houston, TX.

Introduction: Relatively few renal manifestations have been detected in Familial Mediterranean Fever (FMF). We present a case of biopsy proven pauci-immune glomerulonephritis (GN) in a patient with clinically diagnosed FMF and review past treatments of pauci-immune GN in FMF patients.

Case Description: We present an interesting case of a 22 year old man who had suffered for nearly seven years a constellation of symptoms including fever, nausae, vomiting, abdominal pain, arthralgias, chest pain, and an erythematous rash consistent with a clinical diagnosis of Familial Mediterranean Fever. He had a normal serum creatinine of 1.0 mg/dl which peaked at 2.0 mg/dl. Repeated urinalysis indicated 6-10 RBCs per high powered field (hpf) and 6-21 WBCs hpf. Laboratory testing revealed only an elevated C-reactive protein. A kidney biopsy was performed which revealed 41% of the total glomeruli globally sclerosed and 54 % of the viable glomeruli with active crescents and 25% interstitial fibrosis with tubular atrophy. Immunofluorescence revealed minimal C3 staining. This was consistent with Pauci-IgM Glomerulonephritis or ANCA negative vasculitis. It was suspected to have TTP and transferred to our tertiary medical center. Urinalysis revealed 3+ protein and 3+ blood. Blood smear showed schistocytes. A diagnosis for mutations in the MEFV gene in the diagnosis of FMF is ongoing. He has had no relapse of his FMF with initiation of colchicine and now has had resolution of his hematuria, proteinuria, and acute kidney injury.

Discussion: In the literature, there is minimal knowledge about the renal manifestations of Familial Mediterranean Fever and fewer documented reports on the treatments for ANCA negative vasculitis in FMF. We were able to treat ANCA negative vasculitis in a patient with FMF with only pulse steroids and maintenance immunosuppression with mycophenolate mofetil with great response.

SA-PO015
Stress of Surgery – Is It Just Mental or Can It Be Renal as Well? Mitali Nani Patel, Maria M. Picken, Kavitha Vellanki. Nephrology, Loyola Univ Medical Center, Maywood, IL.

Introduction: Waldenstrom’s macroglobulinemia (WM) is a rare clinicopathological disorder with a reported annual incidence of 3 per 100,000 people. It is characterized by Ig M monoclonal gammapathy in the blood and lymphoplasmacytic lymphoma in the bone marrow. Clinical manifestations are non-specific and generally related to Ig M infiltration of hematopoietic tissues. While deposits of Ig M in the glomerular basement membrane may be seen, renal failure per se is unusual. Here, we present a unique case of recurrent episodes of acute kidney injury (AKI) post-operatively in a patient with underlying WM with spontaneous recovery each time.

Case Description: 75 year old woman with WM, hypertension, obstructive sleep apnea and paroxysmal atrial fibrillation presented for an elective surgery for lumbar stenosis to relieve her post-operative shortness of breath and anuria. Under general anesthesia, her renal function and urine output improved and AKI was reversed. She was transferred to rehabilitation floor on day 3. She had gradual worsening of lower extremity swelling and shortness of breath and repeat labs showed a serum creatinine of 3.32 mg/dl (0.94 mg/dl normal).
mg/dl, 5 days prior) and renal service was consulted for AKI. She had a prior episode of AKI with knee replacement in 2008, dialysis-dependent for 33 days with subsequent spontaneous recovery. Further work up revealed fairly active urine sediment with new onset 24 hour urine protein of 3.3 grams. C3 was normal, C4 <5 mg/dl, cryoglobulin was positive, rheumatoid factor of <20 ug/dl, serum Ig M were elevated at 64g/mg/dl (normal 30-304 mg/dl) and serum immunofixation showed an abnormal restricted band between the beta and gamma regions. Kidney biopsy showed strongly PAS positive hyaline-like precipitates in the glomerular capillaries with immunofluorescence strongly positive (3+) for IgM and lambda light chains. There were abundant, confluent electron dense deposits in the mesangial and subendothelial space. Her symptoms improved with diuretics and she refused any other major intervention. Renal function eventually improved with serum creatinine of 1.2 mg/dl at the time of discharge.

Discussion: In conclusion, we believe the stress of surgery precipitated intraglomeruli deposition of Ig M leading to AKI with spontaneous resolution thereafter.

SA-PO016

New Causes of Secondary Hyperparathyroidism: Unforeseen Effects of New Drugs on the PTH-Calcium Axis

Cortese, Xochiquetzal J. Geiger, Nabeel Aslam. Nephrology, Baylor Univ Medical Center, Dallas, TX.

Introduction: Calcium homeostasis is a function of the interplay between GI absorption, renal excretion and bone resorption. Although numerous effectors control these processes, PTH is primarily responsible. PTH affects the kidney and bone through PTH receptor 1. In the kidney PTH decreases phosphorus reabsorption, increases calcium reabsorption and stimulates 1-hydroxylisation of vitamin D. In the bone PTH up-regulates expression of RANKL and decreases expression of osteotoprotein. This process increases RANKL binding to RANK on osteoclast precursors stimulating them to become osteoclasts that increase bone resorption. New drugs that inhibit RANK are used to treat osteoporosis and bone metastases.

We describe two patients who developed chemotherapy agents who developed severe hypocalcemia, and secondary hyperparathyroidism with hypophosphatemia due to renal P400 wasting. We hypothesize that these drugs inhibit RANK.

Case Description: Case 1: A 72 y/o woman with metastatic leiomyosarcoma received Trabectatin, an experimental agent which interacts with DNA. She subsequently complained of weakness. Labs are shown. Case 2: A 73 y/o man with ALL positive for BCR-ABL was t...Downloaded from https://escholarship.org/uc/item/7981n2k7 by guest on 10 April 2023

Creatinine was 0.7 mg/dl in patient 1 and 0.8 mg/dl in patient 2.

Discussion: Both patients developed secondary hyperparathyroidism. The renal effects of PTH appeared to be intact with increased calcium resorption, phosphorous excretion and 1-hydroxylisation of vitamin D. The effects of PTH on bone resorption, however, appeared blunted. Because PTH acts on both kidney and bone through the same receptor, we believe that this represents a posterior receptor phenomena involving the RANKL-osteoprotein system. The tyrosine kinase inhibitor, Imatinib, has been shown to decrease the expression of RANKL and decreases expression of osteoprotegrin. This up-regulates expression of RANKL and decreases expression of osteoprotegrin system. The tyrosine kinase inhibitor, Imatinib, has been shown to decrease the expression of RANKL and decreases expression of osteoprotegrin. This up-regulates expression of RANKL and decreases expression of osteoprotegrin.

Funding: Clinical Revenue Support

SA-PO017

Connection or Coincidence: Behçet’s Disease and Focal Segmental Glomerulosclerosis with Nephrotic Syndrome

Deanne Leonard, Chermise M. Cortese, Xochiquetzal J. Geiger, Nabeel Aslam. Mayo Clinic, Jacksonville, FL.

Introduction: Behçet’s Disease (BD) often presents with aphthous and genital ulcers, uveitis, and erythema nodosum. Rarely, renal amyloidosis, IgA nephropathy and crescentic glomerulonephritis result. Here we present a case of nephrotic syndrome from focal segmental glomerulosclerosis (FSGS) in a patient with BD in evidence to suggest a direct connection.

Case Description: 49 y/o female with history of hypertension and BD on enalapril, colchicine and carvedilol. Following a recent prednisone taper, she developed oral ulcers, uveitis, pathergy reaction and proteinuria. Physical exam: Blood pressure: 170/90, aphthous ulcer, uveitis, and 3+ bilateral leg edema. Laboratory data: serum albumin 3.3 g/dl, total cholesterol 209 mg/dl, uric acid 5 mg/dl, creatinine 1.1 mg/dl. Urinalysis: 3+ proteinuria, 10 RBC/ hpf and a random protein/creatinine ratio of 8.5. Normal complement levels, DS-DNA, SS-A, SS-B, Sm Ab, RNP Ab, ScI 70 Ab, and Jo Ab. Renal biopsy: Light microscopy: focal segmental lesions. Immunofluorescence: IgM trace mesangial granular staining, consistent with immunoglobulin trapping. IgG, IGA, C3, C1q, kappa, and lambda: negative. Electron microscopy: near total visceral epithelial cell foot process effacement with villous formations.

Treatment included losartan and prednisone 1 mg/kg/day which resulted in resolution of edema and reduction of protein to creatinine ratio to 0.14 along with resolution of oral ulcers and uveitis.

Discussion: At present, there is no proven correlation between BD and FSGS with nephrotic syndrome. Our patient presented with BD flare coinciding with the development of nephrotic syndrome both of which improved simultaneously with steroids suggesting a direct connection. Therefore, the clinician should be aware of this possible link and screen accordingly for proteinuria both qualitatively and quantitatively to detect early renal involvement in patients with BD.

SA-PO018

Reversal of Dialysis-Dependent Renal Failure and Nephrotic Syndrome after Conservative Therapy in an Adult with Proliferative Glomerulonephritis with C3-Dominant Deposition

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Introduction: C3 glomerulonephritis (C3GN) is a recently described entity in a reclassification of membranoproliferative glomerulonephritis, characterized by isolated or predominant glomerular C3 deposits. Although abnormalities in the alternative pathway are known to be involved in the pathogenesis, efficient therapeutic approaches have yet to be established.

Case Description: In December 2012, a 55 year-old man was admitted with rapidly progressive glomerulonephritis and nephrotic syndrome. In May 2011, his serum creatinine (Scr) was 0.63 mg/dl. Seven weeks previously, he was admitted to another hospital with hemorrhagic gastric ulcer accompanied by renal failure (Scr 4.61 mg/dl, urinary protein 15 g/gCr, and moderate hematuria), in the absence of preceding infection. At admission to our hospital, Scr increased to 7.60 mg/dl, ANCA, anti-nuclear antibody, and decrease in complement factors were absent. A renal biopsy specimen showed crescentic and endocapillary proliferative GN with dominant C3 and trace IgG. Conservative therapy was started, given the repeated hemorrhagic ulcer, and decreased rate of renal function decline. Hemodialysis was initiated on hospital day 20 because of oliguria, but was ceased on day 60 with recovery of kidney function. Scr decreased to 1.2 mg/dl, and urinary protein decreased to <1 g/gCr. One year after discharge, he developed nephrotic-range proteinuria, and the second renal biopsy revealed the increased sclerotic glomeruli and fibrous crescents with isolated C3 deposits.

Discussion: To our knowledge, this report is the first to describe reversal of dialysis-dependent renal failure after conservative therapy in a C3GN patient. Similarly to the present case, the histological morphology and clinical presentation infrequently mimic the picture of postinfectious GN, although the transient recovery is usually partial. A novel classification of such cases among C3GN may be needed to avoid an unnecessary immunosuppression.
Discussion: MPGN II may cause drusen and choroidal neovascularization. Eye examination is useful to diagnose visually threatening complications. The newer high-speed spectral-domain optical coherence tomography instrument may define the precise location of the drusen-like deposits when using En face OCT.

SA-PO020
Severe Hyponatremia following the Treatment of Pulmonary Strongyloides Stercoralis Infection
Renu Regunathan-Shenk, Woonin Ahn, Sumit Mohan.
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Introduction: Strongyloides stercoralis is a soil transmitted nematode which can cause serious infection in immunocompromised patients through skin penetration. The helminth can cause abdominal and pulmonary symptoms and can continue to autoinfect patients if untreated. It has been infrequently reported to cause hyponatremia which resolves with treatment of the infection.
Case Description: A 59-year-old Dominican man with a history of single lung transplant and chronic abdominal pain was admitted for treatment of pulmonary strongyloides infection found on routine outpatient bronchoscopy. On admission he was found to have an E. Coli bacteremia which was attributed to gastrointestinal translocation. The patient was started on ivmectin (15 mg/day orally) and pipercillin tazobactam (4.5 grams every 8 hours intravenously in 5% dextrose solution). He developed a rapid decline in his serum sodium concentration from 135 mmol/L prior to admission to 109 mmol/L on hospital day 5. Physical exam at this time was notable for euvoletic appearance, lethargy, and inattention. Laboratory evaluation confirmed a hypo-osmolar hyponatremia with elevated urine osmolality (576mOsm/kg) consistent with Syndrome of Inappropriate ADH Secretion (SIADH). Thyroid studies and cerebral fluid studies were unremarkable. He was treated with hypertonic saline and desmopressin until he achieved normonatremia. He has experienced euvolemic hyponatremia, especially in patients who have traveled to endemic areas or who are immunocompromised. Prior case reports have shown resolution of hyponatremia with euvolemic hyponatremia, especially in patients who have traveled to endemic areas or who are immunocompromised. Prior case reports have shown resolution of hyponatremia with strongyloides treatment, however we present a patient who worsened after bronchoscopy and initiation of ivmectin. We propose that this may have occurred due to increased systemic parasite exposure after the bronchoscopy procedure.

SA-PO021
A Case of Disseminated HSV Infection in PD Patient with Bulbous Pemphigoid
Yuiro Machida, Kentaro Fujii, Ayumi Yoshifugi, Naoki Washida, Hirofumi Torukuma, Matushiko Hayashi, Shu Waking, Hiroshi Itoh. Dept of Internal Medicine, Keio Univ School of Medicine, Tokyo, Japan.
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Introduction: Patients with end stage renal disease (ESRD) are affected by various infections with high mortality because of the immunodeficiency. We report a rare case of disseminated Herpes simplex virus (HSV) infection in peritoneal dialysis (PD) patient, who was treated with high-dose steroid for bulbous pemphigoid (BP).
Case Description: A 72-year-old man under the treatment with PD for 2 months for ESRD caused by nephroclerosis was admitted to our hospital because of blisters and ulceration on his whole body for two weeks. He had had BP and been treated with 60 mg of prednisolone. Twenty-nine days after the admission, peritoneal fluid became yellowish-brown and proteinuria was suspected from the elevation of inflammatory markers. Although the cell count of peritoneal fluid was within the normal range, multineuclear, frosted glass-formed cells were detected in PD fluid, which indicated HSV pritisons. Serum HSV-DNA elevated to 6x10^6 copies and he was diagnosed as disseminated HSV infection. After 200 mg of Ayclovir daily was administered, he had a severe disturbance of consciousness. Although differential diagnosis between acyclovir encephalopathy and HSV encephalitis was difficult, the results of spinal fluid tap and head MRI concluded acyclovir encephalopathy. Introduction of hemodialysis recovered his consciousness. HSV-DNA was decreased, although he developed multiple complications of hemophagocytic syndrome, bacterial infection and invasive pulmonary aspergillus, and died 56 days after hospitalization.

Discussion: We experienced a rare case of disseminated HSV infection and PD-related HSV peritonitis. The combination of ESRD, hypogammaglobulinemia, and BP contributed to the severe immune-compromised state and disseminated HSV infection. Since an early diagnosis determines the prognosis of disseminated HSV infection, cell pathology in peritoneal fluid would assist preemptive therapy.

SA-PO022
Use of Rituximab in Goodpasture’s Disease with Pulmonary Hemorrhage
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Nephrology, New York Presbyterian-Columbia Univ Medical Center, New York, NY.
Introduction: Goodpasture’s syndrome (GPS) is a rare autoimmune disease, where pathogenic autoantibodies deposit in the basement membrane. It presents with rapidly progressive glomerulonephritis, with or without pulmonary hemorrhage. The current standard treatment of Anti-GBM disease is immunosuppressive therapy to reduce antibody production and plasmapheresis to remove existing antibodies in circulation. Rituximab, a monoclonal antibody directed against CD-20 antigen present on B-lymphocytes, approved for various B-cell lymphoproliferative diseases has been used in ANCA associated vasculitis with success; however it’s use in anti-GBM disease is scarce and data regarding safety and efficacy is lacking. We report use of Rituximab in the treatment of GPS with pulmonary hemorrhage.
Case Description: A 35-year-old man presented in 2012 with two week history of nausea, vomiting, intermittent fevers and dark urine. Laboratory findings were creatinine 18 mg/dL, potassium 6.1 mmol/L, Hgb 11.6 g/dL, and platelet count 288 x 10^9/L. Urinalysis showed nephrine urinary sediment. Serology test including ANCA was negative. Anti-GBM antibodies levels were greater than 8 with peak 27. CT chest with pulmonary angiogram was normal with no evidence of pulmonary hemorrhage. Renal biopsies were consistent with GPS (cresceni GN linear anti-GBM on IF). Plasmapheresis was initiated and patient received four doses of Rituximab. Anti-GBM level on discharge from hospital was 2.9. Since initial presentation, patient had two admissions to the hospital in 2014 and 2015 with undetectable Anti-GBM levels.
Discussion: Patients with anti-GBM renal disease have high mortality, especially when pulmonary involvement is present. The use of steroid, immunosuppresives and plasmapheresis alone or in combination has led to a significant improvement of both patient survival and clinical symptoms. Anti-GBM disease is a rare disease in which data regarding the safety and efficacy of alternative therapies are lacking. There are few reported cases of anti-GBM disease treated with rituximab. We present a case of anti-GBM disease with pulmonary hemorrhage successfully treated with Rituximab.

SA-PO023
A Rare Case of Aluminum Toxicity
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Nephrology, Northwestern Memorial Hospital, Chicago, IL.
Introduction: Aluminum toxicity was initially described in enchephalopathics patients with renal failure, overdosing of aluminum-based phosphate binders and attributed to contamination of water used for dialysis treatments. Use of alum for irrigation of the peritoneum for treatment of refractory hemorrhagic cystitis was first reported in 1982. It was described as a safer alternative to formalin bladder irrigation. We report a case of bladder perforation after alum irrigation, leading to intra-peritoneal aluminum exposure. Our patient expired despite chelation and renal replacement therapy. Her serum aluminum concentration is the highest reported level to date.
Case Description: 67 year old female with cervical cancer, admitted for uroscopy, was noted to have hematuria and urinary retention. Her catheter was changed due to clot obstruction and bladder irrigated with saline. Following day continuous bladder irrigation was instituted for persistent hemuria. She underwent cystoscopy with fulguration for persistent hematuria secondary to radiation cystitis. Her CRI resumed with alum irrigant. Overnight, alum irrigant was placed on a pump for infusion. Hours later, patient transferred to ICU for hypotension. CT abdomen revealed free intraperitoneal air, large volume of new fluid, air around bladder suspicious for bladder perforation, and absence of contrast outside of the bowel. Bilateral puncetaneous nephrostomy performed for urinary diversion and to evacuate free fluid. Aluminum levels were drawn. Patient was intubated, placed on vasopressors. Had non-gap metabolic acidosis and worsening renal function, concerning for high-dose aluminum toxicity due to intra-abdominal bladder perforation in the setting of alum irrigation. Deferoxamine was started and CVVH for acidosis. However patient developed refractory shock, and expired. Shortly before her death, aluminum level resulted 163.7mcg/L (normal 0 to 20mcg/L). Subsequent levels peaked at 1455.2mcg/L.
Discussion: We report systemic absorption of alum-containing irrigant following bladder perforation. Large aluminum load to the peritoneum resulted in systemic toxicity, multi-organ failure and death. Chelation therapy and CVVH were inadequate. We report the highest serum aluminum level to date.

SA-PO024
Primary Glioblastoma Multiforme in a Renal Transplant Patient
Hernes Garcia-Sanchez, Arshad Ali, Stephen O. Pastan.
Nephrology, Emory Univ, Atlanta, GA.
Introduction: Glioblastoma multiforme is the most common and most aggressive malignant primary Brain tumor in humans, involving glial cells and accounting for 52% of all functional tissue brain tumor cases and 20% of all intracranial tumors. Incidence of 2.3 per 100,000 population. The principal risk factor for primary brain glioblastoma multiforme is non-Hodgkin lymphoma while gliomas are rarely described.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

629A
Improvement in renal function upon thyroid hormone replacement. Subclinical and overt hypothyroidism may be undiagnosed in CKD and ESRD. Further studies are needed to understand these complex interactions.

S fights all the way!
Erythematous Skin Rash and Gastrointestinal Bleeding as Presenting Features of ANCA Negative Pauic-Immune Glomerulonephritis

Introduction:

Pauic-immune glomerulonephritis (PGN) is one of the common causes of RPGN. In most patients with PGN, circulating antineutrophil cytoplasmic autoantibody (ANCA) is present, however 10% of the patients are ANCA-negative. Usually extra renal manifestations in ANCA-negative PGN are rare, but the case reported here is a rare manifestation having skin rash and gastrointestinal (GI) manifestations.

Case Description:

A 50-year-old female was admitted with low-grade intermittent fever, erythematous maculopapular rash all over the body and asymptmetrical arthralgia involving large and small joints for about 3 months. She had one week history of pain abdomen and melena followed by decreased urine output and generalized edema. On examination BP 156/94 mmHg, Birmingham Vasculitis Activity Score of 23/63. Investigations: Hb 9.9 g/dL, serum creatinine 4.0 mg/dL, urinalysis – protein ++, RBC 2-3/hpf, 24 hour urine protein 4.75gm/day. Serum uric acid and C3 were normal. Serum ANA, pANCA, cANCA, and RFA factor were negative. Skin biopsy for IgG, IgM, IgA, C3, C4c was negative. USG showed normal sized kidneys. Renal biopsy: Light microscopy showed segmental fibrinoid necrosis and early cellular crescents with mild increase in cellularity of mesangial matrix. Immunofluorescence: IgG, IgM, IgA, C3, C1q, kappa and lambda chains were negative. Diagnosis of ANCA negative pauic-immune GN with crescents was made and patient was started on systemic steroids and cyclophosphamide pulse therapy. Patient improved symptomatically and creatinine levels gradually declined.

Discussion:

Patients with ANCA negative PGN rarely present with skin and GI manifestations. In a study done in China comparing clinical features of ANCA negative patients only 7% were found to have GI manifestations and 17.9% had skin rash. These patients were treated similarly to ANCA-positive patients, although no study has focused on having skin rash and gastrointestinal (GI) manifestations.

SA-PO033

A Case of ANCA-Associated Nephritis Mainly Localized to the TubuloInterstitial Area, Successfully Treated by Steroid Therapy

Tomomi Nakajima, Yosuke Nakagawa, Takuya Isegawa, Masahiro Koizumi, Masafumi Fukagawa. Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.

Introduction:

The typical pathological findings of antineutrophil cytoplasmic antibody (ANCA)-associated nephritis consist of extracapillary proliferation and necrotizing crescent formation. Nevertheless, a few cases of ANCA-associated nephritis, in which the tubulo-interstitial area was mainly affected, are reported. Here, we present such a case of ANCA-associated tubulo-interstitial nephritis, and review its characteristics compared to ANCA-associated glomerulonephritis.

Case Description:

A 74 year-old generally healthy female developed bilateral hearing loss, and thereafter suffered from persistent fever. With a diagnosis of bacterial pneumonia, she was admitted to another hospital and treated with several broad-spectrum antibiotics without improvement. Four weeks later, she was referred to our hospital. On admission, weight loss and peripheral numbness and weakness was noted in addition to advanced hearing loss and fever. Serum creatinine level was elevated to 3.5 mg/dL, while urinalysis revealed mild proteinuria with few red blood cells and no cast in the sediment. Sinusitis and alveolar hemorrhage were observed by CT scan. Immunological tests demonstrated positive myeloperoxidase (MPO)-ANCA (104 U/ml). In view of multiple organ involvements, ANCA biopsy, thoracic vasculitis was suspected. Renal biopsy showed diffuse interstitial infiltrates and remarkable vasculitis in small arteries and capillaries with only a small number of crescentic glomeruli, which was consistent with ANCA-associated tubulointerstitial nephritis. Steroid therapyameliorated not only kidney dysfunction, but also hearing loss.

HCV-Related Cryoglobulinemic Glomerulonephritis and B Cell Lymphoma: Early Antiviral Therapy Crucial


Introduction:

Untreated chronic Hepatitis C Virus (HCV) infection often leads to a spectrum of severe extra hepatic manifestations related to B cell dysregulation, which include cryoglobulinemia, renal diseases, and lymphoproliferative disorders.

Case Description:

A 58 year-old Caucasian man with history of hypertension, recent ve chronic HCV infection was hospitalized for several weeks with severe extra hepatic manifestations related to B cell dysregulation, which include cryoglobulinemia, renal diseases, and lymphoproliferative disorders.

Type I membranoproliferative glomerulonephritis (MPGN) associated with type II mixed cryoglobulinemia is the most common HCV related kidney disease, with membranoproliferative glomerulonephritis being less frequent.

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Type I membranoproliferative glomerulonephritis (MPGN) associated with type II mixed cryoglobulinemia is the most common HCV related kidney disease, with membranoproliferative glomerulonephritis being less frequent.
dose steroids, plasma exchanges, and a second dose of Rituximab, with clinical and renal improvement. One month after discharge, he was re-admitted with ARDS and diagnosed with B-cell lymphoma.

**Discussion:** There is a paucity of data on anti-HCV therapy in patients with renal failure often resulting in a delay of antiviral therapy. Immunomodulatory therapies may provide transient improvement of symptoms but bear the risk of significant adverse reactions. Early initiation of antiviral therapy is vital in order to prevent spectrum of HCV-related complications.

**SA-PO034**

**A Case of Membranous Nephropathy with an Adjacent Smooth Muscle Cell Tumor**  
Laith Al-Ababdi,1 Cathy J. Byrne-Dugan,2 Stanley D. Crittenden,1 Helmut G. Renkse,1 Laurence H. Beck,1 Boston Medical Center; 2Brigham and Women’s Hospital.

**Introduction:** Different stromal tumors can occur in the kidney and potentially skew the true extent of parenchymal injury induced by different glomerular diseases. Most of these stromal tumors are benign. The value of renal biopsy in assessing interstitial sequelae may be compromised by the mass effect of the infiltrating tumor cells.

**Case Description:** We describe a case of a 65 year old male patient, with a history of primary membranous nephropathy 20 years ago. He had initially been treated with the Pontocell protocol with favorable response. He continued to be in remission until a few months prior to presentation when he developed anasarca. His 24 hour urine collection revealed 8 grams of protein, and creatinine was 1.8 mg/dl. The decision was made for the patient to undergo a kidney biopsy which confirmed recurrence of primary membranous nephropathy with positive staining for PLAC2. It also revealed advanced chronic changes that included focal global glomerulosclerosis (87%) in addition to interstitial fibrosis 80%. However, adjacent to this atrophic area, there was a tumor of spindle-shaped cells with smooth muscle characteristics. There was no atypia or mitosis and no clear capillary but the tumor cells appeared to infiltrate and surround the tubules and vasculature. This was labeled by the pathologist as a fragment of a smooth muscle cell tumor of undetermined malignant potential. The possibility of leiomyosarcoma could not be ruled out. MRI abdomen and pelvis did not show any evidence of extra renal involvement. The possibility of the parenchymal tissue being significantly influenced by its close proximity to the tumor prompted us to pursue another renal biopsy from the other kidney. Surprisingly, repeat biopsy showed only 15% of tubular atrophy and interstitial fibrosis. The patient was initiated on Rituximab and tolerated two courses of treatment. He achieved partial remission with UPCR less than 3 gram with stable Cr at 1.8 mg/dl.

**Discussion:** Coexistence of smooth muscle tumors and membranous nephropathy is rare. The extent of parenchymal involvement should be confirmed, with repeat biopsy, when there are concerns about tissue distortion by neighboring tumor.

**SA-PO035**

**Freezing Point: Sjögren’s Disease Leads to Cryoglobulin Induced Membranoproliferative Glomerulonephritis**  
Manuel A. Fernandez Palmer, Roberto L. Collazo-Maldonado. Nephrology, Methodist Dallas Medical Center; Dallas, TX.

**Introduction:** Sjögren’s disease is chronic autoimmune inflammatory disorder mainly affecting salivary and lacrimal glands but rarely it can present with systemic manifestations including kidney involvement. The kidney manifestations may include hypokalemic RTA, interstitial disease and rarely MPGN.

**Case Description:** This is a 30 year old woman with no medical history who arrived to ER complaining of a three day history of SOB and increasing edema on lower extremities. She denied toxic habits. Review of systems positive for lower extremity rash. She had no prior medical history. She was afebrile, with normal blood pressure of 120/80 mmHg, heart rate of 90/min, temperature of 38.3°C and respiratory rate of 25/min. Patient had no urine output. There is minimal swelling on the dorsum of right hand of the patient. When we detailed history about this finding, she remembered that she saw mice in her working place in the night shift. Peripheral blood smear showed large numbers of fragmented red blood cells. Disseminated intravascular coagulation panel was normal. Viral hepatitis markers and serology for anti-nuclear antibodies, anti-double stranded DNA, Anti-Smith, Anti-La, Anti-Ro, Anti-La, Anti-H, Anti-Ro/SSA, Anti-La/SSB, ANA, Rheumatoid factor, ANCA, Cryoglobulins were all negative. MRI abdomen and pelvis did not show any evidence of extra renal involvement. The possibility of the parenchymal tissue being significantly influenced by its close proximity to the tumor prompted us to pursue another renal biopsy from the other kidney. Surprisingly, repeat biopsy showed only 15% of tubular atrophy and interstitial fibrosis. The patient was initiated on Rituximab and tolerated two courses of treatment. He achieved partial remission with UPCR less than 3 gram with stable Cr at 1.8 mg/dl.

**Discussion:** Coexistence of smooth muscle tumors and membranous nephropathy is rare. The extent of parenchymal involvement should be confirmed, with repeat biopsy, when there are concerns about tissue distortion by neighboring tumor.

**SA-PO036**

**Postinfectious Glomerulonephritis Associated with Escherichia coli Infection Caused by Transurethral Prostatectomy**  
Eleni Cheloti, Alexia Papadakou, Evdokia Efthimiou, Ionnis Xatzis, Maria Tsiilivivou. Dept of Nephrology; General Hospital of Piraeus, Athens, Greece.

**Introduction:** Postinfectious glomerulonephritis (PIGN) is an immune-mediated glomerulonephritis (GN) caused by non-renal bacterial infection. In adults, PIGN is more common in immunocompromised patients, particularly diabetics. The major site of infection is the urinary tract. In terms of causative agents, Staphylococcus is the most common cause in elderly people, followed by Streptococcus. Gram-negative bacteria, including Escherichia coli, E. coli), are responsible for up to 70% of cases of adult PIGN and 5% of cases in the elderly. We report a patient with PIGN associated with E. coli infection caused by transurethral prostatectomy.

**Case Description:** A 76-year-old Caucasian man with a history of coronary artery disease and recent transurethral prostatectomy was admitted with complaint of fever, and urematic symptomatology that necessitated dialysis therapy. Blood and urinary cultures were positive for E. coli and radiographic examination confirmed a renal abscess. We report a patient with PIGN associated with E. coli infection caused by transurethral prostatectomy.

**Discussion:** In post-infectious glomerulonephritis (MGN) it is considered to be an immune-complex disease and patients are treated with prednisone in order to reduce the inflammatory mediator. The present case report describes a man with a history of transurethral prostatectomy and PIGN associated with E. coli infection. In the present case, neither the patient’s regular preoperative medications nor the postoperative medications can be incriminated for the development of PIGN. However, in the present case, PIGN was associated with E. coli infection, which is a rare cause of PIGN. The patient was treated with five days of parenteral antibiotics (gentamicin and ceftriaxone) followed by three weeks of oral antibiotics (trimethoprim-sulfamethoxazole) and prednisone 40 mg once a day. After 3 weeks of therapy, the patient achieved complete remission of proteinuria, decreased renal size, and stabilization of serum creatinine level. The patient was discharged to home on prednisone 10 mg daily. At 6 months follow-up, the patient was in complete remission with normal renal function.

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Underline represents presenting author.  
632A
proteinuria, making it possible to decrease dosage of the other immunosuppressants and gradually stop them, even the GCS. Patient is now in complete remission after 2 years of treatment with no signs of relapse after stopping additional medication. 

Discussion: Belimumab is indicated in treatment of seropositive active SLE in addition to standard therapy, when lack of clinical improvement despite optimal standard therapy. Two large, phase 3, multicenter, prospective, randomized, controlled trials (BLISS-52 and BLISS-76) compared belimumab with placebo in patients with SLE who were receiving standard therapies. Both studies showed significant improvement in SRI (Systemic Lupus Erythematos Responder Index) with 10 mg/kg of belimumab as compared with placebo. A phase 3 study (BLISS-LN) is recruiting patients with lupus nephritis since these post-hoc analysis of the BLISS trials suggest that belimumab may offer renal benefit in patients with SLE. The treatment is so far not recommended in these cases. We can conclude that our case shows excellent results of belimumab in lupus nephritis with persistent nephrotic range proteinuria under conventional treatment. Alternatives are scarce and mostly limited due to toxic effects and by failure to control disease.

SA-PO039

Overlap Syndrome or Drug Reaction? Varun Gaur, Michael T. Eadon, Jesus H. Dominguez. Medicine, Indiana Univ, Indianapolis, IN.

Introduction: The overlap of ANCA-Associated Vasculitis (AAV) with other autoimmune diseases is well known. However, the association of AAV with the use of TNF-α antagonists in Rheumatoid Arthritis (RA) patients is less understood.

Case Description: A 44 y/o white female with RA had prior treatment with methotrexate (3 yr), adalimumab (2 yr) and etanercept (2 yr). She concluded all DMARD therapy 3 yr prior to presentation (PTP), and then her RA flared 5 months PTP. After initiation of leflunamide and steroids, she had partial resolution. Two weeks PTP, she received golimumab for onset of severe neurological manifestations including right foot drop, distal extremity numbness, and a right 4th digit ischemic lesion. Upon presentation, she was admitted with persistence of these symptoms. Her serum creatinine increased from 0.9 (mg/dl) to 1.4 with 2 gm proteinuria. Her urinalysis had hematuria and serology was positive for PR3-positive cANCA. Her renal function deteriorated with a peak creatinine of 6.7, necessitating intermittent dialysis. A biopsy revealed pauci-immune diffuse necrotizing and crescentic glomerulonephritis consistent with AAV. She received pulse solumedrol, cytoxan, and plasma exchange. Her neurological symptoms improved after a month of therapy. After 6 weeks, she did not require dialysis and her serum creatinine was 2.4.

Discussion: We present a case of a patient previously treated with TNF-α inhibitors who then developed PR3-positive AAV years later. An association between AAV and RA has been described and RA may precede AAV by up to 8 years. Different theories explain this association. One reason may be the common genetic predispositions to autoimmunity, involving HLA or PTPN22 genes, reported in a series of both RA and AAV. Second theory suggests TNF antagonists may predispose one to develop secondary autoimmunity. In our case, the patient discontinued DMARDs 3 yr PTP, although had recently received Leflunamide and Golimumab. There are no reports that associate leflunamide use with AAV and only one case report suggests an association of golimumab with AAV. Our case highlights the need to further understand the importance of AAV in RA patients, and the potential role of TNF inhibitors on the development of AAV.

SA-PO040


Introduction: Silver is a transition metal element with a range of industrial and ornamental uses and is known to be toxic when ingested in significant amounts. Silver exposure causing argyria (skin deposition) and argyrosis (eye deposition) is well-recognised but the renal consequences of silver toxicity are poorly understood.

Case Description: A 47 year old woman with a T-cell lymphoma who refused conventional chemotherapy for 18 months but self-medicated with a remedy containing colloidal silver was admitted with acute dialysis-dependent kidney injury. The serum silver concentration was strikingly elevated at 127.1 nmol/l (reference value <2.8 nmol/l). Kidney biopsy demonstrated a pauci-immune crescentic glomerulonephritis and glomerular tufts with fine, dark, granular material scattered within the mesangium and along the glomerular basement membrane (GBM). Electron microscopy confirmed the presence of electrondense granules in the mesangium and along within the GBM.
The patient was treated with pulse IV methylprednisolone and Rituximab 375mg/m2 weekly for four doses. Three months following induction therapy, his creatinine improved from a peak of 3.6mg/dL to 1.4 mg/dL. His CT findings and hematuria resolved. His PR3-ANCA slowly decreased and became negative 6 months after induction.

**Discussion:** This patient’s presentation with lung nodules on chest CT, necrotizing crescentic GN, and a high serum level of PR3-ANCA support a diagnosis of Granulomatosis with Polyangiitis with a strong temporal relationship to vaccination against influenza. This is the 9th case of ANCA associated vasculitis following influenza vaccination reported in the literature. Clinicians should be aware of the possible association between systemic vasculitis and influenza vaccination.

**SA-PO047**

**C3 Glomerulonephritis Associated with Monoclonal Gammapathy**

**Aumyot Prongdong,1 Weeraporn Srisung,1 Mustafa G. Aly,2 Irfan Warraich,1 Faisal Jamal.1 Nephrology, Texas Tech Univ Health Sciences Center, Lubbock, TX;2Pathology, Texas Tech Univ Health Sciences Center, Lubbock, TX.**

**Introduction:** A case of C3 glomerulonephritis associated with monoclonal gammapathy responding effectively with immunosuppressive therapy.

**Case Description:** The patient is a 65 year-old Hispanic female who presented with lower extremity edema and dyspnea. She had acute kidney injury with nephritic urinary sediments. C3 and C4 were low. Hepatitis B & C profile, ANA, ANCA, anti-GBM and SLEP were within normal limits. There was a faint monoclonal band on the gamma region of a serum protein electrophoresis. Kidney biopsy revealed mesangial immune complex deposits.

**Discussion:** C3 glomerulonephritis is related to dysregulation of alternative pathway of complement (AP) that can be associated with monoclonal gammapathy. Treatment of underlying monoclonal gammapathy may be of benefit in such a situation. Genetic studies for dysregulation of AP might be helpful.

**SA-PO043**

**Late-Onset Fabry Disease with a R112H GLA Mutation and Mild Increase in Plasma Globotriaosylsphingosine**

**Akifumi Onishi,1 Reika Takemoto,2 Tsutomu Hiramasa,2 Hidetoshi Kagawa,2 Hiroki Maruyama,1 Ichiei Naria,3 Hitoshi Sugiyama,4 Jun Wada.1 Okayama Univ Graduate School, Okayama, Japan;2Himeji Red Cross Hospital, Himeji, Japan;3Nigata Univ Graduate School, Niigata, Japan.**

**Introduction:** Fabry disease (FD), a lysosomal storage disorder caused by α-galactosidase A (GLA) gene variants, has a heterogeneous phenotype. GLA variants can lead to a late-onset and non-classical phenotype. We herein describe a 42-year-old Japanese male with FD diagnosed by a renal biopsy exhibiting a R112H GLA mutation and a mild increase in plasma globotriaosylsphingosine (Lyso-Gb3).

**Case Description:** A 42-year-old Japanese male was referred to our hospital due to proteinuria. He had never experienced neuropathic pain, cutaneous angiokeratomas, or hypohidrosis. He had no family history of FD. At 32 years of age, positivity for urinary proteinuria. He had never experienced neuropathic pain, cutaneous angiokeratomas, or hypohidrosis. He had no family history of FD. At 32 years of age, positivity for urinary protein. Kidney biopsy showed global proliferative changes along with splitting of glomerular basement membrane. C3 deposits were seen on immunofluorescence. No reactivity was seen for IgA, IgG, IgM, C1q, C4, fibrinogen and albumin. Electron microscopy showed subendothelial and mesangial immune complex deposits.

**Diagnosis** was determined as C3 glomerulonephritis associated with monoclonal gammapathy. Patient was successfully treated with pulse glucocorticoids followed by oral glucocorticoids and mycophenolate mofetil. C5b-9 was elevated whereas factor H, C3 nephrin factor, and factor B were within normal limits.

**Discussion:** C3 glomerulonephritis is related to dysregulation of alternative pathway of complement (AP) that can be associated with monoclonal gammapathy. Treatment of underlying monoclonal gammapathy may be of benefit in such a situation. Genetic studies for dysregulation of AP might be helpful.

**SA-PO045**

**A Unique Case of Granulomatous Acute Interstitial Nephritis from Ipilimumab**

**Kenneth Ralfo,1 Seymour Rosen,2 Melanie P. Hoenig,1 Nephrology, Beth Israel Deaconess Medical Center, Boston, MA;2Pathology, Beth Israel Deaconess Medical Center, Boston, MA.**

**Introduction:** Ipilimumab is a CTLA-4 inhibitor which is used for the treatment of melanoma. We report a case of granulomatous interstitial nephritis due to ipilimumab, which developed after the first dose and featured a prominent component of granulomatous vasculitis.

**Case Description:** A 70 year old man with stage IV melanoma presented with low grade fevers and malaise. He was found to have acute kidney injury with a creatinine of 6.0 mg/dL. Two months earlier, he had received a single dose of ipilimumab at which time his creatinine was 0.9 mg/dL. Laboratory data was notable for the absence of eosinophilia. Urinalysis showed 5-10 WBCs/hpf and many hyaline casts. A renal biopsy showed granulomatous interstitial nephritis with a component of granulomatous vasculitis (figure: H&E, Masson trichrome). He was treated with high-dose prednisone, which resulted in improvement of his renal function without the need for hemodialysis. After ten weeks of steroid therapy, his creatinine had decreased to 1.6 mg/dL.

**Discussion:** Ipilimumab is a potent activator of T cells and can interfere with the immune system’s tolerance of self-antigens. This drug is known to cause a variety of immune-related adverse events including hypophysitis, hepatitis, colitis and dermatitis. Interstitial nephritis is a rare diagnosis, but has been reported to occur after exposure to...
ipilimumab. Additionally, there have been reports of a sarcoïd-like type response involving the lung and skin. This injury pattern is typified by angiocentric non-necrotizing well formed granulomas. Steroid therapy is effective at treating these immune-related adverse events and does not appear to impair the antineoplastic effects of ipilimumab. With the increasing use of immune-modulating antibodies for treatment of malignancies, it is important to be aware of this potential complication.

SA-PO046
Severe Rhabdomyolysis Secondary to Adenovirus Infection Daniel Tevlin, Sharon E. Maynard.

Introduction: A 38-year-old male presented to the ER with a 4-day history of weakness, subjective fever, and diffuse myalgias as well as recent left eye viral conjunctivitis. He noted dark urine and poor urinary output. On arrival to the ER his vitals were stable. He had full muscle strength and no neuro deficits. He was oliguric. His Sctr 5.04, CPK 1,149,533 despite volume resuscitation including bicarb-containing fluid. He required HD. Workup was positive for adenovirus. Muscle biopsy was deferred in setting of known cause. He required 4 weeks of HD and was able to come off with impaired GFR of 67.

Case Description: A 38-year-old AA male presented to the ER with a 4-day history of weakness, subjective fever, and diffuse myalgias as well as recent left eye viral conjunctivitis. He noted dark urine and poor urinary output. On arrival to the ER his vitals were stable. He had full muscle strength and no neuro deficits. He was oliguric. His Sctr 5.04, CPK 1,149,533 despite volume resuscitation including bicarb-containing fluid. He required HD. Workup was positive for adenovirus. Muscle biopsy was deferred in setting of known cause. He required 4 weeks of HD and was able to come off with impaired GFR of 67.

Discussion: Two cases of rhabdomyolysis from adenovirus have been reported. Most commonly manifests as a febrile illness with pharyngitis. Management strategies have been adopted from studies on crush injury victims. Early volume resuscitation is recommended to mitigate renal failure. Despite the theoretical benefits of bicarbonate-containing resuscitation fluids, no consensus exists. Adenoviral infection can lead to rhabdomyolysis with severe acute kidney injury. Respiratory viral panel should be included in workup of rhabdomyolysis when no other cause is evident. Treatment relies on supportive care, intravenous fluid resuscitation, and hemodialysis in cases of severe renal failure.

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<th>Day 3</th>
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SA-PO047

Introduction: The anti CD20 monoclonal antibody Rituximab is an increasingly used therapy in modern medicine. It is associated with rare but potentially serious adverse events, notably Posterior Reversible Encephalopathy Syndrome (PRES), and Acute Respiratory Distress Syndrome (ARDS).

Case Description: A 60 year-old female was admitted with symptoms of peripheral oedema, arthralgia and muscle swelling. She was noted to have a widespread vasculitic rash, nephrotic range proteinuria and new acute kidney injury. Renal biopsy demonstrated mesangio-occlusive glomerulonephritis with multifocal extraglomerular necrotising vasculitis, in keeping with cryoglobulinemia. She was commenced on plasma exchange, prednisolone and Rituximab. 2 days after the initial dose of Rituximab she developed acute respiratory distress and was found to be in florid pulmonary oedema. This was managed with ultrafiltration, furosemide and oxygen therapy. She received a second dose of Rituximab 1 week later, and rapidly developed tonic-clonic seizures,a further episode of flash pulmonary oedema, encephalopathy and hyperreflexia. MRI brain revealed subcortical white matter high T2 and FLAIR signal in the occipital and posterior parietal lobes consistent with PRES.

Rituximab was reintroduced in half of the cases. Mean recovery time was 4 days, and an additional risk factor was present in 5 cases. The occurrence of ARDS in association with rituximab is rare, only 3 confirmed cases exist . ARDS may occur as a delayed reaction.

SA-PO048
Atypical Hemolytic Uremic Syndrome Associated with Rituximab Kristina Angela Rathmell, Shilpa Gadde.

Introduction: Hemolytic uremic syndrome (HUS) is classified as a thrombotic microangiopathies (TMA). Atypical HUS (aHUS) occurs in 0.5 to 2 per million population per year, 50% progress to end-stage renal disease (ESRD), and 25% may die in the acute phase. Atypical HUS is linked to uncontrolled activation of the complement system. A variety of genetic abnormalities of the alternative pathway of complement have been described in aHUS, occurring in 60% of cases. aHUS is diagnosis when toxin producing bacterial infections, ADAMTS13 deficiency, and systemic-associated diseases are all excluded.

Case Description: A 57 year-old woman with a history of dermatomyositis and associated interstitial lung disease (ILD) was being treated for her ILD with Rituximab. She presented with altered mental status, shortness of breath, and fatigue after receiving an infusion of Rituximab. She was noted on physical exam to have peripheral oedema and cardiac rales on lung exam. On laboratory evaluation, her creatinine level was 4.0 (baseline 1), hemoglobin 7, and platelets 20 with schistocytes on peripheral smear and a low C3 and C4. ADAMTS13 showed normal activity. She was initially treated with high dose steroids and plasmapheresis. She was started on Eculizumab. She required hemodialysis. Renal biopsy showed thrombi consistent with thrombotic microangiopathy as well as mild acute tubular necrosis. She is still hemodialysis dependent.


SA-PO049
Acute Renal Failure Associated with Parenchymal Involvement of Lambda-Restricted Neoplastic Plasma Cells Mark C. Siegert, Amanda K. Hall, Mazdak A. Khalighi, Josephine Abrahm. Div of Nephrology, Univ of Utah, Salt Lake City, UT.

Introduction: The pathogenesis of renal disease in multiple myeloma (MM) is diverse, but biopsy shows that cast nephropathy, light chain amyloidosis and monoclonal Ig deposition are the most common. Renal function often correlates to the degree of cellular injury, not the degree of cast burden, amyloidosis or light chain deposition and direct involvement by plasma cells is rare. We present a case of diffuse interstitial involvement by neoplastic plasma cells, contributing to renal failure.

Case Description: A 70-year-old male with MM presented with acute renal failure. He was diagnosed with IgG lambda myeloma 8 years prior but refused therapy until 7 months ago. He failed CyBorD (M-protein remained at 9g/dl) prior to starting Carfilzomib-Revimlud.
On day 8 of therapy he was admitted with a Cr of 3.4, acutely elevated from 1.7. He denied hematuria, oliguria, fevers, edema or NSAID use. Renal ultrasound was without obstruction. He underwent renal biopsy. Pathology revealed diffuse interstitial involvement by lambda-restricted neoplastic plasma cells and minimal cast nephropathy, but no significant interstitial fibrosis, tubular atrophy or monoclonal deposition disease. Congo red studies were negative for amyloid. There were no features of TMA. Chemotherapy was resumed.

Discussion: Kidney disease with MM is common but it is rare to see involvement of plasma cells in the renal parenchyma. Several review articles list renal parenchymal involvement of plasma cells as a cause of renal failure and, to our knowledge, one case report suggests the same. It is unknown the extent to which parenchymal involvement by plasma cells contributes to the pathogenesis of renal failure. To our knowledge, this is one of only several cases of renal failure that can be attributed to neoplastic plasma cell involvement.

SA-PO050

AL Amyloidosis with Rapidly Progressive Renal Failure and Massive Liver Involvement: A Case Report

Introduction: AL amyloidosis is a plasma cell disorder clinically dominated by organ organization of light chains, mainly in renal and cardiac tissues. Although hepatic disease is described, clinical manifestations are usually mild and frequently undetected. We report a severe case of AL amyloidosis with a massive hepatic involvement and rapidly progressive renal failure (RPRF).

Case Description: One month before coming to our attention, a 67 year old male was admitted to another institution for acute and scrotal edema. Past medical history included hypertension, previous hepatitis B virus infection and estimated daily alcohol intake of 60g. Renal function was normal (serum creatinine of SCr 0.7 mg/dL), while hepatic lysis indexes were moderately positive. A serum monoclonal component IgA kappa (0.21 g/dL) was detected and the bone marrow aspirate showed 10% plasma cell infiltration. Hepatic ultrasound showed hepatosplenomegaly and portal hypertension. Final diagnosis was compensated alcoholic liver disease. After discharged, nephrotic syndrome (NS) (albumin 2.4 g/dL, proteinuria 12 g/24h), RPRF (SCr 1.6 mg/dL) and cholestasis appeared (ALP 1359 IUL, GGT 462 IUL, AST-ALT normal). The patient was admitted to our institution and renal biopsy was performed revealing AL amyloidosis, with prominent IgA (++) and Kappa (++) mesangial deposits, coherently with the serology. The hepatic disease was rediscussed, and the liver biopsy revealed coarse deposits of amyloid as for the kidney. Other organs, heart, liver, lungs and bones were normal. Serum protein electrophoresis showed hypogammaglobulinemia. Echocardiogram revealed type II diastolic dysfunction. Renal biopsy showed nodular glomerulosclerosis. Investigation of haematological disease revealed serum kappa light chain band and urine Bence Jones kappa. Free kappa light chains, serum kappa/lambda ratio and serum Beta-2-microglobulin were elevated. Bone marrow biopsy and aspirate showed 10% monoclonal plasmacytosis. No lytic lesions or masses were detected. Immunofluorescence of the renal biopsy revealed linear staining for kappa light chains along the tubular basement membrane and scarcer in the glomeruly. Electron microscopy is underway. Multiple myeloma was diagnosed and started chemotherapy with Bortezomib. Although there was maintained remission of pulmonary hemorrhage she remained on dialysis.

Discussion: Light chain deposits disease (LCDD) should be considered in the differential diagnosis of PRS. Renal involvement is typical in LCDD with nodular glomerulosclerosis as the common pathologic finding. Pulmonary haemorrhage is unusual and might suggest coexistence of fibrillary glomerulonephritis.

SA-PO052

Acute Cadiorenal Syndrome as a Presenting Symptoms for Scleroderma

Renal Crisis

Introduction: Systemic scleroderma is known to have renal manifestations including scleroderma renal crisis. Acute decompensated heart failure was not described in the literature as the presenting symptom.

Case Description: 50 year-old female with benign past history was diagnosed with new acute decompensated diastolic heart failure and hypertension 160/89 and acute kidney injury with elevated serum creatinin (SCr) 2.6 mg/dL from normal kidney function 2 months prior. Right heart catheterization showed elevated right heart pressures. Endomyocardial biopsy showed small vessel vasculitis. Urinalysis was bland. Renal ultrasound was unremarkable. Renal artery Duplex showed high resistant signals with low velocity. Suspensive immunology screen showed elevated antinuclear antibodies >1:1280, elevated RNA Polymerase III >80 and normal C3 and C4. Renal biopsy showed changes consistent with systemic sclerosis; the glomeruli were ischemic in general and one was sclerosed, the arteriols were with marked walls thickening and swelling of the intima, some undergone occlusive changes with onion skinning of their walls, while others undergone focal fibrinoid necrosis, the tubules were with mild to moderate atrophy, the interstitium was diffusely scarred, with mild to moderate focal and scattered cellular of lymphocytes (biopsy). Retrospectively, the patient reported skin tightening noticed 6 months prior to admission. Blood pressure was controlled with nicardipine drip, captopril, diuretics and bosentan. SCr peaked up to 6.72 mg/dL but renal replacement therapy was avoided. She was discharged on bosentan, amlopidine and lisinopril. SCr improved to 1.78 mg/dL after 8 months.

Discussion: Scleroderma renal crisis can present as acute cardiorenal syndrome.
SA-PO053

Dent’s Disease: An X-Linked Tubulopathy

Sambhavi Krishnamoorthy, Tingting Li. Renal Div, Washington Univ in St. Louis, St. Louis, MO.

Introduction: Dent’s disease is an X-linked recessive disorder of the proximal tubule characterized by low-molecular weight proteinuria, hypercalcuria, nephrocalcinosis/ nephrolithiasis, and progressive renal failure. This disorder is caused by mutations in either the CLCN5 gene, or less commonly the OCR1L gene, leading to disruption of tubular endocytosis and the characteristic clinical findings.

Case Description: We describe an interesting case of a 24 year old Caucasian male with a longstanding history of excessive thirst and polyuria. He had no known history of renal disease. He denied history of urinary tract infections, nephrolithiasis, or NSAID use. Physical examination was unremarkable. Laboratory data showed a serum creatinine of 3.6. Hemoglobin A1c was normal. Urinalysis showed 2+ blood and 2+ protein. Urine osmolality was 277 mosm/kg. A 24 hour urine collection showed proteinuria of 1.7 g/day. ANA, ANCA, and hepatitis panel were all negative. Renal ultrasound showed multiple bilateral renal calculi and nephrocalcinosis. Further testing showed a daily urinary calcium excretion of 735 mg, phosphate 2150 mg and sodium 257 mg. His urine beta microglobulin level was significantly elevated at 29817 mcg/L. The presence of significant low molecular weight proteinuria, hypercalcuria, hyperphosphaturia, nephrocalcinosis/nephrolithiasis, hematuria/ subnephrotic proteinuria, and chronic kidney disease fulfilled criteria for the diagnosis of Dent’s disease. No obvious X-linked pattern had been noted in his family history. Further genetic testing is pending at this time. On initiating hydrochlorothiazide, urinary calcium excretion reduced by 50%. Polyuria, which we attributed to nephrogenic diabetes insipidus in the setting of nephrocalcinosis, also improved significantly with the thiazide.

Discussion: This case report highlights the importance of recognizing this rare X-linked tubulopathy when presenting in adulthood. Commercially available genetic testing can be utilized for supporting the diagnosis and for appropriate genetic counseling for family members. The treatment focuses on reducing urinary calcium excretion and formation of nephrocalcinosis/nephrolithiasis with the ultimate goal of slowing progression to end stage renal disease.

SA-PO054

Phlegmasia Cerulean Dolens: Complication of Femoral Vein Catheterization


Introduction: There are three manifestations of acute massive venous thrombosis and obstruction of the venous drainage of an extremity. They are phlegmasia alba dolens, phlegmasia cerulea dolens (PCD) and venous gangrene.

Case Description: We present a 55-year-old hypertensive, presented with pedal oedema and breathlessness. About a month ago, she fell down and had dislocation of left patella. She was treated with a plaster cast and immobilization for 3 weeks. Her serum creatinine was 8.8 mg/dL. She was initiated on hemodialysis via two single lumen catheters in the left forearm. She was started on heparin treatment but blebs increased and limb became blue. Below knee amputation of left leg was started but blebs increased and limb became blue. Below knee amputation of left lower limb was performed.

Discussion: The causative factor in phlegmasia is massive thrombosis and occlusion of the major venous channels. Perkin et al reported that in 10 percent of patients no cause is found. It is common in women between fifth and sixth decades of age. Swelling, pain and cyanosis are the triad of PCD. Amputation rates are 12-20%. In our patient the effect of immobilization is compounded by femoral vein catheterization. PCD after femoral vein catheterization for haemodialysis has not been reported yet.

Figure: The patient presented with a black ulcer on the second finger of her right hand. The ulcer completely healed 4 weeks later after paclitaxel-coated angioplasty balloon.

Given the concerns for steal syndrome, she was referred for a banding procedure. On physical exam, the graft had good thrill and bruits. Right radial artery pulse was very weak. A black ulcer was noticed on the 2nd finger of the right hand. Decreased sensation in the 1st, 2nd and 3rd fingers of the right hand. Fistulogram was performed which demonstrated occluded lesion in the proximal right radial artery, which was recanalized and angioplastied with 2mm, 3mm and 4mm balloon. However, at one-month clinic follow up, her ulcer only had minimal improvement. Repeat arteriogram showed moderate radial artery stenosis, which was angioplastied with 4mm paclitaxel coated angioplasty balloon. The ulcer healed completely 1 month later.

Discussion: Paclitaxel coated balloon was recently approved by FDA to treat PAD in the lower extremities. This case report showed upper extremity PAD can also be treated successfully with paclitaxel coated angioplasty balloon.

SA-PO055

Successful Treatment of Ischemic Hand Ulcer by Paclitaxel Coated Balloon

Jie Cui,1 Yongfeng Liu,2 Zubin Irani.1 1Nephrology, Massachusetts General Hospital, Boston, MA; 2Interventional Radiology, Chinese People’s Liberation Army General Hospital, Beijing, China; 3Div of Vascular Imaging and Intervention, Massachusetts General Hospital, Boston, MA, China.

Introduction: Hand ischemia is a common complication in end stage renal disease (ESRD) patients. Steal syndrome from dialysis access is the most common cause of ischemic hand, and is usually treated with banding procedure. However, exclusion of peripheral arterial disease (PAD) prior to banding is crucial.

Case Description: A 74 year-old women with history of ESRD due to diabetes mellitus on hemodialysis presented to access clinic for right hand ulcer. She had a right side brachiobasilic graft placement 3 years ago and has been dialyzed through this graft without any issues. However, 3 months prior to the presentation, she started to notice severe right hand pain, especially during dialysis treatment. Four weeks ago, she developed an ulcer in the 2nd finger of her right hand.

SA-PO056

Minimal Change Disease Associated with Invasive Ductal Carcinoma of the Breast: A Case Report and Literature Review

Siddhesh R. Lotlikar,1 Julian D. Rose,2 Soumya Patnaik,2 Supakanya Wongrakpanich,2 Mary Carolina Rodriguez Ziccardi,2 Mark S. Morginstin,7 Rasib Raja,2 Eric J. Bloom.2 1Sidney Kimmel Medical College; 2Albert Einstein Medical Center, Philadelphia.

Introduction: A tenth of malignancies have been associated with nephrotic syndrome, the diagnosis of which may precede the detection of cancer. In an adult with Minimal Change Disease (MCD), paraneoplastic etiology should be explored. Here, we describe a rare case of MCD associated with breast cancer.

Case Description: Our patient is a 72-year-old Caucasian female who presented with bilateral lower extremity edema for 1 week. Home medications were notable for occasional Diclofenac use. Urinalysis on admission showed nephrotic-range proteinuria. MCD was suspected and confirmed on renal biopsy. CT ruled out lymphoma and thymoma. MCD was presumed secondary to Diclofenac use and she was discharged on daily prednisone with instructions to avoid NSAIDs. Two months later, she presented with a pulmonary embolus and CT showed concerning breast changes. Biopsy confirmed a stage IIIc invasive ductal adenocarcinoma. She was tapered off steroids, continued on furosemide and started on Paclitaxel.

Discussion: Breast cancer mainly causes antibody-mediated paraneoplastic syndromes. Yet, studies have shown intratumoral IFN-a expression correlates with induction of autoreactive T-cells, presenting a route for breast cancer to cause a T-cell mediated process such as MCD. Our patient had no lymphoma or thymoma and the lack of evidence of AIN and failure of improvement on discontinuation of NSAIDs argue against NSAID-induced MCD. The relationship of MCD with breast carcinoma is reinforced by her improved proteinuria with chemotherapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

Introduction: Donor-derived infections are an unusual but recognized complication of solid organ transplantation. Between 2005-2011, there were 118 reported donor bacterial infections, of which 34 recipients had confirmed transmission of infection and 9 deaths due to donor derived bacterial infections. Herein, we describe a unique case of donor-derived enterococcal pyleonephritis in a kidney transplant recipient with HIV infection.

Case Description: 47 year old male with history of HIV infection (CD4 - 534 cells/mm³, VL<20 copies), ESRD on peritoneal dialysis, hypertension had deceased donor kidney transplantation. Post-op patient was given 1 dose of cefazolin as surgical prophylaxis. Basiliximab and intravenous immunoglobulin was used for induction therapy. Patient was started on tacrolimus, mycophenolate mofetil and prednisone for maintenance therapy. POD#3 we were notified by organ procurement organization (OPO) that donor urine had enterococcal pyelonephritis in a kidney transplant recipient with HIV infection.

Discussion: There is no clear consensus on treatment regimens for donor-derived infections. This case demonstrates transmission of donor-derived enterococcal infection despite timely initiation of appropriate antimicrobial therapy. Because of increased morbidity and mortality associated with post-transplant infection extended duration of antimicrobial therapy should be considered in these patients.


Introduction: Managning patients with end stage liver disease associated with portal hypertension, ascites and end-stage kidney disease using peritoneal dialysis therapy is challenging for a number of reasons including chronic hypotension, poor nutrition, coagulopathy, high infection rates, and encephalopathy. It is difficult to assess accurate dry weights because of the large variation patient weights depending on how much ascites they have at the time of dialysis, with weight fluctuations in excess of 10 kg. There is also a reluctance on the part of the transplant community to utilize PD because of the perception that these patients may not be able to go on to receive a successful liver transplant.

Case Description: Herein, we report our experience with 5 consecutive patients with decompensated cirrhosis who progressed to ESKD and required dialysis support. One patient did not tolerate HD and was switched to PD, the other 5 started with de novo PD. In each case, the patients were admitted to hospital for PD catheter placement with a surgeon experienced with patients who had advanced liver disease and stayed in the hospital for initial recovery period with IV albumin to support blood pressure. By our protocol, ascites fluid was drained in the OR and then drained each morning for the next 2 weeks before dialysis was initiated. Blood pressures ranged from 80/50-110/65 mmHg, patients remained asymptomatic. All patients received oral midodrine for BP support. Adequate ultrafiltration achieved and edema improved. Serum albumin was monitored at regular intervals, ranged from 2.5-3. One patient had peritonitis from time of surgery, which was treated successfully; no other cases of peritonitis were noted.

Focal Segmental Glomerulosclerosis Presenting Concurrently with Chromophobe Renal Cell Carcinoma Injun O. Owoyemi, Denise J. Thornton, Hiren J. Joshi, M.J. Barcheman. Nephrology, East Carolina Univ/Vidant Medical Center, Greenville, NC.

Introduction: Chromophobe renal cell carcinoma (CRCC) is a rare variant of RCC with distinct histochemical, ultrastructural and genetic characteristics. CRCC accounts for approximately 4% of all kidney neoplasms. Chromogloparaphyses are often diaged in patients with malignancies, particularly hematological cancers with membranous nephropathy being the most common variant. We present a case of resistant hypertension in a young adult male found to have focal glomerulosclerosis (FSGS) with concurrent CRCC. This case highlights the association and emphasis of screening for secondary hypertension in resistant patients, early referral and the pitfalls of percutaneous biopsy for solid renal masses.

Case Description: A 34 year old Nigerian male initially presented to the Internal Medicine clinic to establish care in 2011. His past medical history was significant for hypertension and gross hematuria. He was subsequently referred to Nephrology due to persistent microalbuminuria, hematuria and passage of blood clots in his urine. On presentation to Nephrology, he was found to have nephrotic range proteinuria. Renal ultrasound was significant for several lesions in the right kidney with the largest measuring 3 cm. Percutaneous renal biopsy performed for proteinuria revealed focal segmental glomerulosclerosis with moderate tubulointerstitial scarring. He was evaluated on steroids however he was lost to follow up for approximately 9 months. Upon return, his renal lesions were readdressed with an MRI of the abdomen which could not exclude multiple solid masses in the right kidney. A subsequent ultrasound-guided fine needle aspiration and core biopsy of the right kidney lesion diagnosed chromophobe renal cell carcinoma. He underwent a right nephrectomy with biopsy result negative for metastasis.

Discussion: We were able to unravel this unique finding of FSGS co-presenting with chromophobe renal cell carcinoma. The prevalence of FSGS in RCC has not been established with precision. This case highlights the importance of timely evaluation of secondary hypertension and biopsy of suspicious renal masses.

We performed biopsies of the structure. Surprisingly its histology looked like the normal peritenum. On the surface of the biopsy, a single layer of mesothelial cells was present. There are no apparent fibrosis (thickening) and sclerosis. This case suggests that his peritenum-like membrane might be the very early stage of sclerosing capsule of EPS. Since little has been known about transition from a normal state to EPS through pre-EPS state, this case is valuable to identify one part of the mechanisms of EPS. We report this rare case with some literature review.
**SA-PO061**

**Abdominal Compartment Syndrome: An Overlooked Culprit of Acute Kidney Injury in Immediate Post-Liver Transplantation**

Ekamol Tantisattamo, Praveen Ratansirmetha, Siwadon Pitukweerakul.
1. Nephrology, Northwestern University; 2. Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; 3. Presence St. Francis Hospital, Evaston.

**Introduction:** Acute kidney injury (AKI) is a common complication after liver transplantation and often times, dialysis is required. Abdominal compartment syndrome (ACS) is a treatable cause of prerenal AKI without dialysis needed.

**Case Description:** A 60-year-old man with HCV and alcoholic cirrhosis underwent an OLT. He had massive blood loss during the uncomplicated operation and required massive transfusion and fluid resuscitation. Postoperatively, renal function initially was stable at the baseline serum creatinine (Scr) of 0.8 mg/dL. However, hemoglobin dropped from 9.1 to 5.7 g/dL and tacrolimus level elevated up to 53 mg/L on postoperative day (POD) 4. Scr rose up to 1.3 mg/dL and urine output (UOP) decreased on POD 7. Renal function continued to decline with a peak BUN and Scr of 120 and 2.73 mg/dL on POD 14, respectively. Dialysis was initially planned. However, he had progressively increased ascites with markedly tense abdomen. Bladder pressure revealed intraabdominal hypertension (IAP) with the pressure of 20 mmHg. FE_K and FE_lum were 0.7% and 21%, respectively. Therefore, abdominal paracentesis was performed with an 8 L of yellowish clear ascitic fluid removed. UOP significantly increased shortly after paracentesis. Scr continued to rise and dialysis was not required.

**Discussion:** Our patient presented with prerenal AKI secondary to perioperative hypovolemia concomitant with supertherapeutic tacrolimus level. Massive blood transfusion and fluid resuscitation in the setting of major abdominal surgery caused IAH and subsequently ACS contributing to worsening prerenal AKI. Bladder pressure is a bedside diagnostic tool to detect IAH. AKI could be reversed and dialysis could be avoided by abdominal paracentesis.

**Figure 1: Clinical course during perioperative orthotopic liver transplantation.**

**SA-PO062**

**Rasburicase: A Salvage Strategy to Prevent Renal Allograft Loss in Acute on Chronic Urate Nephropathy**

Ekamol Tantisattamo, Praveen Ratansirmetha, Siwadon Pitukweerakul.
1. Nephrology, Northwestern University; 2. Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; 3. Presence St. Francis Hospital, Evaston.

**Introduction:** Chronic hyperuricemia can lead to chronic kidney disease (CKD) and acute on chronic hyperuricemia potentially causes renal failure. Rasburicase is an effective uric lowering agent indicated for the treatment of acute hyperuricemia especially in tumor lysis syndrome. We report a case of kidney transplant recipient with acute hyperuricemia-related acute kidney injury (AKI) which was resolved with rasburicase.

**Case Description:** A 51-year-old man with ESRD secondary to type 2 diabetes underwent a kidney transplantation and often times, dialysis is required. Abdominal compartment syndrome (ACS) is a treatable cause of prerenal AKI without dialysis needed.

**Case Description:** A 38-year-old female presented in 2013 with leg edema and two grams of proteinuria. Creatinine (Cr) was 1.3 mg/dL. Of note, her thyroid function tests were consistent with severe hypothyroidism, with a TSH of 129 IU/ml and thyroid peroxidase antibodies >900 IU/mL. Serologic workup for hepatitis B, C, and HIV and complements were negative. She had a history of Raynaud’s but did not fulfill clinical and immunological criteria for SLE. Kidney biopsy was consistent with immune complex MPGN with immunofluorescence positive for IgG and C3 only. Patient was non-compliant with thyroid replacement therapy and was lost to follow-up. She reappeared in 2015 with arthralgia, dyspnea, and leg edema. Her Cr was worsened to 1.7 mg/dL with 16 gram proteinuria. She was found to have a pericardial effusion. TSH was 174 IU/mL. Repeated testing for SLE was negative and a repeat renal biopsy demonstrated immune complex mediated MPGN with minimal staining for full house immunoglobulins. She was placed on thyroxine hormone and also initiated on mycophenolate mofetil, given that both her thyroid and renal disease appeared to be driven by an autoimmune antibody mediated process.

**Discussion:** HT, immune complex MPGN and clinical findings in our patient were initially thought to be due to SLE however patient failed to fulfill any immunologic criteria for SLE. HT is rarely associated with MPGN and specific mechanisms remain unclear. Proteinuria in glomerular disease associated with HT is not correlated with levels of thyroid hormone. Therefore, de-novo thyrotoxicosis and thyroid hormone mediated MPGN should be considered as a differential diagnosis.

**SA-PO064**

**Immune Complex MPGN Associated with Hashimoto’s Thyroiditis in a Young Female**


**Introduction:** Glomerular disease associated with Hashimoto’s Thyroiditis (HT) is a rare occurrence infrequently reported in the literature. We present a case of membranoproliferative glomerulonephritis (MPGN) that was thought initially to be due to systemic lupus erythematosus (SLE) in a young woman.

**Case Description:** A 38 year old female presented in 2013 with leg edema and two grams of proteinuria. Creatinine (Cr) was 1.3 mg/dL. Of note, her thyroid function tests were consistent with severe hypothyroidism, with a TSH of 129 IU/ml and thyroid peroxidase antibodies >900 IU/mL. Serologic workup for hepatitis B, C, and HIV and complements were negative. She had a history of Raynaud’s but did not fulfill clinical and immunological criteria for SLE. Kidney biopsy was consistent with immune complex MPGN with immunofluorescence positive for IgG and C3 only. Patient was non-compliant with thyroid replacement therapy and was lost to follow-up. She reappeared in 2015 with arthralgia, dyspnea, and leg edema. Her Cr was worsened to 1.7 mg/dL with 16 gram proteinuria. She was found to have a pericardial effusion. TSH was 174 IU/mL. Repeated testing for SLE was negative and a repeat renal biopsy demonstrated immune complex mediated MPGN with minimal staining for full house immunoglobulins. She was placed on thyroxine hormone and also initiated on mycophenolate mofetil, given that both her thyroid and renal disease appeared to be driven by an autoimmune antibody mediated process.

**Discussion:** HT, immune complex MPGN and clinical findings in our patient were initially thought to be due to SLE however patient failed to fulfill any immunologic criteria for SLE. HT is rarely associated with MPGN and specific mechanisms remain unclear. Proteinuria in glomerular disease associated with HT is not correlated with levels of thyroid hormone. Therefore, de-novo thyrotoxicosis and thyroid hormone mediated MPGN should be considered as a differential diagnosis.

**SA-PO065**

**Hypervitaminosis D – A Rare Complication of PJP in a Transplant Patient**

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**Introduction:** Pneumocystis jiroveci Pneumonia (PJP) is a known complication in immunocompromised hosts including transplant recipients, usually in the first six months of transplant. Hypercalcemia (HCa) is not a classic symptom of the disease. We present a case of a patient with simultaneous kidney and pancreas transplantation nineteen years ago who presented with PJP and developed HCa (highest value 14.8mg/dL [8.3-10.5] mg/dL. Parathyroid Hormone (PTH) was appropriately suppressed with a level of 6 [12-88] pg/ml. 1,25-(OH) vitamin D concentration was elevated (125 [18-72] pg/ml). After treatment with taurine and- sulfamethoxazole her Calcium concentration returned to normal along with PTH and 1,25-(OH) vitamin D. It is thought that, like other granulomatous disease-induced HCa, it is likely that endogenous extrarenal production of 1-alpha-hydroxylase by activated macrophages and by interferon-gamma involved in granuloma formation results in increased conversion from 25-(OH) vitamin D to 1,25-(OH) vitamin D and, consequently, in suppression of PTH secretion. Although only few cases of PJP-associated HCa have been reported to date, it is possible that this association is more frequent than previously thought. Hypercalcemia in transplant recipients with pulmonary symptoms must raise suspicion of PJP.
SA-PO066

A Rare Case of Tubulointerstitial Nephritis Associated with Primary Biliary Cirrhosis  Jatinder K. Holdi, 1 Jingyin Yan, 1 William F. Glass. 2 1Dept of Nephrology, Baylor College of Medicine, Houston, TX; 2Dept of Pathology, Univ of Texas Health Science Center, Houston, TX.

Introduction: Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease characterized by positive antimitochondrial antibodies (AMA), immune-mediated epithelial damage of small bile ducts, which leads to liver cirrhosis as the disease advances. In addition to liver injury, other autoimmune diseases, such as Sjögren’s syndrome and Raynaud’s syndrome, are reported in approximately 2-20% patients with PBC. However, the association of PBC and renal injury is rarely documented.

Case Description: Here we present a case of tubulointerstitial nephritis (TIN) in a patient with PBC. A 35-year-old female with past medical history of PBC developed sub-nephrotic range proteinuria and chronic kidney disease stage 3. A renal biopsy showed moderate to severe renal cortical and focal medullary tubulointerstitial inflammation with infiltration of lymphocytes, plasma cells and occasional eosinophils, as well as significant tubulitis.

The patient was treated with a short course of oral prednisone and her renal function improved.

Discussion: This case highlights a very rare cause of TIN and suggests that steroid therapy is effective in this setting.

SA-PO067

Plasma Exchange as Adjunctive Therapy for Crescentic IgA Nephropathy  Jicheng Li, Xinfang Xie, Fude Zhou, Minghui Zhao, Hong Zhang. Renal Div, Peking Univ Inst of Nephrology.

Introduction: Recent KDIGO guidelines recommend an aggressive immunosuppressive therapy in patients with crescentic IgA nephropathy (CreIgAN). While large cohort study from our center suggest that even with such a therapy, the 1- and 5-year renal survival rates remained low at 65% and 28%, respectively. Especially patients who present with serum creatinine (Scr)>580μmol/L hardly recovered from dialysis. In this study we aim to evaluate the efficacy of plasma exchange(PE) in severe CreIgAN.

Case Description: In this pilot study we give PE as adjunctive therapy to patients with severe CreIgAN on the back of high dose steroids and cyclophosphamide. Severe CreIgAN is defined as diffuse crescent forming with kidney failure that needs dialysis or presents with severe CreIgAN.

Overall ten patients with severe crescentic IgA nephropathy received PE from 2011 to 2015.

<table>
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Y: yes, N: No

Among them 7 patients reached dialysis at presentation with serum creatinine (768±176mmol/L). Another 3 cases showed progressively kidney decline even after an aggressive immunosuppressive therapy. Patients received 5-10 PEs. After a mean 13 month follow-up, 4 of the 7 patients who had dialysis successfully recovered from dialysis. One of the 3 patients with persistent kidney progression showed serum creatinine decline.

Discussion: Plasma exchange as adjunctive therapy may achieve benefit for patients with severe crescentic IgAN.

SA-PO068


Introduction: Fibrillar glomerulonephritis (FGN) is characterized by nonbranching randomly arranged fibrils along the mesangium and glomerular capillary walls that do not stain for Congo red, have a diameter of 16-24 nm, and usually show polyclonal IgG, C3, and light chain deposition by immunofluorescence. Found in ≤ 1% of native renal biopsies, FGN is usually idiopathic, although some cases are associated with malignancy, monoclonal gammopathy, and autoimmune diseases. Association of FGN with demyelinating neuropathy has been rarely described.

Case Description: A 38-year-old Indian man with 3-year history of hypertension and 10-month history of end stage renal disease attributed to hypertension, presented to our institution with a 3-week history of progressive, bilateral lower extremity weakness. During his hospital stay, he was diagnosed with non-infectious pleural and pericardial effusions. Lab work revealed normal Anti nuclear antibody, anti double stranded DNA antibody, serum complements, anti nuclear cytoplasmic antibodies. Serologies for hepatitis and human immune deficiency virus were negative. Electromyography revealed demyelinating sensorimotor polyneuropathy. Chest, abdomen and pelvis imaging was unrevealing for malignancy. No monoclonal peaks on serum and urine electrophoresis or immunofluorescence. Fat pad biopsy negative for amyloid. Bone marrow biopsy showed 60% cellularity with tri lineage hematopoietic activity, no B cell clonality or T cell aberrance. He was started on high dose steroids with gradual improvements of weakness. Renal biopsy showed findings of chronic FGN with IgG4 dominant deposition. 44 of 48 glomeruli were globally sclerosed with 80% fibrosis and no activity. Sural nerve biopsy results are still pending.

Discussion: FGN is a rare and leads to ESRD in the majority of cases. There are very few cases describing FGN in association with demyelinating polyneuropathy without associated plasma cell dyscrasias. Although FGN renal prognosis remains poor, early identification is important as it may help identify an underlying malignancy or systemic autoimmune disorder with potential for treatment. FGN may be a precursor for future lymphoproliferative disorder.
SA-PO069
Acute Inflammatory Polyarthritis following Kidney Transplantation
Paul P. Maraj, Nephrology, Baylor College of Medicine, Houston, TX.

Introduction: An acute inflammatory polyarthritis develops one month after deceased donor kidney transplantation in a 54 year old male. He had no prior diagnosis of any form of arthritis, crystalline, inflammatory or otherwise. Following workup he was diagnosed with Rheumatoid arthritis and improved with an increased dose of steroids. To date there are no case reports which described this disorder precipitated by kidney transplantation. This case report describes this unique clinical scenario and the dilemmas with diagnosis.

Case Description: 54 year old man with a medical history of end stage renal disease secondary to hypertensive nephrosclerosis who underwent deceased donor kidney transplant one month prior and was admitted for joint pains. During kidney transplantation he had induction with thymoglobulin, plasmapheresis and rituximab as per institutional protocol for positive DSA. Maintenance immunotherapy consisted of tacrolimus, mycophenolate mofetil and prednisone taper dose. Following transplantation he was asymptomatic until one month after transplantation when he developed bilateral shoulder pains which then migrated to elbows and wrist; this was associated with significant morning stiffness and malaise. Xrays which were negative for bony abnormalities, MRI wrist revealed small to moderate joint effusion. Fluid analysis was negative for septic arthritis and crystals. Serum uric acid was within normal limits. Autoimmune workup negative including ANA, C3, C4. Rheumatoid factor was positive to titer 1:4, anti CCP was significantly positive at>250. He was treated with oral steroids which resulted in resolution of his symptoms.

Discussion: To date there have been no reports of rheumatoid arthritis in the immediate post-transplant period. There have been reports of an acute inflammatory syndrome related to mycophenolate use which improved on discontinuation, anti-CCP titers were unknown in these cases. Mycophenolate was continued in this patient and his symptoms did not recur after steroid taper making a reaction to mycophenolate less likely. Anti CCP is very specific for diagnosis of rheumatoid arthritis but its validity post transplant is unknown. The temporal relation with transplantation also raises the possibility of a drug induced reaction.

SA-PO070
IgM Nephropathy: A Neglected Pathology of Nephrotic Syndrome
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Introduction: IgM nephropathy is defined by the presence of immunoglobulin M (IgM) as the dominant immunoglobulin in the mesangium of the glomeruli in a diffuse and global distribution. Clinically, a poor response to steroids distinguishes this disease from Minimal Change Disease.

Case Description: An 80-year-old man with past history of Hypertension, Alzheimer’s dementia, and benign prostatic hypertrophy complained of progressive shortness of breath associated with severe bilateral lower extremity edema and decreased urine output. Vital signs revealed blood pressure of 171/77mmHg. Lung auscultation was remarkable for bibasilar rales. The patient had anasarca. Laboratory tests showed serum creatinine at 2.2mg/dL (baseline of 1.2mg/dL), BUN of 36mg/dL and albumin of 2.2g/dL. Urinalysis showed microscopic hematuria and proteinuria (> 500mg/dL). Renal sonogram revealed normal kidney size without hydrenephrosis or nephrolithiasis. The 24-hour urinary protein excretion was 6.7gms/day. Serum creatinine rose to 7.7mg/dL a week later. Kidney biopsy was performed and steroid pulse therapy was started. Hemodialysis was initiated. Renal biopsy results showed mild increase in mesangial matrix and interstitial fibrosis. Sections stained for IgG, IgA, albumin C1q and kappa and lambda light chains were negative. Staining for IgM showed granular deposits in the mesangial areas compatible with a diagnosis of IgM Nephropathy. Hemodialysis was discontinued after two sessions since the patient had rapid recovery of kidney function after the 3 day steroid pulse therapy. Steroid therapy was tapered and eventually discontinued. Three months later, 24 hour urinary protein excretion was normal and the serum creatinine was 1.6mg/dL.

Discussion: Patients with IgM Nephropathy are less likely to respond to immunosuppressive agents. The presence of mesangial IgM deposits and interstitial fibrosis entails a worse prognosis. However, in our case, the patient had a prompt response to steroid therapy with resolution of the nephrotic syndrome and recovery of renal function.

Funding: Veterans Administration Support

SA-PO071
Renal Infarct from Traumatic Renal Artery Dissection
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Introduction: Renal infarcts are characterized by acute onset of flank or generalized abdominal pain, nausea, vomiting, and occasionally fever and hypertension. Elevated WBC, CRP and LDH have also been associated. Renal artery dissection secondary to trauma is rare and has been associated with anatomical variations and acceleration/deceleration injury leading to intimal tearing. The two goals of treatment are organ preservation and improvement of renovascular hypertension. The treatment options include surgical reconstruction, endovascular repair, or conservative treatment. Our patient was initially placed on empiric anticoagulation with heparin. After hypercoagulable disorder, vasculitis, and embolic source was ruled out, anticoagulation was stopped. The patient was discharged on conservative treatment.

SA-PO072
Persistent Fever in a Patient with Wunderlich Syndrome
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Introduction: Wunderlich syndrome is spontaneous, nontraumatic renal hemorrhage confined to the subcapsular and periperal space. We present a case of a patient with a Wunderlich syndrome complicated by renal abscess.

Case Description: Patient was a 43 year old male who presented with nausea and generalized weakness, found to have sepsis secondary to urinary source. Ultrasound obtained during work up showed a old right perinephric hematoma. Patient continued to be febrile despite IV antibiotics. Repeat imaging with CT scan showed large abscess in place of the previously described subcapsular hematoma. Successful CT-guided drainage of the abscess led to marked improvement and resolution of fever.

Discussion: Wunderlich syndrome is secondary to neoplastic and non-neoplastic causes. It usually presents as mild flank pain, flank tenderness, or hematuria. Depending on blood loss, symptoms of hypovolemic shock may develop. Treatment varies according to severity, ranging from monitoring of the hematoma to nephrectomy. Our case is interesting since Wunderlich syndrome provided a nidus for infection and eventual abscess formation causing persistent fevers and flank pain with preserved hemodynamic stability. It demonstrated the need for CT imaging in order to fully appreciate the extent of the hemorrhage which in this case converted into an abscess. In the right clinical scenario, Wunderlich syndrome should be evaluated as a possible factor in infectious presentations.

SA-PO073
Gaucher’s Disease and Lupus, Two Diseases in the Same Scope?

Introduction: Gaucher’s disease is a rare inherited lysosome storage disease caused by genetic mutations that encodes for glucocerebrosidase enzyme. It’s deficiency leads to glucocerebroside (GC) accumulation in mononuclear macrophage system, including liver, spleen and bone marrow. Kidney involvement is usually rare. Systemic lupus erythematosus

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Underline represents presenting author.

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Underline represents presenting author.

Case Description: A 32-year-old woman with Gaucher’s disease diagnosed at 17 years old, having velaglucerase, presented several clinical clues suggesting SLE. Months later started presenting face and limbs edema and hypertension. She was admitted with microcytic and hypochromic anemia, 77000 platelets, creatinine serum levels of 1.38mg/dl and hypocalcemia. The urinalysis showed hematuria and proteinuria of 7628mg in the 24h urine collection. The patient had positive anti-nuclear antibodies, Anti-Sjogren’s syndrome related antigen, negative anti-double stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, viral serologies. Both complement levels were low. A kidney biopsy was performed.

It has been suggested that progressive accumulation of GC may trigger macrophage activation resulting in enhanced cytokine secretion and subsequent clonal B-cell expansion leading to chronic stimulation of the immune system. GC changes natural killer T cell function, a regulatory lymphocyte that has a role in infectious, neoplastic and inflammatory processes, therefore having a potential role in inducing other autoimmune disease. NKT lymphocytes are considered to be a link between innate and adaptive immune responses and were shown to have a role in a number of immune-mediated disorders. In an animal model of SLE, a selective reduction in NKT cells precedes the development of autoimmune phenomena.

Discussion: This case highlights a possible immunologic proximity between Gaucher’s disease and SLE, bringing up the already existing doubt that the defects in lipid metabolism, could contribute to the development of autoimmunity.

SA-PO074

Chronic Periaortitis, a Known Cause of Obstructive Uropathy
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1Nephrology, Rutgers-New Jersey Medical School, Newark, NJ; 2Nephrology, East Orange Veterans Administration Hospital, East Orange, NJ.

Case Description: A 59 year-old man with hypertension presented with one week of gradually decreasing urine output, nausea, generalized weakness, and vague dull left lower quadrant pain with radiation to the left flank. He was afibrile with blood pressure of 170/90 mmHg, pulse of 77 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. His abdominal exam was unremarkable except for non-tender scrotal swelling bilaterally. Laboratory studies were notable for the following values: WBC 12.1 x 10^9/L, BUN 62mg/dL, SCr 13.8mg/dL (baseline SCr 1.1mg/dL), ESR 57mm/hr, CRP 67mg/dL, U/A clear, yellow, specific gravity 1.01, pH 6, moderate blood, negative protein, leukocyte esterase, or nitrites. A renal ultrasound showed moderate hydronephrosis with patent renal arteries and veins bilaterally. CT of the abdomen and pelvis revealed moderate bilateral hydronephrosis, an abdominal aortic aneurysm (3.6cm), and a retroperitoneal soft tissue mass measuring 2 cm in diameter with associated ureteral obstruction. There was no inguinal iliac lymphadenopathy or suggestion of discrete malignancy. Based on combined clinical and radiographic evidence the patient was diagnosed with chronic periaortitis and retroperitoneal fibrosis. He was started on mycophenolate mofetil and prednisone taper with complete resolution of symptoms within 6 months.

Discussion: Retroperitoneal fibrosis (RPF) is a relatively rare condition characterized by the presence of fibrosis and inflammation of the retroperitoneal tissues that often surrounds the ureters and other abdominal organs and can lead to renal failure in advanced cases. Our case demonstrates the importance of considering RPF as an etiology of flank pain and renal failure as medical treatment is effective in reversing obstructive uropathy.

SA-PO075

IgA Nephropathy in HIV Positive Patient with Acute Kidney Injury
Giovanna Y. Arteaga Müller,1 Lilía María Rizo Topete,1 Elisa María Guerrero González,1 Gabriela Alarcón-Galván,2 1Nephrology, Univ Hospital José E. González UANL, Monterrey, Mexico; 2Anatomic Pathology, Univ Hospital José E. González UANL, Monterrey, Mexico.

Introduction: Acute kidney injury is common in patients with HIV, being prerenal variant the predominant etiology. Among the intrinsic causes are thrombotic microangiopathy, the antiretroviral drugs associated and the immune complexes associated (3.5%-10%) being the collapsing focal segmental glomerulosclerosis the most frequently found.

Case Description: Male 41 year old, with use of cocaine, marijuana, benzodiazepines tattoos and high-risk sexual behavior, diagnosed with HIV nine years ago, treated with antiretrovirals which suspended two years ago. Begins 3 months before with malaria, a week prior to his admission presented progressive dyspnea on moderate to high stresses accompanied by productive cough and fever. Chest radiogram showed fine intestinal infiltrate, compatible with pneumocystis jiroveci, laboratories: HBv 4.9g/dl, creat 3.0 mg/dl, BUN 350 mg/dl, urine protein 4.7g/24 hrs, the urinalysis reported reddish urine, with granular casts, hematuria and pyuria. Hepatitis B, Hepatitis C, CMV and tuberculosis tests were all negative and the renal ultrasonography was normal. Renal biopsy revealed IgA nephropathy.

Direct immunofluorescence technique (400X).Mesangial granular staining (+) for IgA. Early treatment with anti-proteincuric general measures and prednisone improved renal function with a decreased in creatinine to 1.3mg/dl.

Discussion: The immune complexes associated nephropathy in patients with HIV is more common due to the start of antiretroviral therapy, however IgA nephropathy remains uncommon in this patients. In our patient the indication for renal biopsy was the erythrocyturia and the proteinuria in nephritic range. Early detection and treatment can prevent progression to ESRD.

SA-PO076

Ketorolac Induced Mesangiolysis: A Clinical Example of Anti-Thy 1.1

SA-PO077

IgA Nephropathy in HIV Positive Patient with Acute Kidney Injury
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1Nephrology, Rutgers-New Jersey Medical School, Newark, NJ; 2Nephrology, Centro Hospitalar do Algarve, Faro, Portugal.

Introduction: NSAIDS are known cause of acute kidney injury, but do not usually cause glomerulonephritis. We share an unusual presentation of glomerulonephritis after only one dose of ketorolac. No renal biopsy findings in acute ketorolac-related acute kidney injury appear to have been published based on an Ovid literature search.

Case Description: This is a 42 year old male with past medical history of nephrolithiasis and urethral stricture, who presented to the hospital for a cystoscopy procedure. The patient had urinary obstruction after the procedure and developed oliguric acute kidney injury with serum creatinine of 3.1 mg/dl (baseline 0.8 mg/dl). Of note, the patient also received one dose of ketorolac during the procedure. Urinalysis showed 2+ blood with many red blood cells, and 9 grams of proteinuria as TP/creatinine ratio. Lab work demonstrated high LDH, low haptoglobin but stable hematocrit and platelet count. Peripheral smear did not reveal schistocytes. Urine microscopy showed RBC casts. Renal ultrasound showed normal sized kidneys with no hydronephrosis. Kidney biopsy revealed acute tubule-interstitial nephritis with tubular necrosis and mesangiolysis. Electron microscopy showed patent capillary loops with focal epithelial foot process effacement, visceral epithelial cells with cytoplasmic vacuolization, dilated capillaries with endothelial apoptosis and mesangial lysis. Glomerular basement membrane thickness was increased. There was evidence of acute tubular injury. No electron dense deposits, thrombosis or crescents were identified. Immunofluorescence of glomeruli was negative. The patient remained oliguric and required renal replacement for short term followed by full recovery of renal function.

Discussion: Renal toxicity of ketorolac has been described, and appears generally to be reversible, but could lead to glomerulonephritis in a rare setting. The pathological findings in the glomeruli resembled those described in experimental animals with Thy-1 induced glomerulonephritis treated with rofecoxib (COX-2 inhibitors). In this model, glomerular disease is initiated by immune-mediated mesangial cell damage, resulting in mesangiolysis.

SA-PO077

Disseminated Cytomegalovirus Disease in Induction Treatment with Mycophenolate Mofetil in a Lupus Nephritis Patient

Introduction: Mycophenolate mofetil (MMF) is an immunosuppressive agent that exerts relatively selective antiproliferative effects on T and B lymphocytes and is increasingly being associated with higher incidence of tissue-invasive cytomegalovirus (CMV) disease in transplant receivers and other immune-mediated diseases. The case presented is a patient who developed CMV enteritis while receiving MMF and corticosteroids for lupus nephritis (LN).

Case Description: 59 year-old man with LN class IV (Ga) + V under MMF (2.5g/day) and prednisolone (60mg/day) when started having weight loss, diarrhea, nausea, dysphagia and haematochezia. The blood count showed severe anemia and leucopenia. Comprehensive chemistry profile revealed Pcr 2.7mg/dl improving proteinuria from 11.7 to 2g/day and normal urinary sediment. CMV serology IgM came positive (PCR CMV: 834 copies/mL). Immunology tests were negative. Upper endoscopy and colonoscopy were performed. Biopsies showed CMV infection signs and esophageal candidiasis. MMF was tapered to 1g/day and prednisolone to 20mg/day. The patient was started on intravenous ganciclovir

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Underlines represent presenting author.

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and fluconazole, with favorable clinical response. Proteinuria then worsened to 7.9g/day. Renal biopsy was repeated showing collapse of LN class V. Renal function improved PCR 1.6mg/dl having 2g MMF and prophylactic oral valganciclovir. CMV virus directly infects the bowel causing mucosal erosions or ulcerations. We can only find little evidence that CMV disease explains the gastrointestinal adverse event profile associated with MMF but we bring up again the hypothesis that high local concentrations of MMF have a direct toxic effect on cells of the small intestine, causing gastrointestinal upset. Associated with MMF but we bring up again the hypothesis that high local concentrations of MMF have a direct toxic effect on cells of the small intestine, causing gastrointestinal upset. Data on the incidence of CMV disease with the MMF induction protocol for LN are scarce.

Discussion: Similarly to transplant recipients receiving MMF, LN patients presenting gastrointestinal upset demand exclusion of CMV infection. This report highlights the importance of clinical follow-up of lupus patients with GI symptoms undergoing intense immunosuppression and accurate serological and histological diagnosis.

SA-PO078
Cryoglobulinemic Nephropathy with Successful Childbirth After Recurrent Episodes of Nephrotic Syndrome During Pregnancy Miho Karube, Shinya Kaname, Kazuhiro Fukuda, Hideki Shimizu, Yoshinori Komagata, Yoshihiro Arimura. The First Dept of Internal Medicine, Kyorin Univ School of Medicine, 6-20-2 Shinkawa Mitaka-city, Tokyo, Japan.

Introduction: It is unknown whether pregnancy affects clinical course of cryoglobulinemic nephropathy and how to treat pregnant patients complicated with it.

Case Description: A 35-year-old woman was admitted to our hospital because of massive proteinuria that developed during the third pregnancy. The previous two pregnancies had been terminated for similar episodes of nephrotic syndrome. No history of hypertension was observed, but during the course she presented cryoglobulinemia, a high titer of RF and low serum complement levels. The renal biopsy performed 10 days after the third termination revealed MGN-like lesions with lobulation in glomeruli, double contour of GBM, endotheliosis, and moderate mesangial cell proliferation. Immunofluorescence study showed IgG, IgA, IgM, C3, C4, and C1q all positive mainly along the glomerular capillaries, and subendothelial deposits were confirmed by EM, thus she was diagnosed as cryoglobulinemic nephropathy. Because the histological findings of repeated renal biopsies were not improved two months after the disappearance of proteinuria, treatment with 30 mg/day of PSL was started, followed by intravenous cyclophosphamide 6 times and plasma exchange, since she had a desire for baby. Finally at the fourth pregnancy, she bore a healthy baby weighing 2.342g on vaginal delivery at 36 weeks despite of recurrent appearance of nephrotic syndrome. After delivery, she was given 30 mg/day of PSL and proteinuria subsided.

Discussion: We experienced a rare case of type III cryoglobulinemic nephropathy that repeatedly developed nephrotic syndrome during pregnancy, but finally bore a baby after immunosuppressive therapy. Although the pathogenesis of pregnancy-induced exacerbation of cryoglobulinemic nephropathy was not clear in this patient, aggressive treatment may have been helpful for ameliorating it, leading to successful delivery.

SA-PO079
Renal Recurrence of Acute Lymphatic Leukemia Anna Bertram, Jan H. Brasek, Ansgar Reising. 1Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany; 2Pathology, Hannover Medical School, Hannover, Germany.

Introduction: Renal complications of hematologic neoplasia can be therapy- or neoplasia-associated. We report a case of acute kidney injury (AKI) in the long term follow-up of a patient with acute lymphatic leukemia (ALL).

Case Description: The 42y old patient was diagnosed with ALL in 2009 and treated according to recommendations with chemotherapy and peripheral blood stem cell transplantation. In 2012, extramedullary ALL recurrence in his right knee was treated with irradiation. Starting from September 2014, molecular markers of minimal recurrence without evidence of lymphoblasts were found in bone marrow biopsies, and the patient received donor lymphocytes to induce graft vs. host reaction. In December 2014, ramipril was started for newly diagnosed hypertension, after which creatinine increased within several days to 290µmol/L. Because of this association, we suspected renal artery stenosis, toxic AKI, or acute interstitial nephritis. Ultrasound revealed diffusely swollen and dense kidneys (Fig.1A). Renal artery stenosis could be excluded, but - untypical for interstitial nephritis - segmental arteries seemed compressed. Kidney biopsy revealed ALL recurrence with extensive lymphoblast infiltration. DOTA-CXCR4-PET-CT confirmed diffuse infiltration of both kidneys (Fig.1B) without bone marrow affection. After starting chemotherapy, creatinine rapidly ameliorated. Ultrasound and PET-CT-controls 10 weeks after starting therapy confirmed good treatment response (Fig.1C-D).

SA-PO080
A Rare Cause of Acute Kidney Injury in Non-Renal Solid Organ Transplantation Sameer Gupta, Wasay Humayun, Ramapritya Sinnakruchanen, Liliana Osadchuk. Nephrology, Medical College of Wisconsin, Milwaukee, WI.

Introduction: Acute kidney injury (AKI) is a frequent complication of non-renal solid organ transplantation (SOT). Here we report a case of rapidly progressive renal failure leading to end stage renal disease (ESRD) due to acute oxalate nephropathy (AON) in a patient with non-renal SOT.

Case Description: A 63 year old female with past history of pulmonary fibrosis status post bilateral lung transplant, obesity status post Roux en Y gastric bypass (RYGB) surgery, and hypertension presented with worsening kidney function with BUN and creatinine of 55 mg/dl and 6.18 mg/dl respectively. She had normal kidney function with serum creatinine of 0.5mg/dl prior to transplant 8 months ago. Induction regimen included Basiliximab followed by tacrolimus, prednisone and mycophenolate (MMF) as maintenance therapy. Ensuing transplantation, she had multiple episodes of AKI attributed to calcineurin inhibitor (CNI) toxicity and hypovolemia from MMF and clostridium difficile associated diarrhea. Her average tacrolimus trough level was 12 ng/mL. Several urinalyses showed acute tubular necrosis casts. Renal ultrasound revealed bilateral echogenic small kidneys compared to normal kidney size prior to transplant. Her kidney biopsy unexpectedly revealed oxalate nephropathy. She is currently on hemodialysis.

Discussion: AON has been poorly described in patients with RYGB surgery and SOT. In our patient with prior RYGB, chronic diarrhea, and numerous antibiotics unulled AON. This superimposed with CNI toxicity resulted in rapid progression to ESRD. Antibiotic use depletes colonization of oxalate consuming bacteria (Oxalobacter formigenes). This combined with fatty acid malabsorption from prior RYGB increases colonic oxalate absorption resulting in hyperoxaluria. Diarrhea causes hypovolemia and metabolic acidosis leading to low urinary pH and hypocitraturia promoting calcium oxalate crystallization. Additional steps should be taken for SOT patients with RYGB, like diet modification, probiotic use, citrate supplementation, administration of fatty acid binding agents, and monitoring for hyperoxaluria. High suspicion for AON in patients with risk factors may lead to early diagnosis and treatment.

SA-PO081
Paraneoplastic Membranous Nephropathy and Myelodysplastic Syndrome – A Rare Combination Krishna K. R. Manoh, Madhuri Manne, Dagmar Klinger. Renal Medicine, Univ of Massachusetts Medical School, Worcester, MA.

Introduction: We report a case of Membranous Nephropathy (MN) seen in association with Myelodysplastic Syndrome (MDS). This occurrence is rare and only 3 cases have been reported in literature previously. Up to 5-20% of adults with MN have been reported to have most commonly a solid tumor and less frequently, a hematologic malignancy.

Case Description: Our patient is a 58 y/o man who has chronic kidney disease of unclear etiology with serum creatinine (SCr) of 1.3 and MDS. He was admitted with acute kidney injury in the setting of pneumonia and had nephritic range proteinuria along with dysmorphic red blood cells on the urinary sediment. Renal biopsy showed MN with relatively recent immune complex deposition. There was no colocalization of IgG4 membranous deposits with phospholipase A2 receptor. He was hospitalized again with pancytopenia, marked inflammatory markers and infectious complications. Although bone marrow biopsy was not diagnostic, this syndrome was diagnosed as hemophagocytic
lymphohistiocytosis by clinical criteria and therapy was initiated with high-dose steroids and etoposide. The patient's serum Cr peaked at 1.02 mg/dL and was gradually tapered to 5 mg over 1 month and he was discharged with sCr of 1.39 mg/dL. 5 days after the operation of fracture, he was referred to the nephrology clinic for evaluation of renal dysfunction.

**Case Description:** A 73-year-old male was admitted because of subtrochanteric fracture. On admission, he had normal kidney function with serum creatinine (Cr) level of 1.02 mg/dL. 5 days after the operation of fracture, he was referred to the nephrology department due to abruptly increased level of Cr. On postoperative day 10, despite adequate intravenous hydration, he became anuric and Cr rose to 4.40 mg/dL requiring hemodialysis. Serum C3 level was low (38mg/dL). Kidney biopsy revealed mesangiocapillary glomerulonephritis, duplication of the glomerular basement membranes, subendothelial deposits and predominant C3 immunofluorescent staining suggestive of MPGN type I. Secondary causes such as infection, autoimmune disease, monoclonal gammapathy, neoplasia, complement dysregulation were excluded. He was diagnosed as idiopathic MPGN type I and high dose steroid therapy (40mg/day of prednisolone) was started. After 17 days of therapy, urine output was increased and dialysis was discontinued accordingly. Prednisolone was gradually tapered to 5mg over 1 month and he was discharged with sCr of 1.39 mg/dL.

**Discussion:** The early trials of the treatment of idiopathic MPGN have given inconsistent results, and should be interpreted with great caution since many of the reports likely included cases of secondary MPGN. The clinical presentation of MPGN is variable, from benign and slowly progressive to rapidly progressive, and different therapeutic approaches should be applied in regard of the disease course. Studies are needed to identify the natural course and effective treatment of MPGN.

**SA-PO084**

**A Case of Advanced IgG4 Related Tubulointerstitial Nephritis Complicating Multiple Lymphadenopathy and Intrathoracic Nodule, Mimicking Malignant Lymphoma**

**Case Description:** A 56 year old Caucasian man with history of colon tubular adenoma, NHL - status post chemotherapy and radiation 30 years back, hypothyroidism presented with new-onset nephrotic-range proteinuria. He was not taking any medications and physical examination noted generalized edema. Laboratory exam noted elevated serum creatinine (1.5 mg/dL) and proteinuria (2.4 g/dL). Blood work up for autoimmune and neoplastic causes of membranous nephropathy was negative. Proteinuria worsened to 11 g/24h despite six months of conservative therapy with lisinopril and low protein diet. Additional labs obtained came back positive for PLA2R autoantibodies (IFA 1:1000, ELISA 976.6 RU/ml). Kidney stained positive for PLA2R glomerular deposits suggesting IMN. The patient was then treated with a modified Ponticelli protocol using alternating monthly prednisone and oral cyclophosphamide (2 mg/kg/d) for six months. After three months, proteinuria, albumin and edema improved.

**Discussion:** Relying on histopathologic differentiations to distinguish between idiopathic and secondary membranous nephropathy may lead to incorrect diagnosis and delay in treatment. The presence of circulating and tissue PLA2R autoantibodies may be more relevant to new-onset nephrotic-range proteinuria. It is unclear whether tissue anti-PLA2R antibodies are more specific in the diagnosis of IMN than serum antibodies. The clinical significance of the presence of circulating anti-PLA2R antibodies remains to be determined.

**SA-PO085**

**Presence of PLA-2R Autoantibodies in a Patient with Clinical and Histopathological Evidence Suggestive of Secondary Membranous Nephropathy**

**Case Description:** A 56 year old Caucasian man with history of colon tubular adenoma, NHL - status post chemotherapy and radiation 30 years back, hypothyroidism presented with new-onset nephrotic-range proteinuria. He was not taking any medications and physical examination noted generalized edema. Laboratory exam noted elevated serum creatinine (1.5 mg/dL) and proteinuria (2.4 g/dL). Blood work up for autoimmune and neoplastic causes of membranous nephropathy was negative. Proteinuria worsened to 11 g/24h despite six months of conservative therapy with lisinopril and low protein diet. Additional labs obtained came back positive for PLA2R autoantibodies (IFA 1:1000, ELISA 976.6 RU/ml). Kidney stained positive for PLA2R glomerular deposits suggesting IMN. The patient was then treated with a modified Ponticelli protocol using alternating monthly prednisone and oral cyclophosphamide (2 mg/kg/d) for six months. After three months, proteinuria, albumin and edema improved.

**Discussion:** Relying on histopathologic differentiations to distinguish between idiopathic and secondary membranous nephropathy may lead to incorrect diagnosis and delay in treatment. The presence of circulating and tissue PLA2R autoantibodies may be more relevant to new-onset nephrotic-range proteinuria. It is unclear whether tissue anti-PLA2R antibodies are more specific in the diagnosis of IMN than serum antibodies. The clinical significance of the presence of circulating anti-PLA2R antibodies remains to be determined.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO086
Silent Malakoplakia in a Recipient of Kidney-Pancreas Transplant
Diagnosed on Surveillance Biopsy of Kidney Allograft: A Patient-Centered Approach to Treatment of Malakoplakia

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Introduction: Malakoplakia is an inflammatory disease leading to chronic morbidity and organ dysfunction. It was originally described in association with genitourinary tract infections with coliform bacteria and can manifest as acute pyelonephritis, acute or chronic renal failure, or renal mass. We present a case of a 40-year-old female recipient of simultaneous pancreas-kidney transplant who developed an acute rise in serum creatinine without apparent cause and found to have malakoplakia on kidney allograft biopsy. Patient was started on treatment to reverse of allograft dysfunction and resolution of histological features of malakoplakia.

Case Description: 40-year-old Caucasian female with type 1 diabetes mellitus and end-stage renal disease on peritoneal dialysis underwent SPK transplant. After induction with thymoglobulin, she was maintained on tacrolimus and mycophenolate mofetil. Two months later, she was treated for acute T-cell mediated rejection (Banff Grade IA) with thymoglobulin. Serum creatinine returned to baseline and maintenance prednisone was added to her regimen. Her posttransplant course was complicated by multiple infections including parvovirus B19 infection, primary CMV infection, two episodes of urinary tract infections, and influenza A pneumonia. Due to an increase in serum creatinine without apparent cause, a kidney allograft biopsy was performed which revealed lesions consistent with malakoplakia.

Discussion: Treatment of malakoplakia in kidney transplant recipients is not well established but include surgical resection and use of antimicrobial agents. In the era of cyclosporine and azathioprine, it was speculated that the use of azathioprine may be associated with the development of malakoplakia. Discontinuation of azathioprine was shown to improve more bactericidal activity of mononuclear cells. This case report illustrates that in the era of immunosuppression with tacrolimus and mycophenolate mofetil, the maintenance therapy with tacrolimus may be continued while treating for malakoplakia.

SA-PO087
Common Weight Loss Medication Pill—“Qsymia” Causing Hypokalemia and Renal Tubular Acidosis

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Introduction: The obesity epidemic is growing. Aside from the traditional diet and exercise, weight loss pills are more commonly prescribed. Qsymia is one such weight loss pill consisting of topiramate and phentermine. We report potentially life threatening side effects of Qsymia causing severe hypokalemia, proximal renal tubular acidosis (pRTA), and cardiac dysrhythmia.

Case Description: A 68 year old female with history of hypertension presented with complaints of tingling of her left arm and jaw of one day duration. Her home medications included Aspirin and Hyzara (Losartan and Hydrochlorothiazide). She had self discontinued the Hyzara five days prior to presentation. Patient was recently started on the weight loss medication “Qsymia” three months prior. She denied any alcohol use. On initial presentation, she was noted to be in atrial fibrillation (HR 150s) and hypotensive (BP 84/43 mmHg). Urinalysis showed pH 8 with glucosuria. Urine Lytes showed potassium 38 mmol/L, chloride 43 mmol/dL, and sodium 141 mmol/L.

Discussion: It was suggested that patient’s clinical presentation and electrolyte disorders were due to the weight loss medication, and Qsymia was discontinued. Qsymia was approved by FDA in 2012 for weight loss. Most common side effects reported include paresthesia, dizziness, insomnia, constipation and dry mouth. In the U.S., drug label contains warnings for increased heart rate. Topiramate is known to cause pRTA. Our patient had mild acidoses, hypophosphatemia and glucosuria which we believe was a result of an early pRTA, induced by topiramate. Although hydrochlorothiazide is known to cause hypokalemia, our patient was not taking the medication for five days.

Weight loss medications are now being more commonly used to treat obesity. Prescribers should be aware of the potential nephrotoxic side effects of Qsymia. Monitoring serum potassium and bicarbonate levels regularly should be taken into consideration.

SA-PO088
Multiple Myeloma as the Underlying Cause of Thrombotic Microangiopathy

Venkata Buddharaaju, Liga Yusvirazi, Anastasios Papagou, Savneek S. Chugh, Rahul N. Pawar. Nephrology, Westchester Medical Center, Valhalla, NY.

Introduction: Thrombotic microangiopathy (TMA) describes a pathological process of microvascular thrombosis, consumptive thrombocytopenia and microangiopathic hemolytic anemia, leading to end-organ ischemia and infarction affecting particularly the kidney and brain. TMA is a pathological feature of a number of clinical disorders including Hemolytic uremic syndrome (HUS) and atypical HUS. Rare but important, TMA may also occur in malignancy, connective tissue disease, malign ant hypertension, and renal transplantation (rejection or drug toxicity). We present a rare case where patient developed AKI from TMA but found to have plasma cell dyscrasia as possible underlying etiology.

Case Description: A 42 y/o man with h/o myopathy, questionable mixed connective tissue disorder on prednisone and celiectomy, Pulmonary Hypertension on home oxygen, CHF with preserved EF and Anemia requiring multiple transfusions went to an outside hospital with SOB and pedal edema found to have AKI with serum creatinine of 4 and 2x proteinuria. Serologies were negative except for anti-RNP and ESR, with no improvement in renal function the patient had a renal biopsy which showed TMA, mild fibrosis and atherosclerosis. The patient was started on RRT and then transferred to Westchester medical center for treatment with Eculizumab for atypical HUS. After reviewing the labs we ordered Serum and urine protein electrophoresis which showed monoclonal IgM spike, the patient underwent bone marrow biopsy which showed Plasmacytoma with 18% Plasma cells. The patient’s renal function improved in the hospital stay and stabilized with creatinine of around 2.0 mg/dL, but unfortunately the patient had a severe sepsis and passed away before initiation of management for Multiple myeloma.

Discussion: Multiple Myeloma accounts for 10% of hematological malignancies. Atleast 50% of patients with MM have evidence renal insufficiency and more than 80% have proteinuria. Multiple myeloma can present as has wide range of renal manifestations including myeloma cast nephropathy, Immune deposition disease, CKD Fanconi syndrome. Though rare Multiple myeloma can cause TMA and the Pathogenesis still remains unclear.

SA-PO089
Drug-Induced Acute Interstitial Nephritis Managed with Early and Aggressive Steroid Therapy


Introduction: Pantoprazole (PPZ), a Proton Pump Inhibitor, is known to cause acute interstitial nephritis (AIN). We report a case of PPZ induced AIN in a young adult with just 3 doses of drug exposure.

Case Description: A 21 year old Asian American male with no past medical history was sent to the hospital by his Internist for elevated serum creatinine (Scr). He had nausea and abdominal pain 3 weeks earlier and was prescribed PPZ, which he took for 3 days. He denied use of any other medications including herbal supplements and NSAIDS. Laboratory data showed BUN of 82 mg/dL, Scr 15 mg/dL (baseline 6.6), bicarbonate of 15 mmol/L and normal electrolytes. Urine showed sterile pyuria with no cosinophils, glycosuria with normal blood glucose, mild proteinuria (900mg/24 hrs). Serum and urine toxicology, protein electrophoresis, auto-immune work up were unremarkable. A Renal biopsy revealed diffuse expansion of the interstitium due to accumulation of cellular infiltrates consisting of lymphocytes, plasma cells and eosinophils with accompanying tubulitis consistent with AIN.

He received pulse steroids for 3 days and was continued on prednisone 1mg/kg/day with a plan to taper over 8-12 weeks. He required a few sessions of renal replacement therapy before his renal function started to recover, 6 weeks later his Scr was 1.4 mg/dL.

Discussion: Any drug can cause AIN, although the categories of antibiotics, diuretics and NSAIDs are most commonly implicated. Drug-induced AIN is not dose dependent, and recurrence can occur with a second exposure to the same or a related drug. The data on time of initiation, dosage and duration of steroids in drug induced AIN is limited due to lack of randomized control trials. On review of literature and our experience, we conclude that stopping the culprit agent and early steroid use confers better prognosis in drug induced AIN.

SA-PO090
Metastatic Sarcomatoid Carcinoma of Urothelial Origin in Failed Renal Allograft

Venkata Buddharaaju, Rajat Lamba, Daniel G. Glicklich. Nephrology, Westchester Medical Center, Valhalla, NY.

Introduction: Renal cell carcinomas are more common in ESRD than the general population and renal transplant patients with enhanced longevity may be at particular risk. Sarcomatoid renal cell carcinomas represents 1-15% of all renal cell carcinomas but has been very rare among described cases in renal allograft. The median age at diagnosis is 16 years with 45-77% of patients with locally advanced or metastatic disease at the time of diagnosis. We describe a case sarcomatoid tumor of urothelial origin in a transplanted renal allograft.

Case Description: A 54 y/o man with ESRD from polycystic kidney disease, HTN, aortic dissection repair, mechanical AVR, paroxysmal AFB, who had 2 failed renal transplants in the past and was on dialysis for past 12 years, was admitted for left lower quadrant pain, fever and leukocytosis for which he was started on vancomycin and
astreamet. On imagine, he was found to have a mass around the left transplant kidney, ascites, omental caking, retroperitoneal lymphadenopathy and heterogeneous liver lesions. Retroperitoneal lymph node biopsy and ascitic fluid cytology was negative for malignant cells. Left kidney mass could not be biopsied because of technical difficulties and he had biopsy of the liver lesions which showed sarcomatoid tumor. He developed respiratory failure and septic shock requiring pressor support and expired. An autopsy was performed which showed Metastatic Sarcomatoid carcinoma of urethral origin.

Discussion: Malignancy in post transplant is related to direct effects of immune-suppressants as well as their effects to suppress immune surveillance and to stimulate the activation of oncogenic viruses. It is generally recommended that patients on the active transplant list and renal transplant recipients be screened every several years for renal tumors. However after allograft failure, it is unclear how often to do cancer screening tests. Although in this particular case it is unclear whether screening would have made a difference in outcome, we recommend routine screening for renal cell carcinoma even if the renal allograft has failed.

SA-PO091
Parathyroidectomy on a Patient with Sickle Cell Disease and End Stage Renal Disease
Farid Ilpakil, Mary C. Mallappally, David Kau, Moro O. Salifu. Sunny Downstate Medical Center, Brooklyn, NY.

Introduction: Patients with End Stage Renal Disease (ESRD) can develop elevated parathyroid hormone (PTH) levels with hypercalcemia. Some fail or cannot tolerate medical therapy. They eventually require parathyroidectomy. Tertiary hyperparathyroidism (3PTH) is the autonomous function of the parathyroid gland due to increased mass. Our case is unique as there are no reported cases of tertiary hyperparathyroidism in sickle cell patient, whereas 3PTH was found in renal osteodystrophy in sickle cell crisis which worsened with parathyroidectomy. 25 year old man with sickle cell disease, ESRD on hemodialysis since 2012, (3HTP), presents after many admissions for sickle cell pain crisis. Cause of ESRD was unknown but attributed to sickle cell nephropathy. Current admission for knee pain, imaging showed 36 x 27 x 26 mm mass, with enhancing right kidney mass with parathyroid adenomas. "Sustained scan: "equivocal slow washout focus in region of right lower pole of thyroid gland extending posteriorly. Suspicious for but not definitive for parathyroid adenoma". On the day prior to surgery, PTH (3PTH) was 4078 pg/ml with serum calcium (Ca)=10.3 mg/dL. Immediately after surgery, a 265 pg/ml sample showed Ca=8.9 mg/dL. The first day after surgery, PTH (3PTH)=36 pg/ml with Ca=7.6 mg/dL. Patient admitted for 3 days due to his requirement of intravenous calcium and daily hemodialysis. Since discharge, patient has had fewer admissions for pain. He has however, remained hypocalcemic and is on 5 grams of calcium carbonate, 4 mcg of doxercalciferol, and is dialyzed with a 3 mEq NaCl bath.

Discussion: 3PTH is common in ESRD patients that can leave them debilitated. Those who fail medical therapy may benefit from resection. In sickle cell disease symptoms of 3PTH was masked by vaso-occlusive crises and could be distinguished by marked reduction in symptoms after resection.

SA-PO092
Synthetic Cannabinoids (SC) in End Stage Renal Disease. Chyi Chyi Chong, Pallavi D. Shirsath,1 Ramesh Marahatta,1 Neville R. Dossabhoy.2 1LSU Health Science Center, Shreveport; 2VA Medical Center, Shreveport.

Introduction: Synthetic cannabinoids (SC) are drugs of abuse especially among young adults. They are affordable, widely available and mostly importantly undetectable by standard urine toxicity screen. The avoidance of detection in the urine contributes to their allure and abuse. Acute kidney injury (AKI) related to synthetic cannabinoids has been reported. However, effect of synthetic marijuana in end stage renal disease (ESRD) patients remains unknown.

Case Description: We present a case of severe high anion gap metabolic acidosis (HAGMA) with acute respiratory failure in an ESRD patient. A 37-year-old African American female with ESRD, hepatitis C and hypertension was found smoking synthetic marijuana under a tree, and in a confused state. Upon arrival to the emergency room, the patient was severely hypertensive with blood pressure of 230/140 mmHg, and subsequently developed acute respiratory failure requiring intubation. Chest x-ray showed bilateral pulmonary edema. Laboratory data revealed: WBC 18K/uL, Na 138 mEq/L, K 3.6 mEq/L, Cl 104 mEq/L, CO2 10 mEq/L, Anion Gap 24. On Blood Gas: pH 6.95, pCO2 42 mmHg, pO2 73 mmHg, HCO3 8.3 mmHg. Urine drug screen was positive for benzodiazepine and marijuana. On Admission: creatinine 2.1 mg/dL, Na 138 mEq/L, K 3.6 mEq/L, Cl 104 mEq/L, CO2 10 mEq/L, Anion Gap 24. On Blood Gas: pH 6.95, pCO2 42 mmHg, pO2 73 mmHg, HCO3 8.3 mmHg. Urine drug screen was positive for benzodiazepine. Ionized calcium was 7.6 mg/dL. 

Discussion: Synthetic cannabinoids are sold under different trade names and the exact effect of SC. SC effect on ESRD patients remain unknown. Our patient developed (HAGMA), which could very well be related to synthetic marijuana use. Physicians should be aware of designer drugs use in ESRD patients.
SA-PO095

Leukocyte Chemotactic Factor 2 (LECT2)-Associated Renal Amyloidosis: A Case Report
Alejandro Pepen Romero, 1 James Drakakis, 1 Joseph Mattana. 1
1Nephrology Dept, Winthrop Univ Hospital, Mineola, NY; 2Pathology Dept, Columbia Univ, New York, NY.

Introduction: ALECT2 amyloidosis is a frequent form of systemic amyloidosis, represents 2.7-10% of all cases of renal amyloidosis. Most patients are elderly who presents with chronic renal insufficiency and bland urinary sediment.

Case Description: We report a 76-year-old Egyptian male who presented after a recent hospitalization for self limited gastroenteritis and severe acute renal failure presumed secondary to acute tubular necrosis. Due to non-improving renal function and uremic symptoms, renal biopsy was done and showed patchy Interstitial amyloidosis deposits that did not stain for IgG, IgM, IgA, Kappa, Lambda chains or Amyloid A; sample was sent to Mayo Clinic where Liquid chromatography tandem mass spectrometry detected a peptide profile consistent with ALECT2 Amyloidosis.

Discussion: This case suggests that ALECT2 Amyloid can present with bland uroanalysis and non-nephrotic range proteinuria in elderly patients.

SA-PO096

Monitoring Disease Activity in ANCA Associated Vasculitis (AAV): A Case for Activated Circulating Monocytes? Florin Gunnar Scurti, 1 Leon Brian Schubert, 2 Noemi Rose Emma Doll, 2 Marius Früh, 2 Tobias Hilscher, 2 Andreas Jeros, 1 Dunja Bruder, 2 Peter R. Merz, 1 Christos D. Chatzikyriou, 1 Nephrology, Hypertension, Diabetes and Endocrinology, Otto-von-Guericke Univ Magdeburg; 1Inst of Microbiology, Otto von Guericke Univ Magdeburg.

Introduction: We are still in need for more reliable markers to monitor disease activity in AAV.

Case Description: The clinical course of a patient with therapy refractory AAV is presented.

Disease activity was assessed by means of the BVAS and VDI score and by serial measurements of the CD19/CD20 cell count and the MPO titer. The last renal flare was on 11/2014 and was corroborated by renal biopsy. Monocyte subsets were also identified by flow cytometry with the use of the surface markers CD14, CD16, CCR2 and CxCR3.

The expression of different proteins reflecting antigen presentation or activation status as well as scavenger receptor and toll like receptor functions was quantified in the monocyte subpopulations. Blood samples of a healthy individual were used as controls. Results of the antigen presentation marker HLA-DR and the monocyte activation marker CD11b are presented here.

Renal and pulmonary disease progressed despite the use of an impressive immunosuppressive therapy. The CD19/CD20 cell count and the MPO titer did not predict relapse. The intermediate CD14+CD16+CCR2lowCXCR1++ monocyte subpopulation was increased but expressed less of the HLA-DR protein. The CD11b antigen expression was increased in the classical monocyte subpopulation CD14+CD16-CCR2highCXCR1++, whereas no differences in the HLA-DR and CD11b expression were observed in the non-classical monocyte subpopulation CD14+CD16+CCR2lowCXCR1+high.

Discussion: There appear to be functional alterations in the different monocyte subpopulations during relapse of AAV. Their pathophysiologic significance remains to be elucidated.

SA-PO097

A Case of Rhabdomyolysis Induced AKI with Two Questions: Serum Myoglobin versus CPK and the Potential Role for Rasburicase Mehd Nouri kolouhi. Nephrology, Baylor College of Medicine, Houston, TX.

Introduction: Rhabdomyolysis induced AKI is a common scenario. The mechanisms include myoglobin and uric acid crystal induced tubular injury. The role of uric acid lowering agents in such conditions remains to be defined. Here we describe such a case, in which uric acid lowering agent successfully lowered uric acid level and possibly contributed to renal function recovery. In this case CPK level was not high enough to justify AKI and a very high serum myoglobin level established the diagnosis.

Case Description: A 37 years old man without known history was brought to ER with agitation and delusional-combative behavior. Vital signs included temp=100.4, BP=165/85, RR=12/min, HR=110/min. On examination, he was mildly volume depleted. On lab work, it was found to have AKI with BUN=76, Cr=4, K=6.7 and metabolic acidosis. Urine toxicology was positive for amphetamines. CPK level was 4200 U/L and uric acid level was 21 mg/dL. Supportive management including aggressive IV fluids was initiated for amphetamine toxicity with favorable outcome. Urine exam showed hematocrit casts. Serial CPK levels were not high enough to justify AKI. However serum myoglobin level was very high at >20000 ng/mL and confirmed severe rhabdomyolysis. one session of dialysis was done due to persistent metabolic acidosis and hyperkalemia. However uric acid level remained high at same range. We used a dose of Rasburicase at 3 mg which reduced uric acid level to 5.5 six hours later. After few days, renal function and clinical status started to improve and he was discharged in stable condition.

Discussion: There may be a therapeutic/ prophylactic role for uric acid lowering agents in rhabdomyolysis induced AKI. In our case, Rasburicase successfully lowered uric acid level after it had remained high post-dialysis. Similar results have been reported in the past, however further research is needed in the future. Besides, Although AKI in rhabdomyolysis is usually seen with CPK levels>20000, our patient had much lower levels and a very high serum myoglobin established the diagnosis of severe rhabdomyolysis. Serum myoglobin is more accurate to determine the severity of rhabdomyolysis and predict the risk of AKI.

SA-PO098

Exploring the Utility of Albuminuria in the Setting of Acute Renal Failure
treated with Peritoneal Dialysis: Is There a Role for Albuminuria in the Management of Acute Renal Failure?
Romero 1

Discussion: The current case indicates that a higher degree of albuminuria relative to Cr is needed to confirm severe rhabdomyolysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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underline represents presenting author.

**SA-PO100**

Post Renal Transplant Follow Up in Focal Segmental Glomerulosclerosis with 24 Hour Urine Protein Collection – Traditional and True


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**Introduction:** Random Urine Protein Creatinine Ratio (PCR) is commonly used to estimate proteinuria compared to 24 hour urine protein measurement (24-UP). However, there are concerns over the diagnostic accuracy and reliability of such an approach in post-transplant setting. We present a case of post-transplant focal segmental glomerulosclerosis (FSGS) illustrating this.

**Case Description:** A 39 year old male with primary FSGS, on peritoneal dialysis for 4 years received a cadaveric kidney transplant. His panel reactive antibody was 0% and HLA cross-match was negative. Peri-operative course was uneventful. Given the history of FSGS, PCR was monitored. By post-op day 5, serum creatinine had decreased from 7.3 mg/dl to 3.2 mg/dl and PCR from 4.3 to 2.8. However, his 24-UP came back 8 g, which was markedly different.

<table>
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<th>Days since transplant</th>
<th>Serum Creatinine (mg/dl)</th>
<th>PCR</th>
<th>24-UP (g/24 hrs)</th>
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Early recurrence of FSGS was diagnosed. A biopsy was withheld to avoid delay in timely management and risk of bleeding with plasmapheresis which was immediately initiated. He was switched from tacrolimus to cyclosporine. He required plasmapheresis for 5 weeks and had satisfactory recovery in the ensuing months.

**Discussion:** Logistics have led to the widespread use of PCR in follow-up of kidney transplant recipients. However changing creatinine excretion with recovering renal function, lower precision with heavier proteinuria, and limited data on accuracy compared to 24-UP, potentially limit its utility at detecting early post-transplant recurrence of FSGS. Our case highlights marked discordance between the PCR and 24-UP, detection of which allowed a timely change in management. We conclude that it is prudent to monitor proteinuria by timed urine collection in preference to random PCR in the immediate post-transplant setting for recipients with primary FSGS.

**SA-PO101**

Donor Kidney Lithiasis: A Case of Throwing Out the Baby with the Bathwater?

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**Introduction:** Cadaveric kidneys account for a majority of transplants in the United States. However, only 10% of waitlisted patients receive one annually, making optimal utilization critical. Donor nephrolithiasis represent a small yet significant proportion of kidneys discarded. We present a patient who received such a kidney which otherwise could have been discarded.

**Case Description:** The donor was a healthy 31 year old female who suffered anoxic brain injury in a motor vehicle accident. Her CT abdomen showed 2 stones in the right kidney as represented in the figure’s inset. The kidney became available to us on a regional list after it was declined locally due to concerns over kidney quality. Our recipient was a 50 year old female with hypertensive nephropathy, on hemodialysis for the past 2 years. Her panel reactive antibody was 90% and HLA cross match was negative. Intra-operatively, a large stone measuring 2 cm was identified in the hilum of the donor kidney and was extracted via pyelotomy. A smaller middle calyceal stone was localized by fluoroscopy and successfully removed by irrigation.

**Discussion:** Our case suggests IEP was a transient reaction to the catheter placement rather than a reaction to the PD set or solution.

**SA-PO102**

A Peritoneal Dialysis Catheter Leak Complicated by Burkholderia Gladioli Peritonitis

Ravinder Pal S. Bhatti, Dumitru Rotaru.

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**Introduction:** Dialysate leaks can occur any time after peritoneal dialysis (PD) catheter placement. Early leaks usually manifest as an exit site leak, though may also present with air in the PD catheter. Leaks increase the risk for exit site infections (ESI) and peritonitis. We present such a patient developing peritonitis with an unusual pathogen.

**Case Description:** A 74 year old male who had been on Continuous Cycling Peritoneal Dialysis for 3 years, presented with exit site erythema a week after trying to push in an extruded cuff. Prophylactic antibiotics were started but he declined surgery. The ESI recurred soon after completing 3 weeks of antibiotics. He agreed to catheter replacement with an exit site change. He was started on low volume exchanges. Two weeks later, he noted air bubbles in the PD catheter upon draining.

There were no perioperative complications and the recipient had excellent immediate graft function. Her creatinine progressively improved by time of discharge, remaining normal in subsequent months.

**Discussion:** The new kidney allocation policy aims to address organ shortage by reducing donor and graft survival mismatch. Traditionally, donor hemodynamics, age, serum creatinine and histopathology have influenced decisions on accepting a kidney. The perceived quality and utilization techniques widely vary for deceased donor kidneys with lithiasis. Our case illustrates how this can lead to non-acceptance of an otherwise healthy kidney, which can be transplanted with a favorable outcome.

**SA-PO103**

A rare observation, air in a PD catheter is almost pathognomonic of a dialysate leak. Our case highlights several key points in such a scenario. Firstly, use of sharps is a major risk factor and should be discouraged. Secondly, an increased risk of peritonitis...
including by rare pathogens warrants appropriate antibiotic prophylaxis and lastly a more limited approach than catheter exchange may be used even for leaks close to exit sites based on the location and local experience.

SA-PO103
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Introduction: Acute kidney injury (AKI) after kidney transplantation can occur from myriad of causes. We present an interesting case of a young woman with history of Celiac disease who developed AKI and biopsy-proven oxalate nephropathy within 3 months post-transplantation, as a result of enteric hyperoxaluria associated with gluten noncompliance.

Case Description: A 35 year-old woman with type 1 diabetes mellitus, and celiac disease underwent living unrelated kidney transplantation for ESRD related to biopsy-proven diabetic nephropathy. Her original renal ultrasound did not show nephrocalcinosis. After transplantation, nadir serum creatinine was 1.0 mg/dL. Three months later, she presented with six-day history of diarrhea and AKI. Serum creatinine peaked at 2.6 mg/dL. Since volume replacement did not improve her allograft function and she had high panel reactive antibody levels pre-transplant, a kidney biopsy was performed that showed acute tubular injury with significant oxalate crystalline deposits. Initial serum oxalate level was undetectable, but 24-hour urine oxalate excretion was elevated at 98 mg/dL. Pending gene testing, she was treated with intravenous fluids, low oxalate diet, gluten free diet, vitamin B6, oral alkaI and calcium carbonate. Subsequent gene testing did not reveal an gene mutation in the oxalate pathway. Her urIne output was maintained between 3 to 4L per day. With strict gluten avoidance and low oxalate diet, urine alkalinization and oral calcium, her allograft function has improved to baseline.

Discussion: Celiac disease exacerbation and subsequent malabsorption can lead to significant gut oxalate absorption and hyperoxaluria. Resulting oxalate nephropathy is a rare cause of AKI after kidney transplantation.

SA-PO104
Unusual Presentation of Tumor Related Membranous Nephropathy Tahir Zaman,1 Frederic Clayton,2 Josephine Abraham,1 Nephrology, Univ of Utah, Salt Lake City, UT; 1Pathology, Univ of Utah, Salt Lake City, UT.

Introduction: The literature is laden with evidence of several solid tumors causing secondary membranous nephropathy. It is also described in the literature that solid tumors could also ANA positivity.

Case Description: A 62-year-old male with a history of hypertension presented with oliguric renal failure following an episode of gastroenteritis. History was unremarkable with patient denying smoking or other vices. Urine analysis revealed rare dysmorphic RBC’s and minimal proteinuria (spot protein/creatinine ratio 0.5 gms). Serologic workup revealed +PR3 (ANCA negative) and abnormal Kappa/Lamda Ratio thus renal biopsy was performed, which revealed membranous nephropathy and acute tubular necrosis (ATN). Immunofluorescence was positive for C3, IgG, though negative for PLA-2R, IgA and C1q. ANA was strongly positive (1:10240 speckled pattern), HIV serology was negative. Sublingual mass was found which revealed squamous cell carcinoma. Bone marrow biopsy revealed smoldering multiple myeloma. The patient’s ATN resolved and he subsequently underwent left partial glossectomy. His cancer was staged at T2N0 and he is undergoing chemotherapy and radiation therapy.

Discussion: Secondary membranous nephropathy has a known association with solid tumors. The positive ANA raised the concern of concomitant connective tissue disease. With strict gluten avoidance and low oxalate diet, urine alkalinization and oral calcium, her allograft function has improved to baseline.

SA-PO105
A Case of Severe Adrenal Insufficiency due to Long-Term Glucocorticoid Administration for Pediatric Nephrotic Syndrome Yuko Fujii,1 Akira Ashida,1 Hideki Matsumura,2 Akihiko Shirasu,1 Hyogo Nakakura,1 Motoshi Hattori,2 Hiroshi Tamai,1 1Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; 2Pediatric Nephrology, Tokyo Women’s Medical Univ, Shinjuku, Tokyo, Japan.

Introduction: One of the adverse effects of long-term glucocorticoid therapy in supraphysiologic doses is suppression of the hypothalamic-pituitary-adrenal axis, although symptomatic adrenal insufficiency is considered to be an unusual complication of glucocorticoid therapy for nephrotic syndrome in pediatric patients. Here we describe a case of secondary adrenal insufficiency due to long-term glucocorticoid therapy for steroid-dependent nephrotic syndrome.

Case Description: A 12-year-old boy who had developed steroid-dependent nephrotic syndrome at the age of 2 years had been treated repeatedly with corticosteroid, cyclosporine and mizoribine. On relapse of the disease at 4 years of age, the nephrotic syndrome had been resistant to steroid therapy including 2 mg/kg prednisolone and 4 courses of methylprednisolone pulse therapy, but had responded to additional cyclophosphamide therapy at 7 months after relapse onset. During tapering of the glucocorticoid therapy, the patient had shown various symptoms, including general fatigue, facial edema, decreased urine volume, appetite loss, and dizziness from the age of 5 years. At that time, the basal value of cortisol was not detectable and a rapid ACTH loading test elicited a low response. In the CRH and insulin loading test, the basal value of ACTH was not detectable and an over-response of ACTH was demonstrated. Therefore the patient was diagnosed as having glucocorticoid-induced hypothalamic adrenal insufficiency and treated with cyclosporine, a decreased dose of prednisolone, and hydrocortisone supplementation. The supplement ACTH and cortisol values increased gradually. An insulin loading test at the age of 12 years demonstrated normal responses of the ACTH and cortisol levels.

Discussion: The very long-term nature of the therapy for this patient with idiopathic nephrotic syndrome resulted in glucocorticoid-induced adrenal insufficiency. Periodic evaluation of adrenal function and re-evaluation of the treatment is important for patients with nephrotic syndrome receiving steroid therapy.

SA-PO106
Henoch-Schönlein Purpura in Adult, from a Clinical Case Migdal Goucsel, Pedro Vieira, Jose Duras, Luis Resende, Nuno Rosa, Jose Alves Teixeira, Gil Silva. Nephrology, Hospital Dr. Nélio Mendonça, Funchal, Portugal.

Introduction: Henoch-Schönlein purpura is a small vessel vasculitis mediated by IgA-immune complex deposition with multisystemic involvement. Rare in adults, it is characterized by purpura, arthralgias, abdominal pain, and renal involvement. Viral infections have been reported as trigger.

Case Description: The authors present the case of a 25 years old male, without relevant medical history, admitted to the Nephrology Department in May 2014 by severe hypertension, renal failure (creatinine 6.7mg/dL), erythrocyturia and proteinuria. Renal ultrasound was normal. Renal biopsy revealed IgAnephropathy (M1E1S1T2). Our investigation revealed chronic hepatitis B virus (HBV) of vertical transmission origin (viral load 150 IU/mL). Corticosteroid therapy was started, with slight improvement in renal function. He was readmitted 2 months later by asthenia, epistaxis, weight loss, palpable purpura, altered mental status and oral and nasal ulcers. Laboratory tests revealed hemoglobin 9.2g/dL, creatinine 4.3mg/dL, normal transaminases, albumin 20g/L, urinary spot protein:creatinine ratio 1300mg/g, hypocomplementemia, negative p-ANCAs, e-ANCAs and cryoglobulins, HBV load 379.980IU/mL. During hospitalization the patient initiated progressive pancytopenia, diffuse abdominal pain, generalized skin purpura and fever (with no identifiable infectious origin and interpreted as immunologic). We made clinical diagnosis of Henoch-Schönlein purpura and started with cyclophosphamide and entecavir. A few days later appeared hypoxemia and oliguria, requiring urgent dialysis. Cneli CT scan showed microangiopathic leukoencephalopathy of unspecified etiology and alveolar hemorrhage in chest CT scan. Due to life threatening multisystemic involvement we started methylprednisolone pulses, intravenous immunoglobulin and plasmapheresis. Patient completely recovered, but remained dependent on dialysis. 6 monthly cycles of cyclophosphamide were maintained, with no signs of recurrence.

Discussion: We emphasize the rare severe multisystemic involvement of a Henoch-Schönlein purpura in an adult, the onset of the disease with exacerbation of viral infection, and the therapeutic challenge of an HBV patient with a vasculitis.

SA-PO107
Rare Etiology for Chronic Kidney Disease: Bronchiectasis Related Secondary Amyloidosis Alper Alp,1 Hakam Akdam,2 Aysegul Ormeci,1 Ibrahim Meteoglu,2 Alparslan Unsal,1 Yazuv Yenicieroglul,1 1Nephrology, Van Education and Research Hospital, Van, Turkey; 2Nephrology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey; 1Pathology, Adnan Menderes Univ, School of Medicine, Aydin, Turkey.

Introduction: Here we present an elderly patient with a known posttuberculosis bronchiectasis, nephritic-range proteinuria and renal failure was detected. Renal biopsy revealed AA amyloidosis. Tuberculosis and tuberculosis related systemic disorders still have clinical impact in nephrology practice especially in developing countries.
Case Description: A 67 yo man was referred to our hospital with renal failure and proteinuria. PMH was remarkable for tuberculosis (41 years age) and posttuberculosis bronchiectasis for long years. On physical examination pretilial edema was evident. Chest X-ray, thorax CT revealed left sided total bronchiectasis and pulmonary nodules. Malignancy was excluded with PET/CT and bronchoscopy. On admission biochemical tests: urea: 220mg/dL, creatinine: 5.86mg/dL, potassium: 4.8mmol/L, GFR: 10.3mL/min/1.73m2, ANA 1/100 positivity (cytoplastic). Renal ultrasonography revealed bilateral echogenic kidneys with normal size and shape. 24 hour urinary proteinuria, albuminuria was 7924 mg/dL, 4789mg/dL respectively. Renal biopsy was compatible with AA amyloidosis (segmental homogeneous deposits of amyloid in the glomeruli and interstitium). Immunohistochemistry was positive for staining of AA amyloid. There was no immunofluorescence staining with IgG-A-M-C3 fibrinogen.

Tunneled catheter was placed and hemodialysis was started.

Discussion: FMF and rheumatological disorders are the leading causes of amyloid AA in Turkey. However other rarely seen etiologies should not be missed in clinical practice. Secondary amyloidosis as a multisystemic disease has a high mortality risk. Renal manifestations include nephrotic syndrome and renal failure.

SA-POI08

Sunitinib Induced Acute Renal Failure and Nephrotic Syndrome in a Patient with Metastatic Neuroendocrine Tumor: A Case Report and Review of the Literature

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Introduction: Sunitinib is a chemotherapeutic agent used to treat advanced malignancies via inhibition of tyrosine kinase phosphorylation. We present a case of sunitinib induced acute renal failure with nephrotic syndrome, occurring within one week of initiation for persistent carcinoid syndrome secondary to hepatocellular carcinoma of a primary small intestinal neuroendocrine tumor.

Case Description: A 63 year old man with metastatic neuroendocrine tumor was initiated on sunitinib to treat persistent carcinoid syndrome despite initial therapy. Within one week of initiation, he developed new onset peripheral edema, 20 pound weight gain and acute renal failure with nephrotic syndrome, occurring within one week of initiation for persistent carcinoid syndrome secondary to hepatocellular carcinoma of a primary small intestinal neuroendocrine tumor.

Discussion: Literature review reveals reports that vary both in time to onset and degree of resolution of renal disease after initiation and discontinuation of sunitinib therapy, respectively. Renal pathology also varies, including acute tubular necrosis, acute interstitial nephritis, diffuse podocyte foot process effacement, and thrombotic microangiopathy. Our patient developed a greater severity of renal failure than most reported, including a higher peak serum creatinine, longer duration of renal replacement therapy and current lack of renal recovery. To our knowledge, this is also the first report of the onset of renal failure in the specific clinical scenario described. Given the near immediate adverse effect of sunitinib in our patient, we recommend monitoring of creatinine and urine protein at baseline and within the first three to five days of medication initiation.

SA-POI09

Cryoglobulinemic Glomerulonephritis After Successful Treatment of Hepatitis C

Nupur Gupta, Chad A. Zarse, Allon N. Friedman. Nephrology, IU School of Medicine, IN.

Introduction: The optimal treatment of cryoglobulinemic glomerulonephritis (GN) in the setting of Hepatitis C (Hep C) with sustained viral response (SVR) is unknown. Only expert opinion obtained from case reports provide guidance to the clinician. Some reports show no benefit with Rituximab may be beneficial.

Case Description: 58yo male with h/o treated Hep C currently with an undetectable viral load, gastric ulcer, anemia, and HTN presented to clinic for evaluation of CKD. Hep C was initially diagnosed when he was found to have leukocytoclastic vasculitis on a skin biopsy of skin rash. Labs were positive for serum cryoglobulins, rheumatoid factor, low C4, and Hep C viral load. Renal function was normal and he was successfully treated for cryoglobulinemic vasculitis due to Hep C with interferon alpha, telaprevir and ribavirin and achieved a SVR. He presented 1 year later with renal insufficiency (creatinine -2.2 mg/dL) and proteinuria. He had minimal proteinuria and no hematuria. He had no new evidence of vasculitis. SPEP revealed IgM kappa monoclonal with negative UPEP. C4 was low and cryoglobulins remained positive. Kidney biopsy showed immune complex GN with organized deposits. Bone marrow biopsy was negative for lymphoproliferative disease. He was diagnosed with cryoglobulinemic GN with SVR. Initially, he was treated with prednisone followed by Rituximab and plasmapheresis. He failed the treatment and was started on hemodialysis.

Discussion: Cryoglobulinemic GN is frequently due to Hep C but is rare in patients achieving a SVR. In our case an underlying B cell lymphoma was ruled out and it was felt that B cell immune dysregulation due to Hep C was the culprit, in part due to prior published cases. However, in our case treatment with rituximab and plasmapheresis was unsuccessful. It remains possible, as others have demonstrated, that the virus may persist within the liver, macrophages, lymphocytes, and even kidney. The pathological basis for persistent vasculitis in setting of a SVR requires further study so that targeted and more effective treatment strategies can be designed.

SA-POI10

Diagnostic Intrapartum Dilemma: Distinguishing Glomerulonephritis from Preeclampsia in Pregnancy

Harsharan Kaur Singh.

Introduction: Distinguishing glomerular disease from preeclampsia intrapartum can be challenging due to overlap of clinical findings. Unfortunately, this diagnostic dilemma can result in unwarranted early delivery. Here we present 5 cases of glomerulonephritis (GN) complicating pregnancy.

Case Description: 3 patients (ages 22, 31 and 33) presented during pregnancy with proteinuria, dysmorphic hematuria and persistent kidney dysfunction. In 2 cases, acute kidney injury. In all 3 cases, the concern for preeclampsia prompted induction of labor (IOL), and postpartum kidney biopsy showed IgA nephropathy. 2 patients were treated with steroids and ACE inhibitors (ACEI) with improvement in proteinuria. The one with the most severe kidney dysfunction was treated with cyclophosphamide (CYC). Unfortunately, she became dialysis-dependent 1 month postpartum. The fourth patient (age 20) presented with HELLP syndrome at 25 weeks and underwent IOL. 5 months post-partum, she developed clinical symptoms of lupus in the setting of proteinuria, dysmorphic hematuria and persistent kidney dysfunction. Kidney biopsy was performed. She showed diffuse proliferative glomerulonephritis, which was true proliferative lupus nephritis, which was positive for anti-PCNA on IF, and negative for ANA and CYC. Unfortunately, she continued to have renal dysfunction despite treatment. The fifth patient (age 37) had minimal change disease (MCD) and was in remission at the time of pregnancy. She did well on cyclosporine until 25 weeks gestation when she developed hypertension, edema, and nephrotic-range proteinuria. It was unclear whether this represented preeclampsia or a MCD flare since she underwent IOL. Subsequent placental pathology failed to show signs of preeclampsia. She was treated postpartum with steroids and ACEI and re-entered remission.

Discussion: Here we show that pregnancy can aggravate (as in the case of our patient with MCD) or unmask (as in the other 4 cases) underlying glomerular disease. Diagnosis can be delayed due to risks related to kidney biopsy during pregnancy, and treatment is complicated by safety concerns for the developing fetus. Further work is needed to identify meaningful mechanisms to accurately differentiate preeclampsia from GN during pregnancy.

SA-POI11

A Case of Rapidly Progressive Glomerulonephritis Associated with Metastatic Lung Cancer

S. Mendes,1 Eduarido J. D. de Sa Carneiro Filho,2 Victor Longo Silva,1 Lilian Cordeiro, Veronica T. Costa e Silva,3 Elerson Costalonga.

Introduction: Several solid malignancies have been associated with glomerulonephritis. Rapidly progressive glomerulonephritis (RPN) has been reported in association with renal cell carcinoma and lung cancers. We report a case of RPN associated with metastatic lung cancer treated with chemotherapy agents.

Case Description: A 57-year-old male with metastatic epidermoid lung cancer, treated previously with paclitaxel plus carboplatin, cisplatin plus gemcitabine and carboplatin plus docetaxel, was admitted with dysuria and hematuria for last 1 week. Upon physical examination: edema of the lower limbs. Laboratory results demonstrated normal liver function, positive anti-Hbc, negative HbsAg and anti-Hbs, hemoglobin 6.5 g/dL, serum creatinine of 3.78 mg/dL (baseline 1.5), C3 154 mg/dL, C4 24.8 mg/dL, negative ANA, negative MCV. Urinalysis showed proteinuria (>1 g/L), more than 100 leukocytes per field and more than 100 red cells even after antibiotic treatment for presumed urinary infection. Due to persistent

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proteinuria (3.7 g/24h), evidence of dysmorphic hematuria and worsening of renal function
(Cr 4.1 mg/dL), he received methylprednisolone 1g for three days and renal biopsy was
proposed. It revealed pauci-immune crescentic glomerulonephritis. Immunofluorescence showed
mesangial deposition of C3 (++) and lambda chains (++). Treatment was followed by monthly
i.v. cyclophosphamide and proteinuria decreased to 0.87 g/24h. aCtANCA became positive
(1/160) 4 months after diagnosis.

Discussion: Membranoproliferative glomerulonephritis is the most commonly reported glomerulonephritis
especially with pulmonary cancer, but several reports suggest an association between rPgn and
malignancies. The increased risk for malignancy has been confirmed in a retrospective
review of 200 patients with ANCA-associated vasculitis, demonstrating a significantly
increased relative risk (6.02) compared with age-matched controls. Biaya et al reported
seven cases of rPgn associated with a coexisting nonrenal malignancy (6 carcinomas and
1 lymphoma). The pathogenetic mechanisms by which neoplasms lead to the development
of ANCA-associated vasculitides and rPgn are largely unknown.

SA-PO112
A Case of Encapsulating Sclerosing Peritonitis in a Type I Diabetic on Peritoneal Dialysis
Zachary Freestone, Josephine Abraham, Akram M. Shaaban.
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Introduction: Encapsulating sclerosing peritonitis (ESP) is a rare disorder associated
with PD. It is characterized by peritoneal fibrosis and encapsement of the bowel. Symptoms
associated with ESP are non-specific and may be attributed to other etiologies. Abdominal
imaging is required to evaluate ESP and diagnostic confirmation is achieved by laparoscopy.
ESP should be considered in patients on peritoneal dialysis with symptoms involving the
gastrointestinal tract, weight loss, or inadequate solute clearance.

Case Description: A 34 year old Caucasian male on PD presented to the clinic with complaints of nausea and abdominal pain. He had a history of type I DM, ESRD,
neuropathy, and gastroparesis. He was started on PD 8 years ago and has had 3 prior episodes of peritonitis. The patient appeared ill and malnourished. His abdomen was soft
on examination and non-tender to palpation. An abdominal x-ray indicated that he had calcification in the abdomen and pelvis. CT imaging showed calcification of the parietal
peritoneum, abdominal cavity, omentum, and bowel. The patient underwent exploratory
laparotomy with simultaneous PD catheter removal. The visual examination revealed a
brown, inflamed rim encompassing the peritoneum, omentum, bowel, and colon. Peritoneal
dialysis was discontinued and the patient was transitioned to hemodialysis.

Discussion: Encapsulating sclerosing peritonitis (ESP) is a condition associated with
peritoneal dialysis. Its presenting symptoms are often non-specific and may be attributed to
other causes. Abdominal imaging is necessary to evaluate for suspected ESP, CT being the
preferred method. ESP is characterized by peritoneal thickening and fibrosis that encases
the bowel. Treatment includes cessation of PD with transfer to hemodialysis and bowel rest.
Other attempted treatments of this disease have included steroids and total enterolysis.

SA-PO113
Acute Kidney Injury from Enterovesical Fistula Secondary to Squamous Cell Carcinoma of Bladder
Eleni Chelioti, Evdokia Efthimiou, Alexia Papalexandrou, Maria Sotiraki, Ioannis Xatris, Maria Tsiviligou.
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Introduction: Squamous cell carcinoma (SCC) of the bladder is a relatively rare tumor.
Predisposing factor is chronic irritation of the bladder by urinary infection, calculi and
non-tender to palpation. An abdominal x-ray indicated that he had calcification
necrotizing enterocolitis. review of 200 patients with ANCA-associated vasculitis, demonstrating a significantly
increased relative risk (6.02) compared with age-matched controls. Biaya et al reported
seven cases of rPgn associated with a coexisting nonrenal malignancy (6 carcinomas and
1 lymphoma). The pathogenetic mechanisms by which neoplasms lead to the development
of ANCA-associated vasculitides and rPgn are largely unknown.

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formation in tubular lumens with severe tubular atrophy. Cell accumulation and fibrotic lesion were also detected in interstitium. Mesangial matrix was mildly expanded in glomeruli. Amyloid deposition was not observed.

Discussion: Herein, we showed clinical course and renal pathology of the patient with IgG-lambda type MM. Although steroid pulse therapy decreased serum levels of IgD, renal function did not improve. Renal pathology showed cast nephropathy, interstitial fibrosis and cell infiltration. The renal manifestation of IgD type MM requires further investigation.

SA-PO116
Sunitinib-Induced Nephrotic Syndrome and Acute Kidney Injury in a Malignant Insulinoma Patient: A Case Report
Wakana Shoda, Naofumi Yui, Shokaro Naito, Soichiro Imori, Koichiro Susa, Takayasu Mori, Nahoiro Nomura, Eisei Sohara, Tomokazu Okado, Tatemitsu Shi, Shinichi Uchida. Dept of Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.

Introduction: Sunitinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFR), has been proven to be effective in the treatment of several types of cancer, including pancreatic neuroendocrine tumors. However, its risk of renal complications, such as proteinuria, renal dysfunction, and hypertension, are underestimated.

Case Description: A 71 year-old man with malignant insulinoma treated on sunitinib for six months, developed proteinuria, acute kidney injury and hypertension. Kidney biopsy showed thrombotic microangiopathy (TMA) like lesions such as double contour, edematous endothelial cells and microaneurysms, suggesting injuries induced by sunitinib. Decreased VEGF expression in podocytes was demonstrated by immunohistochemistry, supporting the diagnosis. Sunitinib was discontinued and partial remission of the renal complication was achieved in two weeks. However, the patient mandatorily needed to restart sunitinib because of poor control of blood glucose level due to pancreatic cancer exacerbation. By reducing the dose of sunitinib and administering losartan concurrently, the patient was able to maintain stable renal function with serum creatinine level of 1.4 mg/dl and urinary protein level under 1.0 g/day.

Discussion: VEGF blockade by sunitinib is featured by adverse effects including hypertension and renal injury. In the present case, renal injury partially improved after discontinuing sunitinib. Reducing the dosage of sunitinib and administering losartan made it possible to restart sunitinib treatment while controlling its renal side effects. VEGF, which is expressed and secreted by podocytes, is an important factor for development and maintenance of glomerular endothelium. Renal biopsy in this case showed down regulation of postoperative renal recovery.

SA-PO117
Liver-Kidney versus Liver Transplant Alone: Decision Making in the Operating Room
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Introduction: Acute kidney injury (AKI) is a common complication of decompensated chronic liver disease and hepatorenal syndrome (HRS) is one of the leading causes. Liver transplantation (LT) is a definitive treatment for HRS; however, simultaneous liver-kidney transplantation (SLK) is pursued due to the severity of preoperative AKI with uncertainty of postoperative renal recovery.

Case Description: A 60-year-old Caucasian woman with ESLD due to alcoholic cirrhosis had been readmitted twice over 2.5 months with AKI from HRS. Even though, she was treated with albumin, midozolam, and ocotroide, serum creatinine (SCR) had been elevated from the initial baseline of 1 mg/dL and had never returned to the baseline. Instead, it was worse every time she had AKI (Figure 1). After the last episodes of AKI, SCR had been stable at 2.5 mg/dL and she was listed for SLK. One week later, she was offered for SLK. After the LT, she started making a significant amount of urine immediately; therefore, the kidney was not transplanted and transferred to other potential kidney transplant recipient in another transplant center. Postoperatively, SCR had trended down to 1.1 mg/dL.

Discussion: Even though, our patient had recurrent episodes of AKI from HRS and persistently elevated SCR even >3 months period, it was thought that the chance of meaningful renal recovery was small and SLK was initially planned. Fortunately, her renal function was recovery immediately after the LT alone. Preoperative evaluation for SLK versus LT alone sometimes becomes uncertain. Intraoperative finding of signs of renal recovery after LT is crucial as it can avoid unnecessarily kidney transplantation and provide opportunity to utilize kidney organ to other potential kidney transplant recipients.

SA-PO118
Is Portopulmonary Hypertension Patient a Good Candidate for Liver Transplantation? Ekamol Tantisattamo,1 Praveen Ratanasirirnetha,2 Siwadon Pitukweerakul,3 1Nephrology, Northwestern Univ; 2Faculty of Medicine Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; 3Presence St. Francis Hospital, Evaston.

Introduction: Portopulmonary hypertension (PPH) is one of the most feared complications of end-stage liver disease (ESLD). Liver transplantation (LT) may reverse this complication with uncertain outcomes. We report a case of ESLD women complicated by severe pulmonary arterial hypertension (PAH) secondary to PPH and acute kidney injury (AKI) who had prolonged pre- and post-operative simultaneous liver-kidney transplantation (SLK) with partial liver improvement, un-meaningful renal recovery, and bed bound with reconditioning.

Case Description: A 48-year-old women had ESLD from cryptogenic cirrhosis complicated by portal hypertension, PAH-related to PPH and sarcoidosis presented with AKI requiring CRRT. She was treated with treprostinil, sildenafil, and ambrisentan until suitable for SLK. Postoperatively, liver and renal allografts worked well and PA pressure was decreased. However, she still required treprostinil and diuresis to control PAH and volume status. After 5 months of ICU stay, she developed severe deconditioning and malnutrition. She had AKI with SCR of 0.5 mg/dL up to 1 mg/dL over 3 weeks. Calculated average clearance from 24-hour urine collection was 15 ml/min. Transplant renal allograft biopsy revealed moderate ATN and borderline changes. Diuretic dose was decreased and SCR was improved to 0.7 mg/dL. She still required treprostinil as well as intensive rehabilitation and nutritional supplementation. She remains in ICU for the majority of the time posttransplantation.

Discussion: PPH is one of the challenging scenarios for ESLD requiring LT. Reversibility from PPH after LT is uncertainty. It is still a dilemma in managing this difficult situation between LT to prolong life with poor quality and conservative management. LT is a life-saving surgery but may not always reverse a severe complication of ESLD such PPH and thus prolongs no postoperative quality of life. Therefore, LT in such a complex underlying condition needs to be individualized.

SA-PO119
Flash Pulmonary Oedema in Renal Artery Stenosis: An Indication for Stenting? Elise Chiu, Martine David, Neil Chapman. Medicine, Imperial College, United Kingdom.

Introduction: Renal artery stenosis (RAS) is an unusual but potentially treatable cause of flash pulmonary oedema. Although national guidelines recommend percutaneous revascularization (level of evidence B), we present a case of recurrent flash pulmonary oedema which suggests a need for further evidence to support use of revascularization therapy in elderly patients with multiple comorbidities.

Case Description: A 78 year old woman presented with a fourth episode of sudden onset dyspnoea in 4 months. Her medical history included CAD, AF, hypertension (HTN) and severe pulmonary HTN due to heart failure with preserved ejection fraction (HFPEF). On admission, there were bilateral respiratory crackles and pulmonary congestion on chest XR. BP 164/95, creatinine 110umol/L, eGFR 42. Echocardiogram showed concentric LVH, preserved EF and raised PAP. Because of recurrent symptoms despite apparently adequate medical management of HFPEF, she underwent CT angiography which revealed bilateral ostial RAS (70% right, 40% left). Following multidisciplinary team discussion, bilateral balloon angioplasty with stent insertion was performed with radiologically successful results and she was discharged on ticauroxaban for stroke prevention. Since then, she has had no further episodes of pulmonary oedema. However, renal function deteriorated post-procedure (max creatinine 228umol/L, eGFR 18 at 6 weeks; no evidence of in-stent thrombosis) and she has diuretic-resistant pedal oedema severely impacting quality of life.

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SA-PO120
Complement Mediated Hemolytic Uremic Syndrome Secondary to SLE
Aala Complement Mediated Hemolytic Uremic Syndrome Secondary to SLE

Discussion: This case highlights the importance of recognizing RAS as a cause of flash pulmonary oedema, especially in bilateral disease due to lack of compensatory mechanisms. Observational studies and case series have demonstrated that angiotensin +/- stenting reduces the incidence of flash pulmonary oedema. However, there is limited literature to guide management (eg. on risks and benefits of unilateral vs. bilateral intervention, degree of stenosis) and limited experience in the elderly in whom comorbidities may increase the risks of procedural complications such as deterioration of renal function due to contrast nephropathy and/or cholesterol emboli.

SA-PO121
Idiopathic Nodular Glomerulosclerosis Presenting with Nephrotic Range Proteinuria and Normal Renal Function
Hassan E. Osman, Dany H. Issa.
Dept of Internal Medicine - Div of Nephrology, Saint Louis Univ, Saint Louis, MO.

Introduction: Idiopathic Nodular Glomerulosclerosis (ING) is a well-established but uncommon entity that has been described in 1985 by Chan JY et Al. It is common in older white men with history of long-standing hypertension, obesity, and smoking and typically presents with renal Insufficiency & Nephrotic Range Proteinuria. Multiple reports and meta-analyses of patients with ING demonstrate an average creatinine ~ 2.0 mg/dl and progressive kidney dysfunction leading to ESRD.

Case Description: We report a case of a 57 year old Caucasian obese female who presented with edema and heavy proteinuria (9 gms/day). She is a 40-pack year smoker with long-standing hypertension with variable control. Serum Creatinine on presentation was 0.7 mg/dl. Hba1c was 6.0% and fasting/random sugars never met criteria for overt Diabetes Mellitus. Urine showed 3-10 rbcs/hpf and none where dysmorphic with an otherwise bland urinalysis. The patient was treated with diuretics and ACE-Inhibitor lead to improvement in volume status and recovery of renal function. Nine-months into follow up renal function remain stable.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

SA-PO122
Hemofiltration Reinfusion Equilbrium Can Be An Answer to Malnutrition and Hypotension in Dialysis
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Introduction: We analyze the impact of A-HFR on intradialytic tolerance, nutritional status and on the clinical condition of two malnourished patients of our dialysis center.

Case Description: We performed an observational study for 12 months on 2 patients shifted to A-HFR caused to dialysis intolerance towards other methods. We monitored Blood Gas (pre and post treatment), clinical, biochemical, and dialitic data. Patient 1: 62 years old man on dialysis since 2008, suffering from malnutrition and anorexia due to cerebellar stroke (BMI 15.8) with intra and interdialytic hypotension. On February 2014 he started IPDN (Intradialytic Parenteral Nutrition) + HDF online without any clinical improvement. On June 2014 he was shifted to A-HFR+IPDN with improved hemodynamics control, weight (10% compared to its initial), nutritional and inflammatory indexes. In addition, he improved his quality of life with disappearance of hypotensive episodes and reduced consumption of EPO. Patient 2: 44 years old woman: kidney-panceases transplanted, on dialysis since 2011. In 2012 she started an antibiotic therapy for curing a pulmonary TBC, burdened by malnutrition and severe peripheral neuropathy with persistent hypotension, also during dialysis. In 2015 she was shifted to A-HFR and improvements regarding bodyweight, blood pressure, inflammatory markers and peripheral neuropathy were observed.

Discussion: A-HFR has dynamic profiles of ultrafiltration and conductivity of the dialysate: this aspect creates an iso-osmolar dialysate, ensuring a better periferal refilling and improving compliance during the dialysis treatment. This is due to the use of biosensors. A-HFR also reduces the Amino acids loss. This report has numerical limitations but provides encouraging data on the use of AHFR in malnutrition and disequilibrium syndromes. This experience underlines the importance of further efforts towards customized dialysis procedures.

SA-PO123
Monoclonal Gammopathy of Renal Significance: The Significance Is Not Always Unknown
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Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury noted on microscopy. It is less commonly associated with monoclonal gammapathies, including monoclonal gammapathy of unknown significance (MGUS). Case Description: Patient is a 67 years old female, with a history of rheumatoid arthritis, on Methotrexate, who presented to an outside facility with progressively worsening fatigue for four months. Investigations showed pancytopenia, following which she was transferred to our hospital for further management. On arrival at our hospital, patient was noted to have an acute kidney injury. A random urine protein/creatinine ratio showed 5.5 gm proteinuria. Serum protein electrophoresis showed a monoclonal spike, with an Ig M kappa clone. Immunglobulin (Ig) G was low at 161 mg/dl, while Ig M was increased at 378 mg/ dl. Bone marrow biopsy done showed 5 % plasma cells, with no morphological features of a plasma cell neoplasm, leukemia or lymphoma. Serum electrophoresis showed a monoclonal spike, with an Ig M kappa clone. Immunglobulin (Ig) G was low at 161 mg/dl, while Ig M was increased at 378 mg/ dl. Bone marrow biopsy done showed 5 % plasma cells, with no morphological features of a plasma cell neoplasm, leukemia or lymphoma. Kidney biopsy done showed MPGN, with positive immunofluorescence for IgM, C3, kappa, along with large subendothelial and mesangial deposits. Both C3 and C4 were low. Work up was negative for hepatitis B and C. Serum cryoglobulin levels were normal. No evidence of lupus was noted. Infectious work up was also unremarkable. Patient was diagnosed as having MGUS by the hematologic service. MPGN was assessed to be secondary to MGUS in the absence of other possible etiologies. Patient was started on high dose steroids for 3 days followed by a taper, along with intravenous Rituximab 375 mg/m² weekly for 4 weeks. Due to worsening renal functions patient was started on hemodialysis. Unfortunately due to lack of renal recovery, patient was declared as having end stage renal disease.

Discussion: MGUS is the most common plasma cell disorder and may be a precursor for myeloma. It is characterized by a lack of end organ damage. A small subset of patients, however, may rarely have renal involvement, with MPGN being noted on renal biopsy. MGUS can therefore be associated with morbidity and mortality, and therefore its significance may not always be unknown.
SA-PO124
A Case of Chronic Unilateral Hematuria Treated by Segmental Renal Artery Embolization
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Introduction: Chronic unilateral hematuria is characterized by intermittent or continuous hematuria that cannot be diagnosed using standard radiographic and hematologic methods. Unilateral hematuria is probably a benign condition that seldom requires surgical treatment, but some cases were managed with partial or total nephrectomy. Recently, a variety of treatments, including the ureteroscopic interventions have been attempted if the bleeding focus is identified. However, if not identified on ureteroscopy, surgical treatment has been considered a priority. We report the case of treatment of chronic unilateral hematuria with segmental renal artery embolization.

Case Description: We experienced a case of chronic unilateral hematuria in a 42-year-old woman who was admitted to our hospital due to intermittent gross hematuria and anemia for 31 months. About 29 and 19 months ago she already underwent CT scan, renal angiography, and renal biopsy at other tertiary hospitals, but didn’t find any other specific abnormalities repeatedly except some blood clots in left renal pelvis on ureteroscopy. She underwent CT urography, renal arteriography, cystoscopy and ureteroscopy again. Ureteroscopic findings only showed bleeding in the upper third of left renal calyces but definite bleeding focus could not be identified. Thus we decided to manage with segmental renal artery embolization than partial nephrectomy to minimize the reduction in renal function and to reduce operational risk. The superior and superoanterior segmental renal arteries were successfully embolized with 3mm coils and gelatin sponge. Gross hematuria disappeared on the 4th day after the procedure, microscopic hematuria disappeared on the 5th day. In 11th day, infarction in the upper third portion of left kidney was confirmed on CT scan. In 13th day, the patient was discharged. Thereafter serial urinalysis showed no hematuria.

Discussion: Patients with chronic unilateral hematuria often require surgical or upper urinary tract endoscopic procedures. Segmental renal artery embolization will be a better treatment for patients unable to identify the bleeding focus on the upper urinary tract endoscopy.

SA-PO125
An Unusual Cause of Acute Kidney Injury in a Patient Several Months Post Renal Transplant
Sweta Carpenter, Karthik M. Rangan. Nephrology, Drexel Univ.

Introduction: Urinary anastomosis leaks after kidney transplants are no longer a common phenomenon. Due to advancements in reconstruction techniques, urologic complications after renal transplant are now reported to occur in only 2-2.5% of patients. If a urinary anastomosis leak develops, the patient needs to be managed with segmental renal artery embolization than partial nephrectomy to minimize the reduction in renal function and to reduce operational risk. The superior and superoanterior segmental renal arteries were successfully embolized with 3mm coils and gelatin sponge. Gross hematuria disappeared on the 4th day after the procedure, microscopic hematuria disappeared on the 5th day. In 11th day, infarction in the upper third portion of left kidney was confirmed on CT scan. In 13th day, the patient was discharged. Thereafter serial urinalysis showed no hematuria.

Case Description: We present a case of a 60 year male with a history of a living unrelated kidney transplant who developed acute kidney injury 5 months after transplant. He had a baseline creatinine of 1.5-1.7 mg/dL and initially presented to the hospital with fevers and a creatinine of 2.96 mg/dL. A fungal urinary tract infection with Candida Albicans was deemed the culprit of his symptoms and so he was promptly started on fluconazole with only a slight improvement in his creatinine. A renal ultrasound of the kidneys revealed a 12.4 cm R and 12.6cm L kidney with multiple cysts. Taking into account the history of candida infection, urine culture, and the absence of significant hematuria, initial workup for causes of renal failure was negative. She underwent CT urogram, CT angiogram and CT cystoscopy. She was admitted to hemodialysis and a kidney biopsy was performed which showed Candida Albicans.
SA-PO129
Clostridium Difficile Associated Peritonitis in a Patient on Peritoneal Dialysis

**Dimpu M. Patel,** Gaurav Jain. Nephropath, Univ of Alabama at Birmingham, Birmingham, AL.

**Introduction:** Culture negative infectious peritonitis (CNP) is a common and serious complication in peritoneal dialysis (PD) patients. It is usually a result of samples failing to reach the threshold of microbiological detection, recent antibiotic exposure, or simply unusual symptoms. Our patient tested positive for Clostridium difficile (C. diff) infections have become more frequent, and more refractory to treatment, and dialysis patients are often affected by C diff secondary to repeated exposure to antibiotics, as well as hospitalizations. C diff infection should be considered in the differential for CNP in dialysis patients.

**Description:** A 41 AA male on PD since 2012 presented to PD unit with complaints of abdominal pain and cloudy fluid. He started on intraperitoneal antibiotics (Vancomycin and Cefazidime) as an outpatient, though his symptoms of abdominal pain worsened requiring a hospital admission within 48 hrs of onset of symptoms. He complained of nausea and cloudy fluid for 12 hrs on his day of admission. On exam, he was diffusely tender in his abdomen, with no guarding/rigidity. Lab data was significant for peritoneal fluid WBC count of 7,130 with 85% polys and he was continued on broad-spectrum IV antibiotics. Stool C diff toxin resulted positive on day 2 of hospitalization and he was started on IV metronidazole. His abdominal pain persisted, and a recheck of PD fluid cell counts on Day 3 revealed a WBC count of 17,671 with 79% polys. The PD fluid cultures were negative for unusual organisms not routinely tested for. Clostridium difficile (C. diff) infections have become more frequent, and more refractory to treatment, and dialysis patients are often affected by C diff secondary to repeated exposure to antibiotics, as well as hospitalizations.

**Results:**
- Our case study describes culture negative peritonitis in a patient with C diff that did not respond to broad spectrum IV antibiotics. This prompted further investigation of C difficile peritonitis that was confirmed on lab testing. This case highlights the importance of suspecting C diff peritonitis in PD patients with CNP.

**SA-PO130**

Adequacy of Australian Nephrology Training

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**Background:** There has been an increase in the number of doctors training in nephrology in Australia. This study aimed to assess the adequacy of nephrology training by measuring self-determined competency and skill relevance among recently graduated nephrologists.

**Methods:** A survey was developed by the Nephrology Advanced Training Committee of the Royal Australasian College of Physicians. The survey was administered on-line in 2015 via the annual subscription to the Australian and New Zealand Society of Nephrology. Nephrologists who were awarded Fellowship after 2002 were invited to participate.

**Results:** 113 of a 306 eligible Fellows (37%) completed the survey. 8 respondents had moved overseas and were excluded. Median age was 41 years (interquartile range 37-44) and 63% were male. Medical school was completed in Australia (59%), India (15%), and New Zealand (7%). 35% received at least some training in a rural area and 25% were qualified in another specialty (mainly internal medicine). 56% had completed and 21% commenced a higher degree. Higher degrees were undertaken for career development (43%) and desire for a research career (30%). Respondents indicated good training and competency in most clinical skills that were relevant to their practice. In training home hemodialysis (37%), and living kidney donor assessment (51%) were considered less adequate, despite these areas being considered very relevant to practice. There was a greater mismatch identified between training and importance of skills for management and research. This included inadequate training in managing complaints (82%), managing a private practice (98%), health system knowledge (86%) and regulations (93%), medical directorship (94%), ethics approval (76%), research funding (88%), and quality assurance (73%).

**Conclusions:** Nephrology training in Australia meets the clinical needs of new nephrologists. Similar to findings in USA, training in management and research was considered insufficient for the practices of new nephrologists and should be addressed in updates of the curriculum.

**SA-PO131**

Pediatric Nephrology Workforce and Training: An International Perspective

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**Background:** There is a shortage of pediatric nephrology providers in a number of areas around the world. We sought to determine pediatric nephrologists’ perspectives on this issue.

**Methods:** A voluntary web-based survey was deployed via the Qualtrics™ survey engine. Members of the International Pediatric Nephrology Association responded anonymously to questions about their geographic location, time spent on training, practice setting, and impressions on local workforce challenges and opportunities.

**Results:** The number of responses to date was 38, representing 21 countries from all continents. Six percent of the respondents treat both children and adults. The number of years required to train in pediatric nephrology was reported as: 2 years (35%), 3 years (58%) and 4 years (8%). Nearly 80% of practices were associated with academic settings. Specialty training programs are reported in 63% of the respondents’ institutions and 50% of those with training programs stated that it was difficult or very difficult to recruit trainees. Forty two percent of the respondents stated that it was difficult or very difficult to find a job after training. The themes most frequently cited on qualitative analysis include low availability and interest in the field by trainees, poor compensation, demanding schedule and competing family demands.

**Conclusions:** In this preliminary study of an international cohort of pediatric nephrologists, our data suggests a perception of a decreased pediatric nephrology workforce. There is also a perceived shortage of available positions in the field. Further data collection on workforce issues as it pertains to country-related factors is needed.

**SA-PO132**

Taking Guessed Out of Milestone Ratings -- Simplify the Evaluation System to Easily Achieve the Next Accreditation System (NAS) Report

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**Background:** In an effort to translate into competency-based training, the ACGME has developed 24 milestones specific to fellowship. While the milestones are comprehensive, it is challenging to determine an individual’s rating through faculty evaluations; many of whom are untrained in this system. We aimed to create a simple scoring system that translates the milestones into observable nephrology activities that can be completed daily on a handheld device.

**Methods:** For each nephrology rotation, a list of 5-10 frequent activities was developed. For every activity, a description for the five levels of competency was written to standardize the score. The activities were completed in 1-4 NAS milestones. The evaluations were built in Google Forms and delivered daily to supervising faculty members. Using a four-click system, the observer can submit a fellow evaluation with most done on mobile devices. If faculty members wish to express a narrative, a free-text response box is provided for comments.

**Results:** Of the 914 possible evaluations over a nine-month period of time 727 evaluations were returned. This provided data points to distinguish scores among all fellows in all of the NAS milestones.

**Fellow Performance Per Milestone-Yearend 2014-15**

In Clinical Competency Committee meetings thus far, 1 of 276 scores have been adjusted from the scores provided by the evaluation system.

**Conclusions:** This is an easy to use scoring system that has resulted in immediate feedback that is activity-specific and feed into NAS milestones easily and effectively. By translating the evaluation system into specific activities that any nephrologist can observe, a robust amount of valuable data has been obtained. The 4-click system has yielded an excellent response rate with more narrative comments than were previously obtained with monthly evaluations.
Methods: ITE annual reports provided by the National Board of Medical Examiners were reviewed and summarized.

Results: Scale score for all was 480: 104 (mean ± SD); 1st-year fellows (n = 2,020) 445.96, 2nd-year (Y2, n = 2,005) 515±100, and 3rd-year and higher (n = 112) 509±113. Standard error of the mean ranged 41-45. The 2010 ITE had 150 core items only. 2011 and 2012 ITE had separate OS-TE, urinalysis and renal pathology modules administered to Y1 and Y2 respectively (not included in total test statistics). In 2013 and 2014, all completed 20-item modules on these topics (included in statistics). A mean of 6.6 core items (4.4%) were deleted per year after adjudicating items with high difficulty or negative discrimination. Content areas aligned with American Board of Internal Medicine Certification Exam: General Aspects of Chronic Kidney Disease (CKD), Glomerular/ Vascular (GV), Tubulointerstitial/Cystic (TUC), Acute Renal Failure/ICU Nephrology (ARF/ICU), Kidney Transplant, Hypertension, Sodium/Water (Na/H2O), Acid-Base/ Poisoning, Mineral Metabolism (M/M), and Clinical Pharmacology (CP). Ethics. Though examinee abilities typically vary yearly, overall total average test p-value was 0.67. ARF/ICU, Na/H2O, MM, and CP tended to be less difficult (average p value 0.7) and TUC more difficult (average p-value 0.58). Total test mean item discrimination bias correlation averaged 0.21, highest for A-B/K (0.28) and lowest for CKD (0.18). Total test reliability (α) averaged 0.81; highest for GV (0.46) and lowest for TIC (0.25).

Conclusions: As expected, scale scores were higher for Y2 than Y1 fellows. Over 95% of administered items were scored; among those, mean item difficulty, item discrimination, and reliability varied among content areas.

Funding: Private Foundation Support

SA-PO134
What Are We Doing? A Survey of U.S. Nephrology Fellowship Program Directors

Methods: We distributed a survey for nephrology program directors via the Training Directors’ website. The survey addressed fellows’ service load and the scope of educational activities offered by the fellowship.

Results: 57 out of 147 programs responded (39%). Most are 2 years long, with a mean of 7 fellows, and are “front loaded”- 64% require ≥ 7 months of inpatient service during year one. Inpatient services are usual (93%) covered by one fellow with significant resident involvement. NP’s and PA’s help cover about 15% of services. The busiest services have about 21-25 patients, although 13% of programs averaged ≥ 26 patients. At their busiest, these services have more than 30 patients, occasionally surpassing 50 patients. About one quarter of these programs are exclusive of patients in which a fellow is involved for which a fellow is involved. Night call is most often divided equally among all years. Weeknight call is typically one night at (74%) covering a single hospital (66%). Fellows in the call rotation typically cover ≥ 10 nights over a three month period and ≥ 1 week-end a month. Most fellows do one weekly half day clinic, averaging 4-6 patients per session with a faculty: fellow ratio typical ≥ 1:2. Clinic structure is not usually modified during fellows’ inpatient service. Longitudinal coverage of HD and PD patients is provided by 82% and 61% of program respectively. Educational conferences ranged from 2-6 hours per week. Faculty didactic teaching varies from < 1 hour a week to 5 hours per week; one hour is typical. Fellows usually give 2-6 formal presentations yearly, although in some programs this is significantly more.

Conclusions: Our survey underscores the large variety in workload, practice patterns and frequency of educational conferences at different institutions and provides a framework to help address the service/education balance during nephrology fellowship.

SA-PO135
Perceptions of Nephrology Among Internal Medicine Residents

Methods: This is a repeated cross-sectional survey of IM residents to assess perceptions of nephrology and the impact of these perceptions on career decisions. All categorical IM residents in the last two years of training were invited to participate in 2012, prior to the initiation of a nephrology fellowship program (Group 1); and in 2015, three years following initiation of a nephrology fellowship program (Group 2).

Results: 131 of 156 residents (84.0%) completed the survey. A total of 14.8% (19/131) of residents indicated interest in a nephrology career, with 6.25% (8/131) indicating Nephrology as their first choice. Cardiology (21.1%) and Hospitalist (12.5%) were the most popular career choices. The presence of a Nephrology Fellowship program did not increase resident interest in nephrology (14.5% in Group 1 vs. 15.1% in Group 2). In perceptions of nephrology were not significantly different in Group 1 vs Group 2. Negative perceptions of nephrology most commonly endorsed by residents were: renal pathophysiology is too complex (22%), poor preparation in medical school (22.14%), few opportunities for procedures (26.7%), long work hours (24.4%), and long hours/desire call for nephrology fellows (27.5%). The majority of residents (83.2%) reported exposure to positive role models in nephrology. Experiences cited as having a high impact on career choice included: mentors/role models in the field (71.65% of residents) and rotations during residency (57.14%).

Conclusions: The presence of a nephrology fellowship program had no effect on IM residents’ interest in nephrology careers. Residents endorsed several negative perceptions of nephrology which may affect career choice.

SA-PO136
Insight into the Declining Interest in Nephrology

Methods: A web-based survey was conducted using survey monkey. 10 questions designed to help understand the reasons behind the decline of interest in nephrology were utilized. The survey link along with recruitment letter and consent form were sent to all US IM residency programs. Email addresses were obtained from the Alliance for Academic Internal Medicine website.

Results: 531 residents responded to the survey. 81% of those who completed the survey answered “No” to the question asking if they had interest in nephrology. The most common reason cited was a disheartening patient population, followed by salary, work hours & lack of understanding. 50.9% found nephrology “difficult” with the most challenging topics being glomerulonephritis (GN), acute base & transplant. The respondents noted that exposure to interventional nephrology, transplant & GN might increase their nephrology interest. Of those interested, more exposure to GNS during residency was felt to likely increase their interest.

Conclusions: These survey results demonstrate that most IM residents aren’t interested in nephrology and that restructuring of nephrology electives in residency programs to include enhanced exposure to GNS, transplant, and nephrology procedures might increase interest. Nephrology rotations are primarily an inpatient experience with exposure to critically ill AKI patients or complicated ESRD patients with significant recidivism. This experience leads to the perception that the nephrology population is disheartening. Since this is the most common reason why residents lack interest, changing the structure of nephrology electives in IM residencies to allow for more outpatient exposure with emphasis on GNS and transplant might be crucial for enhancing interest in nephrology fellowship training and a career in this subspecialty.
SA-PO138
Creating and Enhancing Interest in Nephrology Careers: A Novel Nephrology Elective Experience for Medical Students
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Background: Interest in nephrology careers continues to decline in the United States (US). The type of nephrology elective that US medical students experience may play an important role in creating and enhancing interest in nephrology careers.

Methods: At our institution, we created a novel 4-week nephrology elective experience for medical students. Our redesigned elective included both 2-week inpatient (IP) and 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of various nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of hemodialysis clinic, 2 half-days of peritoneal dialysis clinic, and 3 half-days of outpatient hemodialysis unit rounding. The redesigned elective also included education conferences. From 7/2012 to 2/2015, nine 4th year medical students (all from different US medical schools) completed our redesigned nephrology elective. To evaluate the novel elective experience, all medical students were asked to complete an anonymous online survey upon completion of their rotation.

Results: All students responded to our survey. All reported adequate OP nephrology exposure during their elective. 89% had worked with 1 or 2 faculty members during the IP setting. In comparison, 78% were exposed to at least 4 different faculty members during the OP experiences. All students had interacted with at least 3 fellows. All reported that the elective experience enhanced their exposure and knowledge in nephrology and that they would recommend this elective to other medical students. They also thought that this elective structure provided them with a better insight into what nephrologists do in practice. 78% reported that this elective experience created an interest in nephrology career. 56% responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: We believe that the restructured nephrology elective provides the medical student with a much needed and realistic exposure to nephrology careers. Based on our experience, we recommend all training programs to consider this elective structure for medical students.

SA-PO139
Journal Publication of Nephrology Fellows Case Report Presentations at ASN Kidney Week 2012-2013
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Background: The inception of the fellows case report (CR) category at the ASN Kidney Week (KW) occurred in the year 2012. However, the number and types of CR abstracts accepted for presentation at ASN KW is not known. Peer-reviewed journal publication (PR-JP) of these previously presented CR abstracts at ASN KW is also not known.

Methods: All previously accepted fellows CR abstracts from ASN KW 2012-2013 were reviewed and categorized as follows: glomerular diseases (GN), tubulointerstitial diseases (TIN), acute kidney injury (AKI), fluid-electrolyte and acid-base disorders (FE-AB), dialysis (D), kidney transplant (KT), genetic disorders (GD), mineral diseases (MD), and other (O) cases. To determine the PR-JP rate of these CR abstracts, a literature (PubMed) search was performed in November 2015.

Results: A total of 415 abstracts were presented in the fellows CR category at the ASN KW 2012-2013. Compared to KW 2012, there was a 7.5% increase in CR abstract presentations at KW 2013. Over these previous two KW meetings, nearly one-third (31.6%) were CR abstracts. The remaining abstracts were FE-AB (15.2%), AKI (14.4%), KT (11.8%), D (11.8%), TIN (5%), MD (4%), and O (4%), and GD (2.2%) related presentations. Compared to KW 2012, there was an increase in GN related presentations (from 55 to 76) at KW 2013. So far, only 72 (17.3%) out of the 415 abstracts have been published as papers in peer-reviewed journals. One abstract was published as a letter to the editor format. Of those that were published, 31.5% were GN related case reports. Interestingly, 22% of these journal publications did not list the lead author of the KW CR abstract as the primary author of the paper.

Conclusions: Based on our study, it seems that there is an increased interest among fellows to present CR abstracts at ASN KW. Nearly one-third were GN related case presentations. However, so far, less than one-fifth of the fellows CR abstracts presented at KW 2012-13 have been published in peer-reviewed journals. Reasons for this low publication rate is not known. Measures to enhance CR publications need to be considered.

SA-PO140
Analysis of Published Medical Student Related Nephrology Medical Education Research
Sarah B. Baveyksly, Hitesh H. Shah, Kenan D. Jhaveri. Hofstra NSLIJ School of Medicine; Nephrology, Hofstra NSLIJ School of Medicine.

Background: Undergraduate (medical student) related medical education research in nephrology is not well studied. This analysis aims to assess the rigor of the studies describing teaching methods used in medical student education in nephrology.

Methods: A review of the English literature on nephrology education of medical students was conducted on two major online academic search engines (PubMed and ERIC). References from the papers discovered in this search were also reviewed. Conference abstracts were not investigated. The empirical studies were categorized by subject within nephrology. The research design of each study was then recorded.

Results: 26 original studies were found in which a method of teaching nephrology to medical students was described. The studies dates from 1977 to 2015. The focus of these teaching experiences was as follows: anatomy (3.3%), physiology (23.3%), pathophysiology (26.7%), pathology (10%), treatment (20%), and general nephrology (16.7%). 4 of the pathophysiology studies were also classified under other categories, so there were 30 studies. The papers were also categorized into types of assessment. One type of assessment containing two different types of studies for a total of 28 types of assessment. 14.2% had either no assessment of the educational experience or had a description too vague to categorize it; 3.6% involved a questionnaire about the existing educational approach prior to implementing the new teaching method; 14.2% rated the effectiveness of the new teaching method based on student performance; 14.2% rated student performance. 22% of these journal publications did not list the lead author of the KW CR abstract as the primary author of the paper.

Conclusions: Based on our study, it seems that there is an increased interest among fellows to present CR abstracts at ASN KW. Nearly one-third were GN related case presentations. However, so far, less than one-fifth of the fellows CR abstracts presented at KW 2012-13 have been published in peer-reviewed journals. Reasons for this low publication rate is not known. Measures to enhance CR publications need to be considered.
SA-PO143

Awareness of AKI in Low Resource Settings: A Global Survey
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Background: The ISN has set a goal of eliminating preventable deaths from AKI by 2025—the “0x25” initiative. However, there is limited awareness of the challenges presented by AKI in terms of diagnosis, treatment and management in low resource settings (LRS).

Methods: We reached out to nephrologists working in LRS using a web-based instrument of 18 questions. Responders were asked what strategies should be considered to increase the awareness of AKI in LRS and recommend approaches to heighten this awareness. A total of 5 respondents from 5 WHO world regions, including 54% from Africa.

Results: The major barriers to raising awareness cited by all were inadequate training, shortage of adequately trained health workers and lack of awareness of the significance of AKI by healthcare workers, government officials and the general public. Additional factors cited were limited patient access to health facilities, limited diagnostic and treatment facilities, lack of support for AKI programs, lack of clinical practice guidelines for AKI, poor communication systems, limited research funding and lack of linkages of AKI programs to other health projects. Health centers (HCs) were broken down into rural, district and regional HCs. Supplies available for diagnosis (serum creatinine and BUN) and management (IV fluids, antibiotics, anti-venom) of AKI are limited in rural HCs. All noted that hemodialysis services were available but only in selected, large urban centers.

Conclusions: Increasing the awareness of AKI in local, district, and regional HCs requires a multi-faceted approach, reaching out to government officials, hospital administrators, physicians, nurses, local health care workers, community leaders, international organizations and the general public. The success of this initiative involves the development of meaningful and targeted educational programs, training materials, and treatment guidelines tailored to the local situations. Alliances will need to be formed with governmental agencies, non-profit organizations and global health programs. Support needs to be provided for additional research programs.

SA-PO144

Acute Kidney Injury Education to Nursing and Assistant Health Care Staff Mansoor N. Ali, Renal Medicine, Calderdale and Huddersfield Hospitals NHS Foundation Trust, United Kingdom.

Background: Acute kidney injury (AKI) is a global healthcare problem. It carries significant mortality and incurs heavy costs to the National Health Service. Extensive work has been done recently both at undergraduate and postgraduate level to ensure front line medical staff have better understanding in managing AKI. One such important area of focus involves the need for training nursing and assistant healthcare staffs who care for patients presenting with AKI.

Purpose of the study: To gauge the understanding of AKI amongst nursing and healthcare assistants working on busy acute medical admissions unit.

Methods: The anonymous questionnaire was aimed at the nursing and assistant health care staff working on the admissions unit at two large district hospitals. The length of time since qualification ranged from few weeks to 16 years. The questionnaire was followed by planned teaching, simulation training and workshop sessions. The process was carried out within a period of 2 months.

Results: The questionnaire was completed by 50 staff members. It included series of questions aimed at defining and managing AKI from a nursing perspective. 24 out of 50 were able to define AKI. Only 5 out of 50, have never cared for patients with AKI. Not many were aware of the symptoms of AKI; common answers given by 40 respondents were “reduction in urine output” and “dehydration.” All participants answered “yes” to monitoring urine output and understood the significance of fluid monitoring but all admitted more needed to be done to ensure accurate documentation in the patient’s notes. Other questions asked were if nurses check patient’s blood results on the system server to which most replied “no” and if medications were regularly reviewed during drug rounds. Surprisingly, not all were aware of nephrotoxic medications and only 20 respondents would regularly review drug charts in the context of renal failure.

Conclusions: The questionnaire and the training sessions identified lack of better understanding of AKI and its management. There needs to be a stronger emphasis on the introduction of AKI and its management during their training years and development of mandatory online e-learning modules.

SA-PO145


Background: AKI occurs in 1-in-3 hospitalized patients, and majority of those are managed by non-nephrology specialties, including trainees.

Methods: The renal fellowship program designed an online anonymous survey, distributed to trainees (students, residents, fellows), to understand their level of knowledge in recognition and management of AKI. 37 questions were classified into following categories: knowledge of guidelines; prognostic factors; and drug safety. Results are represented as % age and awareness.

Results: 104 trainees responded to the online survey; 50% were male, 84% US medical graduates and 70% were residents/fellows. 50% were affiliated to medical specialties; and 53% had spent at least one elective in nephrology. In terms of AKI definition: 51% use serum creatinine (SCR) as the most important factor to diagnose AKI, whereas 20% use urine output. Majority (76.1%) agreed that rise of 0.3 mg/dl or 1.5 times of baseline SCR was clinically relevant, in concordance with current guidelines. RIFLE criteria were most commonly used (42%), followed by KDIGO (13%); and 90% agreed that guidelines help in standardization, and management of patients. 85% concurred that AKI impacts short and long-term outcomes, however, majority (60%) felt dialysis requirement was the most important clinical predictor of outcome. Majority (67%) felt that early involvement of nephrology services is helpful in AKI management; 66% sought nephrology input to determine the cause of AKI/co-management, and 7% viewed nephrology role purely for procedural delivery of dialysis. As for drug safety, 89% reported to pay attention to renal function while drug dosing, but 70% felt that this was the responsibility of either pharmacy or ordering team. In terms of follow-up 61% of subjects felt that follow-up was only needed in moderate to severe AKI cases or in non-recovery; 86% preferred that in > 30 days, and 64% preferred that to be with primary care.

Conclusions: Most of the trainees displayed good knowledge of AKI guidelines (RIFLE), seek timely nephrology involvement and view it to be beneficial. More work needs to be done in terms of improving knowledge/practice about drug safety and follow-up care in AKI.

SA-PO146

Adherence to Care Bundles for AKI – Challenges in Supporting Education and Measuring Compliance Melanie Louise Sally, Christopher J. Mulgrew. Renal Medicine, Royal Devon & Exeter Hospital, Exeter, Devon, United Kingdom.

Background: AKI typically occurs as a consequence of intercurrent illness in patients with multiple comorbidities and risk factors. The use of clinical guidelines to assist medical and nursing staff in AKI management has been adopted by most secondary care institutions in the UK. We have previously presented our use of e-alerts for AKI as a prompt to improve AKI care (Mulgrew et al, ASN, 2013). Clinical guidelines were prompted by the e-alert and widely publicised to staff.

Methods: In a model similar to the NHS Safety Thermometer, snapshots of compliance with 6 key elements of the AKI guidelines on 4 medical wards was measured by identifying patients from AKI e-alerts. These included documentation of AKI, medication review, clinical judgment and ongoing investigation/monitoring. Awareness was supported by an AKI Education nursing team, working with medical and nursing staff. Monthly compliance was assessed over a period of one year.

Results: Mean compliance for all elements of the guidelines improved from 52% to 69% over the year. Significant variability was seen, often associated with notable workforce challenges such as new medical staff or periods of increased activity.

Conclusions: Supporting medical and nursing teams to manage AKI in secondary care in order to prevent progression and treat promptly remains challenging. A number of external factors frequently impact upon adherence to guidelines and support needs to be planned in order to continue to maintain high standards and optimise patient care. The use of a Safety Thermometer, allowing performance to be analysed and comparisons made between clinical areas, may continue to be useful in improving performance and patient outcomes in AKI.

SA-PO147

Internal Medicine Residents Knowledge of Vein Preservation in Chronic Kidney Disease Patients Sandesh Joshi, Jamie Alton Green, Maria C. Bermudez. Nephrology, Geisinger Medical Center, Danville, PA.

Background: Vein preservation is important among CKD patients for future arteriovenous fistula potential. House staff plays critical role in managing these patient population and preserving their vein for future arteriovenous fistula. Their knowledge and current practices directly affects the outcome for vein preservation among these patients.

Methods: We conducted a survey among 44 internal medicine residents to understand their baseline knowledge and current practices regarding vein preservation. The survey was conducted at Geisinger Medical center, Danville, PA.

Results: 44 residents were included in the survey. Only 6.8% (3) were able to correctly identify patient population, on whom we should avoid particular arm for IV draws, BP measurements, peripherally access or peripherally inserted central catheters. Two-third (27) answered non-domain arm to avoid for these procedure and 13.5% (6) responded side does not matter. 81.8% (36) answered that nephrology should be consulted prior to peripherally inserted central catheters placement for CKD 4 patient. 93.1 % (41) answered...
and transplant nephropathy (all p-values <0.01). Factors associated with improvement in adjustments were endurers after July 2014, ICU encounters and less than 10 years of academic experience (all p-values <0.01).

Conclusions: Standardized templates led to significant reductions in revenue/work RVU losses per encounter at a large academic nephrology center. Nephrologists with more than 10 years of academic experience and transplant nephropathists performed worse than their peers. Efforts to improve documentation and billing may have important implications for academic nephrologists.

SA-PO150
Nephrology Documentation and Billing Educational Needs at an Academic Medical Center Leslie P. Wong, Emilio D. Poggio, Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH; Transplant Center, Cleveland Clinic, Cleveland, OH.

Background: Reimbursement in nephrology depends on accurate documentation and billing. Academic nephrologists are under increasing pressure to meet financial productivity targets. An analysis of nephrology reimbursement was performed at an academic medical center to find deficiencies and identify targets for education.

Methods: 75,097 inpatient nephrology encounters by 22 nephrologists from January 2012 and March 2015 were reviewed. Data included the current procedural terminology (CPT) code specifying the type of service and any charge adjustments made by the coding department. Adjusted charges were accompanied by the reason for adjustment, the corrected CPT code and a revenue change based upon Medicare reimbursement. RVUs were calculated using the Medicare National Physician Fee Schedule. Multivariate regression analysis was performed to identify factors associated with RVU adjustments.

Results: 5615 (7.5%) of encounters were adjusted by coders. 3832 (68%) were due to incorrect documentation or billing and 1683 (32%) were due to services performed but not billed by nephrologists. For submitted charges, revenue was reduced by $995,976 and 4227 work RVUs as a result of incorrect documentation or billing. The potential loss of revenue from unbilled services was $603,014 and 2823 work RVUs. Inadequate documentation of physical exam (p<0.01) and inadequate documentation of supervision of medical students/residents/fellows (p<0.01) were independently associated with RVU adjustments. Incorrect charge selection, duplicate charges, competing charges from another nephrologist and conflicting discharge/observation/post-operative care CPTs were also independently associated with RVU adjustments (p<0.01).

Conclusions: There was a substantial loss in gross revenue and work RVUs due to incorrect documentation and billing in an academic nephrology setting. These reductions in reimbursement and productivity might be avoided through better physician education and training. Specific targets include documentation of physical exam and supervision of trainees, correct CPT charge selection and ensuring all services performed are billed.

SA-PO151
Reaching Renal Goals – A Quality Improvement Project Mihran V. Nalivian, Oksana I. Ninkivech, Vecheslav Fedorchenco, Sara Jacob Coulon, Kimberly Cox Fremin, Zohayr M. Al Shaial. Medicine, LSUHSC School of Medicine, New Orleans, LA.

Background: The purpose of this study was to improve our patient care in a renal clinic at a large university hospital by using one of the core competencies- patient care, systems based practice, and practice based learning and improvement.

Methods: A check-out sheet was developed and given to all trainees in the nephrology clinic. Data was collected for 174 visits over 6 months. Data include age, gender, eGFR, and CKD stage. Each patient’s blood pressure, hemoglobin, phosphorus, Vitamin D, PTH, bicarbonate, and the extent of renal replacement therapy planning were acquired and further analyzed to determine whether nephrology goals were met based on KDOQI/KDIGO guidelines.

Results: Achievements in goals for CKD 3-5 as per KDOQI/KDIGO guidelines based on a percentage value of the patients seen each month. Data are from April to October. Hemoglobin of <10 g/dl were met in 64%, 64%, 76%, 98%, 96% and 83%, respectively. Blood pressure of <140/90 mmHg (or <130/80) were met in 52%, 64%, 45%, 67%, 68%, 54% and 71%, respectively. Vitamin D of >30 mg/ml were met in 36%, 36%, 78%, 30%, 41%, 48% and 47%, respectively. PTH of ≤ 150 were met in 52%, 27%, 67%, 45%, 63%, 45% and 71%, respectively. Proteinuria (<300 mg/day) were met in 12%, 9%, 22%, 26%, 53%, 80%, and 55%. Phosphorus ≤ <5.5 mg/dl were met in 76%, 73%, 89%, 85%, 81%, 88% and 96%, respectively. Attending renal education classes were met in 40%, 73%, 56%, 41%, 50%, 59% and 42% respectively.

Table 1. Referral in patients with GFR <20 in different study phases. Results presented as number of patients (%)

<table>
<thead>
<tr>
<th>GFR</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
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<tbody>
<tr>
<td>15-20</td>
<td>9 (11%)</td>
<td>18 (50%)</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>15-20</td>
<td>15 (67%)</td>
<td>8 (44%)</td>
<td>19 (66%)</td>
</tr>
<tr>
<td>15-20</td>
<td>26 (72%)</td>
<td>16 (73%)</td>
<td>21 (72%)</td>
</tr>
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</table>

Conclusions: Referral rates for kidney transplantation by Nephrology fellows improved by 32%. A chart review and educational intervention were performed. Vascular access referrals from this study remained stable. This work suggests that outpatient performance improvement projects conducted by Nephrology fellows confer peer review accountability for outpatient practice habits, heightens trainee awareness of key referral issues, and appears to help sustain or improve referral rates for vascular access and kidney transplantation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Our project was helpful in educating trainees in the treatment goals and actions for patients in the renal clinic and standardized an approach to patient care. Overall, the results show a trend towards improvement in all goal areas except for renal education. This study did not account for patients who were new to our clinic and therefore had never received renal education previously.

SA-PO152
A Simulation Exercise to Assess Renal Replacement Therapy and Kidney Biopsy Communication Skills Lisa K. Prince,1 Maura A. Watson,1 Anna M. Howle,1 Christina M. Yuan,1 Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; 2Medical Simulation, Walter Reed National Military Medical Center, Bethesda, MD.

Background: We piloted a nephrology-specific “Breaking Bad News” simulation to assess Interpersonal Communication Skills and Professionalism during renal replacement therapy (RRT) and kidney biopsy (Bx) counseling. Assessment tools were a 9-point Likert Mini-Clinical Examination Exercise (Mini-CEX) adapted for RRT and Bx counseling, and the Essential Elements of Communication-Global Rating Scale 2005 (EEC-GRS).

Methods: There were three cases: 1) a middle-aged woman with polycystic kidney disease and CKD5, 2) a critically-ill elderly man with AKI whose wife was his surrogate decision maker, and 3) a previously healthy soldier with nephrotic syndrome. There were 5 nephrology fellow examiners. One patient actor performed for each case, assessing each examinee with the EEC-GRS. One faculty assessed all examinees for one case using the EEC-GRS and mini-CEX. Encounters lasted 15 minutes, followed by 5 minutes for examination counseling by the actor and faculty.

Results: Post-simulation, 3/3 faculty surveyed felt that the examice met objectives, and was an excellent assessment tool. 4/5 examinees felt the exercise was “good” and met objectives. 5/5 felt that simulation time was too short to assess communication skills. 2/5 felt that a mini-CEX assessing a real patient encounter was superior. Median examined EEC-GRS performance assessed by actors and faculty was 4 (range 3-5). Median mini-CEX performance was 6 (range 5-9).

Conclusions: Based on feedback, the original mini-CEX was too detailed for a 15-minute encounter, and was simplified. Instructions now stress that, because of encounter brevity, counseling is unlikely to be completed, and completion is not required for satisfactory grading. A second set of scenarios was developed to permit a yearly simulation in a two-year cycle. We plan to test the revised simulation in a larger group of nephrology fellows within the next year. The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense or the United States Government.

Funding: Other: U.S. Government Support

SA-PO153
Implementation of KDIGO CKD Guidelines Leads to Decreased Diagnosis of CKD Heather M. Mascio,1 Deeti S. Moon,2 Ryan J. Altenburg, Lisa K. Prince, Dustin J. Little, Nephrology Service, Walter Reed National Military Medical Center, Bethesda, MD.

Background: Estimated glomerular filtration rate (eGFR) is used to diagnose and classify CKD. The accuracy of creatinine-based eGFR-Creat is inferior to eGFR calculated using multiple renal filtration markers. CKD guidelines suggest using serum creatinine and cystatin C to evaluate for CKD in select patients, but methods for, and results of guideline implementation have not been reported.

Methods: We reviewed new patient nephrology clinic encounters in a three month period to establish baseline guideline adherence. Combined creatinine/cystatin C (eGFR(Creat,CysC)) was considered indicated in patients eGFR-Creat 45-59 ml/min/1.73m2 and no albuminuria, urine sediment abnormalities, or other markers of kidney damage. Consultation review was modified such that a nephrologist reviewed every referral request, with the option of ordering labs to be obtained prior to a clinic visit. During a six-month implementation period, guideline awareness was targeted via didactics, signs posted in exam rooms, and “cystatin C—just check it” t-shirts. Seven months of charts were reviewed following the intervention period, and pre and post-intervention adherence was compared using Fisher’s exact test. Patients with eGFR-Creat,CysC<60 ml/min/1.73m2 were considered to have no evidence of CKD. Inpatients for whom eGFR-Creat,CysC was obtained, mean eGFR-Creat and eGFR-Creat,CysC were compared using paired t test. Results: Cystatin C was significantly higher in the post-intervention period compared to the pre-intervention period (testing obtained in 30 of 40 (75%) vs.12 of 32 (37.5%)) indicated cases; p =0.002). Mean eGFR-Creat,CysC was significantly higher than eGFR-Creat (77.1 ± 13.5 vs. 58.3 ±9.1ml/min/1.73m2; p=0.001). eGFR-Creat,CysC was ≥60ml/min/1.73m2 in 85.3% of cases.

Conclusions: By modifying our consult review process and raising awareness among nephrology providers, we significantly implemented eGFR-Creat,CysC guidelines and determined that the vast majority of tested patients had no evidence of CKD. Our results suggest testing as suggested in the guidelines has the potential to markedly decrease the number of inaccurate CKD diagnoses.

SA-PO154
Improving Pathology Curriculum for Nephrology Fellows Enrica Fung,1 Orlando Camacho,1 Michelle M. O’Shaughnessy,1 Adetokunbo A. Taiwo,1 Gabriela Velez,1 Neeraja Kambham,2 Timothy W. Meyer,1,2 Nephrology, Stanford; 1Pathology, Stanford; 2Nephrology, VA Palo Alto

Background: Stanford fellows were previously exposed to renal pathology through attendance at monthly hour-long “biopsy conferences” where faculty and fellows discussed difficult cases; and informal quarterly “fellows-only conferences” where fellows asked pathologists questions on core topics. Our project sought to improve fellows’ education in renal pathology.

Methods: Twelve first to third year fellows participated in this project. Two renal pathologists led five orderly review sessions, dedicated to fellows only: 1. Common renal pathologies: 2. Primary glomerulonephritis; 3. Secondary glomerulonephritis; 4. Plasma cell dyscrasia-related renal disease; 5. Renal transplant pathology. Second year fellows helped in preparation of teaching material. Fellows were encouraged to ask questions. Participants completed a survey to measure their satisfaction with renal pathology teaching and their confidence in interpreting renal biopsies before and after this project. Five 10-question pre-session quizzes and a comprehensive 40-question post-project final measured knowledge acquisition.

Results: Prior to our project, 55% of fellows felt somewhat satisfied to “satisfied” with the current pathology conferences, and 10% of fellows felt somewhat confident in their abilities to interpret biopsy findings. Most fellows (83%) viewed renal pathology to be an “important” or “very important” part of their overall nephrology training. After the project, 100% of fellows felt somewhat satisfied to “very satisfied” with the project, and 66% of fellows felt “somewhat confident” in their abilities to interpret biopsy findings. To date, fellows answered 63% of quiz questions correctly prior to the project and 60% of final questions correctly after the project.

Conclusions: Survey of nephrology fellows revealed poor confidence in interpreting renal pathology prior to our project despite perceived importance of the topic. To date, post project evaluation suggested improved confidence in renal pathology but lack of significant change in knowledge base. This may be due to issues with knowledge acquisition, inter-test comparability or instruction method.

SA-PO155
Improving the Communication Skills of Nephrology Fellows by Utilizing MBTI Training Anna Marie Burger,1 Julia Lewis,1 Vanderbilt Univ School of Medicine, Nashville, TN.

Background: Communication skills can both positively and negatively affect the patient-physician relationship. Although many things impact successful communications, individuals’ personality types affect the way they communicate and the way they interpret the communications of others. It has been suggested that a lack of understanding of the basic difference between personality types contributes to poor communication and unsuccessful interactions. Nephrologists work in a unique environment in the dialysis unit with a complex interdisciplinary team and a “captured” audience of anywhere from 10-40 patients in a single room. In the dialysis unit, communication between the multi-disciplinary team and the patients and between the multidisciplinary team’s individual members impacts the successful achievement of dialysis outcomes.

Methods: Eleven nephrology fellows underwent a curriculum designed to increase their awareness of their own Myers Briggs Type Indicator (MBTI) personality preferences, their knowledge of the different basic personality preferences, and how those differences impact communication. Knowledge of the MBTI preferences was tested pre-intervention, immediately post intervention, and 8 weeks post intervention. Communication skills were measured pre-intervention and through dialysis nurse observations of fellows during fellow-real patient interactions. Fellows were also asked to describe how they used their knowledge at 8 weeks post intervention.

Results: The intervention led to a sustained increase in the nephrology fellows’ MBTI personality preference knowledge. At 8 weeks post intervention, fellows reported utilizing their personality preference knowledge to improve their communication with their patients as well as with members of their team. However, nephrology fellows’ communication skills, as measured by the Kalamazoo Essential Elements Communication Checklist Adapted (KEECC-A), did not change.

Conclusions: Although training in MBTI personality preferences led to a significant, sustained increase in MBTI knowledge and fellows continued to report utilizing their knowledge at 8 weeks post intervention, there was no change in their measurable communication skills utilizing nurse observations.

SA-PO156
Lung Ultrasound: A New Skill for Nephrologists for Volume Overload Quantification in End Stage Renal Disease Patients on Hemodialysis Marc M. Saad,1 Wissam Mansour, Elias Moussaly, Jeanne Karam, Boutros Karam, Cara Brown, Monica Kapoor, Elic El-Charabaty, Suzanne E. El Sayegh.1 Internal Medicine/Nephrology, Staten Island Univ Hospital, Staten Island, NY.

Background: Many methods have been tried to assess the volume status in patients on hemodialysis (HD). While the estimated dry weight is still the only method widely used, it is often inaccurate and poses a clinical challenge. Pulmonary congestion detected as B lines on ultrasound (BLUS) is rising as a novel parameter for assessing volume status; we evaluated the accuracy and reliability of measuring BLUS performed by residents following training in the technique.

Conclusions: Overall, the results show a trend towards improvement in all goal areas except for renal education. This study did not account for patients who were new to our clinic and therefore had never received renal education previously.
Methods: Residents underwent a 3 hour course under the supervision of ultrasonound-fellowship trained Emergency Physicians (EP). The course included a didactic section, a simulation hands-on training, and an Objective Structured Clinical Examination prior to enrolling the trainees as investigators; Residents performed lung ultrasound (LU) on ESRD patients post HD sessions in a supine position over 28 intercostal windows. They obtained at each window a 6s clip that were reviewed by 2 blinded EP. BLUS was summed up categorizing patients into different classes of pulmonary congestion mild (0-14), moderate (15-30) and severe (>30).

Results: A total of 81 ESRD patients on HD were scanned. 71.6% were males; mean age 59.74 years, mean BMI 28.59±5.62 kg/m²; mean test duration was 15 min. The B-lines score found by the study investigators and EPs was 15.8±21.3 and 12.06±21 respectively. The difference was 3.77±16.8 (0.0475). When categorized into the 3 classes, there was no significant difference between both classification (0.085), and were in moderate agreement-kappa 0.56 [0.42-0.71].

Conclusions: B-lines visualized on bedside LU can provide a reliable and quantifiable assessment for lung congestion. Our study shows that a short training course can render novice users of ultrasound capable of performing this quick evaluation. This can aid in objectively assessing volume overload in a timely manner in HD patients who present a unique clinical challenge. LU has emerged as a new tool, readily available at bedside, providing immediate results, yet is an easily learned skill.

SA-PO157

Background: Percutaneous kidney biopsy is the gold standard for diagnosis of kidney disease but is underutilized due to wariness of complications. Based on clinical and laboratory data, Nephrologists try to predict the renal pathology (clinical gestalt). However, to our knowledge, no study has compared the diagnostic accuracy of the clinical gestalt with the kidney biopsy result.

Methods: Division of Nephrology at Stroger Hospital of Cook County conducts a monthly biopsy conference. Three case summaries are presented followed by discussion and presentation of the biopsy findings. Between September 2014 and April 2015, using a structured form Fellows and Nephrologists were asked to provide their top diagnosis for each case and this was compared with the actual histologic diagnosis. All physicians apart from the primary Nephrologist were blinded to the diagnosis. The study was deemed exempt by IRB.

Results: 23 cases were discussed in the biopsy conference involving 13 unique diagnoses and 286 unique responses were obtained. Overall diagnostic accuracy was 53.49% (153/286); Fellows (52.5%) and Nephrologists (54.36%). Diagnostic accuracy for nephrologists was 100% for ANCA vasculitis and Minimal Change Disease (MCD) and 86% for Diabetes but < 50% for stages of Lupus and other seronegative GNs.

<table>
<thead>
<tr>
<th>Biopsy Diagnosis</th>
<th>Pre-biopsy diagnostic accuracy (%)</th>
</tr>
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<tbody>
<tr>
<td>ANCA vasculitis</td>
<td>100</td>
</tr>
<tr>
<td>MCD</td>
<td>100</td>
</tr>
<tr>
<td>DM</td>
<td>86</td>
</tr>
<tr>
<td>Lupus class II</td>
<td>80</td>
</tr>
<tr>
<td>Amyloid</td>
<td>57.14</td>
</tr>
<tr>
<td>Lupus class III +V</td>
<td>50</td>
</tr>
<tr>
<td>Idiopathic Membranous</td>
<td>45.45</td>
</tr>
<tr>
<td>HIVAN</td>
<td>42.85</td>
</tr>
<tr>
<td>IgA</td>
<td>38.46</td>
</tr>
<tr>
<td>Lupus class V</td>
<td>33.33</td>
</tr>
<tr>
<td>HTN</td>
<td>33.33</td>
</tr>
<tr>
<td>Fibrofatty GN</td>
<td>25</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
</tbody>
</table>

Nephrologists with > 10 years’ experience tended to more accurately predict the diagnosis than those with < 10 years’ experience (64.4 vs. 48.3%, p=0.07).

Conclusions: Nephrologists more accurately diagnosed ANCA vasculitis, MCD & Diabetics by clinical gestalt, but were less accurate for stages of lupus and other seronegative GNs. Regardless of training and experience kidney biopsy is still the diagnostic tool of choice in patients with kidney disease.
for lupus, polycystic kidney disease, and genetics. Regarding patient compliance within specialty clinics, 40% indicated no change, 40% improved, and 20% much improved. On patient satisfaction, 32% indicated no change, 49% improved, and 19% much improved. No respondents perceived decreased patient compliance or satisfaction. Trainees participated in 98% of specialty clinics with a 91% satisfaction rate; 29% were very satisfied. 45% of specialty clinics had ongoing research projects, with an average of 5.5 research projects in those clinics.

Conclusions: Subspecialty clinics can be an irreplaceable tool for both trainees and patients; both groups reported high satisfaction levels. These clinics also enable research by providing a well-established database of patients with specific disease processes. Access to such information is essential to quality research and may streamline the development of key clinical trials.

SA-PO161

Background: The distribution of renal replacement therapy (RRT) modalities among patients varies from country to country, and is often influenced by non-medical factors. In our department, patients progressing towards end-stage renal disease (ESRD) go through a structured Pre-Dialysis Education Program (PDEP). This PDEP is conceived with patients association and nursing educator.

Methods: Forty nine patients with CKD who were receiving care in a multidisciplinary predialysis clinic (mean age 73.5, 63% men). The patients are accompanied by family members. They have received educational education, followed by two workshops in groups and a final educational evaluation. The workshops are carried out in groups of 6 to 10 patients. The PDEP consisted of: (1) psychosocial assessment, (2) education about dialysis and choice of modalities, (3) counseling sessions with patient, family members, (4) education about dietetic and dialysis.

Results: - Choice of the substitution method at the end of the workshops: 61% peritoneal dialysis, 18% haemodialysis and 21% absence of choice - 94% of the patients began the substitution treatment with a chosen modality. - 100% Satisfaction of the patients, 26% decrease of the anxiety. (p=0.0005), 25% (p= 0.0001) increase in the consent for the treatment, 61% increase in the engagement in the treatment (patient ready to receive treatment) (p=0.00001), 47% increase knowledge of RRT (p=0.00001).

Conclusions: Most studies dealing with the pre-dialysis information show a balanced choice of the RRT, but only 50% of the patients actually begin DF. Our workshops of help and assistance to the choice enable to significantly reduce the anxiety linked to the dialysis and thus increase the adherence and engagement for the chosen method RRT. A two-phase educational intervention can increase the proportion of patients who intend to initiate dialysis with self-care dialysis. In our centre offering all treatment RRT modalities, a high percentage of patients exposed to a structured PDEP start with a self-care RRT modality.

SA-PO162
Frequency of Use of Social Media in CKD Patients on Hemodialysis: Pilot Study in Ecuador Fabian A. Ortiz-Herbert, Juan Carlos Calderon, Walter Mejías, David J. Jurado, Byron Jose Haz, Ivan Manuel Cherrez. 1Inst Ecuatoriano de Diálisis y Transplantes, Guayaquil, Guayas, Ecuador; 2Respiral, Guayaquil, Guayas, Ecuador; 3School of Medicine, Univ de Especialidades Espiritu Santo, Samborondon, Guayas, Ecuador.

Background: CKD on dialysis is defined as <15% of kidney function. In Latin America, 461 per million are on dialysis. Region is the third largest Internet user. Social media includes communications spread electronically, shared by individuals and discussed by a committed population. Hispanic Americans with CKD used it, to inform and be informed, includes communications spread electronically, shared by individuals and discussed by a committed population.

Methods: Observational, cross sectional, pilot study. Patients were recruited in dialysis center in Guayaquil. Survey included demographical and clinical items, Charlson score and 4 questions about frequency of use of social media were included. Also, questions about obtaining information; and interest in receiving or asking physician questions related to illness in social media. Frequencies and mean (SD) were employed. Chi-square, ANOVA and M-W U was used for comparisons. Also, Cronbach were calculated.

Results: 34 patients participated, with mean age of 56.5 (SD 16.3), mean years on dialysis of 3.9 (SD 4), 52.0% were women. Comorbidity’s rate was very high (82.4%). 70.6% of patients believed that dialysis control symptoms of disease. 11.8% hadn’t got cellular-phone neither Internet. 61.8% hadn’t got SMS. Almost half of patients had smartphones. Women had a high comorbidity (41.2%), p<0.05. Around 30.0% reported using SMS, Facebook, YouTube, Internet an email at least once a week. 46.7% use Internet as principal source of information, YouTube (20.0%) and email (16.7%). 40.0% of patients reported high interest in receiving information by SMS, Facebook (33.3%) and email (26.6%). 33.3% reported high interest in asking by SMS, email (26.7%) and Facebook (20.0%). 25.5% reported interest in receiving information and asking by whatsapp. Conrach was 0.884.

Conclusions: Internet use is very common for searching information related to disease. WhatsApp, SMS, Facebook and email were reported as new tools for providing illness related information to the patient. The survey had a good reliability and consistency.

SA-PO163
The Impact of Predialysis Education on Patient Understanding, Preparedness, and Decisional Conflict Regarding Renal Replacement Therapy Options Syed Amir Hamid Ali Shah,1 Ion D. Bucaloiu,1 Amanda Young,2 Jamie Alton Green.1 1Nephrology, Geisinger Medical Center, Danville, PA; 2Center for Health Research, Geisinger Medical Center, Danville, PA.

Background: Predialysis education is recommended to prepare patients with advanced chronic kidney disease (CKD) for initiation of renal replacement therapy; however, the impact of various approaches to medical decision-making is not well understood.

Methods: We surveyed 91 advanced CKD patients before and after a 2-hour nurse led group education class to assess patient understanding of renal replacement therapy options (1=poor to 5=excellent), preparedness to make a decision (1=not at all to 5=very prepared), and decisional conflict using a validated scale (0=no decisional conflict to 100=extremely high). The class included a combination of direct verbal instruction and video presentation, tailored to patients with a variety of health literacy and sociodemographic backgrounds. Content included the advantages/disadvantages of hemodialysis (HD), peritoneal dialysis (PD), transplant, and conserving renal function.

Results: Mean age was 66.58, 58% male, 94% white, 44% had a high school or lower level of education, and 46% had low health literacy. Mean level of understanding increased significantly for all modalities pre-post (2.02 vs. 4.10 for HD, 1.95 vs. 4.14 for PD, 2.35 vs. 4.15 for transplant, and 2.10 vs. 4.12 for conservative management; all p<0.001). Decision preparedness also increased significantly from 2.44 to 3.50 (p<0.001). Improvements were similar regardless of age, gender, educational level, or health literacy. At the end of the class, overall decisional conflict was low (median score 10; IQR 0, 20). Equal proportions of patients preferred HD (24%) or PD (22%), compared with transplant (12%) and conservative management (4%), yet nearly (30%) of patients remained unsure of their decision.

Conclusions: Despite significant improvements in patient understanding and preparedness about renal replacement therapy options, a substantial number of patients remain uncertain of their decision after routine predialysis education. Additional decision supporting interventions may be needed to improve decision-making in advanced CKD patients.

SA-PO164
Chronic Kidney Disease Knowledge Among English and Non-English Speakers Anushya Jeyabalan, Pranaav S. Garimella, Lesley Inker. Nephrology, Tufts Medical Center, Boston, MA.

Background: Patient education regarding CKD is an important part of pre-dialysis care. While educational interventions have also shown to improve clinical outcomes among dialysis patients, there is little information however, on health literacy in CKD populations.

Methods: We performed a cross-sectional survey of patients identifying themselves as proficient English or Chinese (Mandarin or Cantonese) who were visiting an outpatient nephrology clinic at a single tertiary hospital. A validated Kidney Knowledge Survey (KiKS) that has been used to assess CKD knowledge in previous studies was translated into Chinese and then self-administered in English or Chinese. All patients had at least 1 prior visit with a nephrologist.

Results: 102 participants completed the survey of which 70 were English speakers and 32 were Chinese speakers. Chinese speakers were older, more likely to have less than high school education and had a greater prevalence of diabetes (Table). Estimated glomerular filtration rate (eGFR) and urine protein to creatinine ratio were not different between groups. Mean KiKS score was lower in Chinese speakers compared to English speakers (11.9 vs. 17.2; p<0.001). Chinese speakers scored lower in all domains of the KiKS; general kidney knowledge (6.2 vs. 4.5), knowledge of kidney function (5.5 vs. 4.0) and knowledge of medications (0.4 vs. 3.7).

Conclusions: While our results for CKD knowledge among English and Chinese speakers are comparable to previously published data (mean score 18.0), scores among non-English speaking CKD patients is lower than English speakers. Whether this finding is associated with differences in care management and clinical outcome needs to be evaluated. Furthermore, educational material and programs may need to be tailored to specific populations to improve health literacy.

SA-PO165
Follow-Up with Doppler Ultrasound of Asymptomatic Arteriovenous Fistula (AVF) After Renal Biopsy (RB) Maite Rivera,1 Saul Enrique Pampa,1 Ingrid Viviana Raoch Michaels,1 Emanuel Lope de la Manzanara P,1 Saul Enrique Pampa,1 Cristina Gareano,1 Ingrid Viviana Raoch Michaels,1 Rodolfo Hernandez Loyola,1 Amanda Liano.1 1Nephrology, Hospital Unam Ramon y Cajal UAH, Madrid, Spain; 2Nephrology, Hospital Unib San Carlos, Madrid.

Background: RB is an essential percutaneous technique in Nephrology that entails major and minor complications, one being the AVF which is usually asymptomatic and underdiagnosed because of the absence of routine Doppler examination post RB. We analyzed the natural history of asymptomatic AVF post RB of native kidney (NK) and transplanted (RT) detected by Doppler examination following RB. We evaluated the natural history of asymptomatic AVF post RB of native kidney (NK) and transplanted (RT) detected by Doppler examination following RB.

Methods: We analyzed the presence of AVF on 327 RB between January 2011 and December 2013, included in our database. 47 (14%) RB developed AVF detected by Doppler ultrasound performed at 24th post RB. We studied the following data: AVF size and its relation to the needle caliber and time to spontaneous closure and its relationship to the AVF size. All RB were real-time ultrasound-guided RB performed with a biopsy gun (Acuson, Tok., Japan), the RT caliber 16G and 14G in the NK.
SA-PO166
The Role of Post Biopsy Ultrasound in Predicting Complications After Percutaneous Renal Biopsy of Native Kidneys
Dept of Nephrology, Allama Iqbal Medical College/Jinnah Hospital Lahore, Lahore, Pakistan.

Background: The percutaneous renal biopsy (PRB) of native kidneys has been an essential tool in the diagnosis and management of renal diseases. Despite all advances, clinically evident bleeding complications do occur in up to 30% of patients after PRB of native kidneys. Traditionally patients are kept under observation for 24 hours after the procedure. An earlier investigation to anticipate the likelihood of complications will help to reduce the overall length of stay for these patients and thus the resource burden. Post PRB ultrasound is a non-invasive, accurate diagnostic tool in predicting procedure related major complications. Our purpose was to conduct a study to evaluate the role of early post PRB ultrasound to predict procedure related complications in our patient population.

Methods: 46 patients undergoing renal biopsy at department of Nephrology, Jinnah Hospital were considered for this study. Renal biopsy was performed using a 16-gauge automated core biopsy needle. After the biopsy, patients were closely monitored in the recovery room and after 1 hour, the biopsied kidney was examined by ultrasound. These patients were admitted and were kept under observation to assess any complications for next 24 hours. Results: Of these 46 patients, 24 (52%) were males with mean age 39 (16 to 60 years). More than 3 cm hematoma was seen in 2 (4.3%) patients at 1 hour post biopsy ultrasound scan. Of those 2 patients, only 1(2%) patient had major complications including hypotension, decrease in hemoglobin etc. Thus 45 (97.8%) patients had uneventful recovery. Sensitivity of more than 3 cm hematoma formation at 1 hour post biopsy in predicting major complications was 100% with specificity of 97.7%.

Conclusions: Our study showed that the frequency of major complications was minimal in patients without >3 cm hematoma formation at one hour post-PRB. Post-PRB ultrasound is a non-invasive, accurate diagnostic tool in predicting procedure related major complications.

SA-PO167
1Pediatric Nephrology, Children’s Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY; 2Pediatric Rheumatology, Children’s Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY.

Background: Most children with SLE develop LN, which significantly worsens morbidity and mortality. Progression to ESRD occurs in 5-10%. Early diagnosis and treatment improve long-term outcomes, thus prompt evaluation is essential. Therefore, a combined pediatric nephrology/rheumatology clinic (LN Clinic) was started in 2013. The primary aim was to evaluate the number of days between onset of proteinuria (first-ami urine pc ≤0.2) and performance of a renal biopsy (bx) for SLE patients (pts), pre- and post-establishment of the LN Clinic. We aimed for a 20% reduction in time to renal bx within 2yr of establishment of this clinic. The secondary aim was a reduction of steps in the referral process.

Methods: SLE pts with an outpt renal bx were identified by an EMR query. Pts were selected if a bx was performed within 5yr pre or 16mo post establishment of the LN Clinic. Our sample selection was cross-referenced with an established lupus registry. A chart review provided the date of proteinuria onset, disease activity markers, and LN class. Pts diagnosed in the inpt setting were excluded. A process map determined the number of steps occurring between new-onset proteinuria and first evaluation by a nephrologist.

Results: We show that pre LN clinic, the median number of days between onset of proteinuria and renal bx was 51 (IQR=25–83.5d), compared to 34 (IQR=14–48d) post (p=0.057). This is a 33% decrease in time. There was a negative association between amount of proteinuria and days to bx (r=–0.5826, p=0.001). There was no association between hematuria or markers of disease activity and days to bx. There was also no association between LN class and days to bx. Pre LN clinic, a referral required 10 steps, which was reduced to 6.

Conclusions: The LN clinic has resulted in earlier renal bx and fewer steps in the referral process. For pts with proliferative LN, this translates to earlier initiation of treatment and a chance at improved outcome.

SA-PO168
Antidepressant Efficacy and Safety Observations: USRDS ACTIVE-ADIPOSE Study
Nancy G. Kutner, Rebecca H. Zhang, Yiyan Huang, C. Barrett Bowling,2 1Emory Univ, Atlanta, GA; 2Atlanta VA Medical Ctr.

Background: Although depression is a prominent issue, depression management in advanced CKD and ESRD patients is not well understood. Antidepressant medications are the most frequent therapy, but efficacy and safety data are limited (Hedaya et al. 2012). A new treatment paradigm for depression management in MHD patients, the focus of a current PCORI trial, is important.

Methods: The primary exposure of interest was use of antidepressant medications among 771 maintenance hemodialysis (MHD) patients ages 20-92 in 14 outpatient clinics who were enrolled 2009-2011 in the ACTIVE-ADIPOSE special study (median ESRD treatment 3.2 years). Gender distribution and ESRD etiology were similar to the overall MHD population, but the proportion non-white and younger than age 65 was higher in the study cohort. Medication efficacy was defined by participants’ scores (<18 vs. 18+) on the Center for Epidemiologic Studies-Depression (CES-D) scale (Hedaya et al. 2006). Adjusted odds for recent falls observed in association with antidepressant use and CES-D score provided an indicator of safety.

Results: Antidepressants were prescribed for 15% of study participants. 40% of those with prescribed antidepressants had an elevated CES-D score, suggesting lack of drug efficacy. Efficacy did not appear to vary by patients’ age or vintage, but more whites had elevated CES-D scores. Recent falls were more frequent among patients on antidepressants with elevated CES-D score (adjusted odds ratio 2.27 [1.05, 4.90], p = 0.04, compared with patients not on antidepressants and CES-D score <18). Fall risk was similar across type of prescribed antidepressant (SSRI, atypical, and tricyclic drugs).

Conclusions: Efficacy of antidepressant medications was unclear for 40% of those with these drugs prescribed, and safety hazard was suggested by increased fall risk. Continued evaluation of nonpharmacologic as well as pharmacologic options for depression management in MHD patients, the focus of a current PCORI trial, is important.

Funding: NIDDK Support

SA-PO169
Sofosbuvir Use in Patients with Hepatitis C Virus Infection and Severe Chronic Kidney Disease
Alberto J. Sabucedo, Marie Essen Antoine, Delvis Jorge, Aileen Andreu, Fernando E. Pedraza, Maria Del Pilar Hernandez, Lennox Jeffers, Marco A. Ladino/Avelaneda. Dept of Medicine. Divs of Nephrology and Hepatology, Miami VA Medical Center/Univ of Miami, Miami, FL.

Background: Chronic hepatitis C virus (HCV) infection is a major health problem. The use of new direct acting antiviral (DAA) based regimens has been shown to provide a high sustained virologic response with less adverse reactions compared to interferon–ribavarin regimens. The American Association for Study of Liver Diseases recommends expert consultation on patients with eGFR less than 30 mL/min because safety and efficacy data are not available on these patient populations. We propose that these DAAs are safe to use in patients with advanced kidney disease.

Methods: A total of 23 HCV positive patients had the following descriptive statistics, 20 males (87%) and 3 females (13%). 15 patients had Genotype 1a (65%), 7 patients had Genotype 1b (31%) and 1 patient had Genotype 2b (4%). 3 patients (13%) had End Stage Renal Disease (ESRD) and were on hemodialysis, 9 patients (39%) had Chronic Kidney Disease stage IV (CKD IV - eGFR<30 mL/min) and 11 patients (48%) had Chronic Kidney Disease stage IIIb (CKD IIIb - eGFR<45 mL/min). The HCV viral load of the 23 patients (100%) had a statistically significant decrease as the therapy progressed through completion with a statistically significant T-test with a p < 0.05. No side effects were present on the patients during DAA therapy. Patients with CKD grades IIIb and IV on DAA treatment had a preserved kidney function by the end of therapy.

Conclusions: Efficacy of sofosbuvir in patients with a preserved kidney function by the end of therapy.
Conclusions: Sofosbuvir is safe and effective in patients with Hepatitis C Virus infection, particularly in severe Chronic Kidney Disease, controlling infection and close monitoring by Hepatology and nephrology is necessary due to the lack of data in safety and efficacy.

SA-PO170

Enoxaparin as Bridging Therapy in Veterans with Advanced Kidney Disease Chui L, Low Renae A. Minnema. Pharmacy, VA San Diego Healthcare system, San Diego, CA.

Background: Patients with CrCl < 30 mL/min on anticoagulation require temporary bridging therapy. Low-molecular weight heparins (LMWH) have longer half-lives and predictable anticoagulant effect but require anti-Xa monitoring in CKD. This study aims to evaluate the safety and efficacy of lovenox as a bridge therapy in patients with CrCl < 30mL/min.

Methods: A retrospective study was conducted from Jan 1, 2012 to Dec 1, 2014. Patients with CrCl < 30 mL/min, received enoxaparin 1 mg/kg as a bridge therapy to warfarin, and had at least one anti-Xa level checked were included in the study. Patients were excluded if they had major bleeding or thromboembolism in previous 3 months before enoxaparin, history of bleeding disorders, or used enoxaparin for other indications. A dosing nomogram was used to guide dosage adjustment to keep anti-Xa levels within the target range (0.5-1.0 mcg/mL). The primary outcomes are 0 of minor/major bleeds and thromboembolic events. The proportion of anti-Xa levels within goal range was assessed.

Results: 12 patients met inclusion and exclusion criteria. The mean age was 62.4 ± 11.9 years, 91.7% were male, 58% were diabetic and 46% had congestive heart failure. 50% were on both warfarin and aspirin. The mean treatment duration of enoxaparin was 11.4 ± 4.6 days, the average CrCl was 17.6 ± 4.5 mL/min. A total of 19 anti-Xa levels were included for analysis. There were 2 (16.7%) bleeding events, 1 (8.3%) major and 1 (8.3%) minor bleed. None of the patients developed thromboembolic complications. The most common adverse event was bruising at the injection site that did not lead to any early discontinuation of therapy. Seventeen (89.4%) were within target range.

Conclusions: Majority (83.3%) of patients had minimal or no adverse events and none with thromboembolic outcomes. In patients with bleed, no correlation was seen with the anti-Xa levels. The dosing protocol is effective, with 89.4% of anti-Xa levels within goal range. The results of this study support the safety and efficacy of the enoxaparin dosing protocol as a bridge therapy peroperatively in patients with CKD. Funding: Veterans Administration Support

SA-PO171

Thiopurine Methyltransferase (TPMT) Genotyping to Predict Myelosuppression Risk in Chinese Patients with Nephropathy Xuehui Li, Jie Ma. Nephrology, Peking Union Medical College Hospital, Beijing, China.

Background: Pharmacogenetic study in nephritis is mainly focused onrogens involved in the metabolism of Azathioprine (AZA). Use of AZA is limited by its toxicity. Variants in the Thiopurine S-methyltransferase (TPMT) have been associated with AZA toxicity. The aim of this study was to determine the contribution of TPMT variants in the development of AZA-related myelosuppression in Chinese patients with nephropathy.

Methods: Variants associated with the decrease of enzymactivity in TPMT genes were genotyped in 42 nephritis patients treated with AZA, and correlated with the clinical response and development of adverse drug reactions in a retrospective case-control study. Three common mutation alleles of TPMT [TPMT* 3A (G460A/A719G), TPMT* 3B (G460A/A719G), TPMT* 3C (A719G)] were detected by polymerase chain reaction-high resolution melting and sequencing in 12 patients, included 4 patients with myelotoxicity and 8 patients without myelotoxicity.

Results: Genotypic analysis showed only one of the 4 patients with myelotoxicity was detected TPMT*3C polymorphisms, no TPMT*2, *3A, *3B or *3C polymorphisms were detected in any of the 11 patients.

Conclusions: Single-nucleotide polymorphisms of TPMT could not explain the azathioprine-related adverse events.

SA-PO172

Lanthanum Carbonate-Induced Granulomatous Gastritis Francesco Iannuzzella,1, Loredana De Marco,2 Sonia Pasquali.1 1Dept of Internal Medicine, Nephrology and Dialysis Unit, Aretespital Santa Maria Nuova, IRCCS, Reggio Emilia, Italy; 2Dept of Human Pathology, Aretespital Santa Maria Nuova, IRCCS, Reggio Emilia.

Background: Long-standing non-calcium based phosphate binders administration has been recently associated with a number of different gastroduodenal lesions. We describe a rare case of lanthanum carbonate-induced granulomatous gastritis. A 58-year-old woman was admitted to our hospital because of nausea, vomiting and weight loss. Because of a well-known stage 5 chronic kidney disease, she was started on peritoneal dialysis. About one month later, CAPD was well-tolerated with an adequate dialysis dose. Nevertheless, she continued to complain of nausea, vomiting and dyspepsia. A gastroscope revealed chronic granulitis with superficial erosions and a histopathology consisting of non-necrotising, sarcoid-like granulomas with aggregates of multinucleated giant cells. Orange crystalloid material was seen within granulomas. Special stains for fungi and mycobacteria were negative. Her previous medical history was only significant for hypertension and type 2 diabetes mellitus. Physical examination was unremarkable. A chest X-ray was normal. A tuberculin skin test was negative. ANCA titres was negative and serum angiotensin converting enzyme (ACE) level was in the laboratory reference range. At the time of our evaluation, she had been receiving lanthanum carbonate 1 g bid for about 6 months.

Conclusions: At the best of our knowledge, so far, only 7 cases have been described in the literature.

The histopathologic picture in our patient was compatible with a lanthanum carbonate-induced gastritis with some peculiar characteristics: a granulomatous reaction and the appearance of lanthanum carbonate crystals not only within histiocytes/multinucleated giant cells but also inside the cytoplasm of the epithelial glandular cells.

SA-PO173

Relative Incidence of Adverse Events with Ferumoxytol versus Other Intravenous Iron Products in Non-Dialysis-Dependent Chronic Kidney Disease Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN.

Background: All intravenous (IV) iron products confer risk of hypersensitivity reaction (HSR). The relative safety of ferumoxytol versus other IV iron products is not established. We used Medicare claims to assess relative safety of ferumoxytol versus other IV iron products in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: We analyzed a 20% sample of Medicare Parts A and B claims in 2009-2012. Patients received a first dose of IV iron between Jan 1, 2010, and Nov 30, 2012, and had diagnosed NDD-CKD without IV iron treatment during the 1 year before first dose. For each ferumoxytol user, we identified 1 propensity score-matched control who used another IV iron product; the score included demographics, comorbidity, and concomitant IV medication. Patients were followed until change in IV iron product, end stage renal disease, death, or Dec 15, 2012. With Cox regression stratified by matched pair and cumulative number of prior IV iron doses, we assessed relative incidence of anaphylaxis, HSR symptoms, hospitalizations, emergency room visits, hospitalization, and death within 1 day of first dose and within 1 day of each subsequent dose.

Results: We identified 7358 ferumoxytol users and 7358 matched controls. Baseline characteristics were balanced across groups. There were too few cases of anaphylaxis and death to permit comparisons. However, after first dose, hazard ratios (ferumoxytol users vs. matched controls) were 0.90 (95% confidence interval, 0.80-1.01) for HSR symptoms, 1.06 (0.66-1.72) for hypotension, 0.72 (0.55-0.94) for ER visit, and 0.78 (0.60-1.02) for hospitalization. After subsequent doses, corresponding hazard ratios were 1.07 (0.90-1.27) for HSR symptoms, 0.91 (0.80-1.01) for hospitalization, and 0.87 (0.63-1.18) for ER visit, and 0.90 (0.70-1.35) for hospitalization.

Conclusions: Relative to other IV iron products, ferumoxytol was not associated with excess risk of adverse events in NDD-CKD patients, following both first dose and subsequent doses. The incidence of anaphylaxis and death was very low in ferumoxytol users and matched controls.

SA-PO174

Efficacy, Safety, and Pill Burden of Sucroferric Oxyhydroxide, an Iron-Based Phosphate Binder, Over 52 Weeks in African American Dialysis Patients Jie Ma, Anjay Rastogi, Mark Ketteler, Adrian C. Covic, Jürgen Floege, Viacheslav Rakov, Liera Armando Salums, M. Coburg Clinic and KFH-Dialysis Center, Germany; *Go. T. Popa University of Medicine and Pharmacy, Romania; ‡RWHU University Hospital Aachen, Germany; †Vifor Pharma; ‡Temple Univ, Philadelphia.

Background: A post hoc analysis of data from a randomized, open-label, Phase 3 study and its extension investigated the efficacy and safety of the iron-based phosphate binder sucroferric oxyhydroxide (SFOH; VELPHORO®) vs sevelamer carbonate (SEV, Renvela®) in African American dialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12 weeks’ dose titration then 12 weeks’ maintenance. Eligible patients enrolled in a 28-week extension study.

Results: Of the 549 patients who completed the extension study, 100 were African American patients, equally distributed between the treatment groups despite the 2:1 randomization (n=48, SFOH; n=52, SEV). Serum phosphorus decreased rapidly and to a similar extent with SFOH and SEV, and remained relatively constant thereafter (Table). Mean ± standard deviation number of tablets/day was lower for SFOH (3.4±1.35) vs SEV (7.6±2.92) over 52 weeks. The incidence of serious or severe treatment emergent adverse events and deaths were similar in both treatment groups. Gastrointestinal-related disorders were the most frequently observed adverse events for SFOH and SEV.

Conclusions: SFOH efficacy was maintained long-term, with a lower pill burden than SEV and similar safety profile, in African American dialysis patients. Post hoc results reflect those from the overall study population.

Table: Treatment efficacy and safety in African American patients.

<table>
<thead>
<tr>
<th>Efficacy (complete set, N=100)</th>
<th>SFOH (n=48)</th>
<th>SEV (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus, mg/dL</td>
<td>7.4 (1.97)</td>
<td>7.3 (1.36)</td>
</tr>
<tr>
<td>Δ at Week 12</td>
<td>-2.0 (1.58)</td>
<td>-2.0 (1.79)</td>
</tr>
<tr>
<td>Δ at Week 24</td>
<td>-2.1 (2.26)</td>
<td>-2.0 (1.79)</td>
</tr>
<tr>
<td>Δ at Week 52</td>
<td>-2.1 (2.59)</td>
<td>-2.1 (1.89)</td>
</tr>
</tbody>
</table>

Safety parameters (safety set, N=205), SFOH (n=130) vs SEV (n=75).

<table>
<thead>
<tr>
<th>% Withdrawal due to AEs</th>
<th>SFOH (n=130) vs SEV (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal due to AEs</td>
<td>8.0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>16.0</td>
</tr>
<tr>
<td>Deaths</td>
<td>27.0</td>
</tr>
<tr>
<td>Gastrointestinal-related adverse events</td>
<td>9.2</td>
</tr>
<tr>
<td>Darnear</td>
<td>15.4</td>
</tr>
<tr>
<td>Disclosed leses</td>
<td>13.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>9.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.0</td>
</tr>
</tbody>
</table>

*Mean (standard deviation) serum levels, AEs, adverse events; SEV, sevelamer carbonate; SFOH, sucroferic ocyhydrilide.

Funding: Pharmaceutical Company Support - Viller Pharma

SA-PO176

Safety and Adherence in End Stage Renal Disease Patients on Chronic Hemodialysis


Background: Missed hemodialysis and abbreviated hemodialysis sessions are common in end stage renal disease patients on maintenance hemodialysis. Dialysis non-adherence has been associated with increased mortality and morbidity in chronic hemodialysis patients. Our quality assessment performance improvement data revealed that on an average 15% of patients missed and abbreviated hemodialysis (HD) sessions over a period of 6 months.

Methods: We evaluated patients’ perception about missed and abbreviated sessions, and safety during HD sessions at our dialysis center. A questionnaire regarding patients’ views about missed, abbreviated and safe hemodialysis sessions using a visual analog scale (0–100 mm, where 0 means ‘No’ and 100 means ‘Yes’) was conducted in-person by a nephrology fellow or a social worker on all HD patients. Data are presented as mean ± SD.

Results: Ninety patients participated in the survey. Sixty eight (75.6%) patients with a mean score of 78±29.6 felt like coming for their HD sessions during the last one month. Fifteen of 89 (16.9%) did not know why they came for HD sessions. Twenty seven percent came because they wanted to live while 18% came because they did not want to die. Eighty nine (98.9%) patients with a mean score of 94.5±17.3 felt safe during the HD sessions. Seventeen (18.8%) patients indicated missing the HD sessions. Thirty six of 83 (43.4%) patients with a mean score of 71±37.6 wanted to miss HD sessions during the last one month. Fifteen of 89 (16.9%) signed against medical advice for the abbreviated HD sessions during the last one month.

Conclusions: Data suggest that safety of HD sessions does not appear to be a factor for missing HD sessions. Lack of patients’ understanding of importance of HD treatments as well as lack of adherence likely leads to non-adherence and abbreviation to HD sessions. The safety of HD treatment was not the core issue behind increasing patients’ absenteeism. Active patients’ participation and individualization of HD sessions may improve adherence to HD sessions.

SA-PO177

Validation of a Tool to Assess Nursing Workload in Hemodialysis

Clara Bohm,1 Brett M. Hiebert,1 Joe A. Buetti,1 Jan Schneider,2 1Univ of Manitoba; 2Winnipeg Regional Health Authority.

Background: Patient classification scales (PCS) to assess nursing workload predict staffing needs and facilitate transparency in assignments resulting in improved work environment, patient safety and quality of care. Few validated PCS tools exist for hemodialysis (HD). This study validates a point-of-care PCS developed for in-centre HD at a Canadian tertiary care centre.

Methods: Using LEAN framework, from Sept 1, 2013 to Mar 1, 2014 at the Health Sciences Centre in Winnipeg, Canada, iterative consultations with stakeholders resulted in creation of a PCS consisting of 9 domains and 67 subdomains. At each HD session between April 7-21, 2014, bedside HD nurses completed both a visual analogue scale (VAS), which assessed general level of nursing care required, and the PCS tool. Karnofsky scale and time-series studies were completed in 50 and 28 randomly selected HD patients, respectively. Analysis: Internal consistency and reliability were assessed using Cronbach’s alpha and Intraclass Correlation Coefficient (ICC), respectively. Multi-trait multi-method analysis (MTMM) determined item homogeneity. Spearman’s correlation of PCS with VAS, Karnofsky Score and time-series studies assessed criterion and predictive validity. Linear regression was performed to determine the association of each subdomain with PCS score.

Results: A PCS and VAS data for 1640 HD sessions (380 patients) was obtained.

<table>
<thead>
<tr>
<th>PCS Score</th>
<th>VAS Score</th>
<th>Karnofsky Score</th>
<th>Time Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>10.7 (5)</td>
<td>3.7 (1.9)</td>
<td>66 (14.4)</td>
</tr>
<tr>
<td>N</td>
<td>380</td>
<td>380</td>
<td>50</td>
</tr>
<tr>
<td>Time</td>
<td>27</td>
<td></td>
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</tbody>
</table>

PCS correlated well with VAS (0.769). Correlation of PCS with Karnofsky scale and time-series studies was -0.56 and 0.39, respectively. ICC was 65%. MTMM identified 4 subdomains never used and 2 which were redundant. Linear regression identified 16 subdomains with minimal contribution to overall PCS score. Reconsultation with stakeholders resulted in a revised 41-item PCS tool. Correlation between the revised tool and VAS, Karnofsky score and time-series was similar to the original model (0.77, -0.51 and 0.316, respectively).

Conclusions: Preliminary results suggest excellent reliability and validity of this PCS tool. Validation studies at other HD centres with expanded time-series and reliability studies continue.
Feasibility of a Hemodialysis Safety Checklist for Nurses and Patients

Methods: Patients received the checklist for the first 3 months. The checklist was completed for 556 of 757 (73%) treatments. The most common reasons for non-completion were the availability of nursing staff trained in Hemo intervention. The checklist was completed for 556 of 757 (73%) treatments. The primary outcome was Hemo Pause completion, which was determined weekly using the percentage of checklists in the patient chart with all 17 items assessed. We also measured Hemo Pause acceptability using local patient safety surveys.

Results: There were 799 hemodialysis treatments pre-intervention and 757 post-intervention. The checklist was completed for 556 of 757 (73%) treatments. The most common reasons for non-completion were the availability of nursing staff trained in Hemo Pause and patient admission to hospital. Among hemodialysis nurses, 93% (15/14) agreed that Hemo Pause was easy to use and 79% (11/14) agreed it should be expanded to other patients. Among hemodialysis patients, 73% (16/22) agreed that Hemo Pause made them feel safer and should be expanded to other patients. Negative comments by nurses or patients occurred on 4% (7/200) of survey responses.

Conclusions: A hemodialysis safety checklist (Hemo Pause) was acceptable to both nurses and patients over a 3 month period. Our next step is to spread Hemo Pause locally and conduct a mixed methods study to determine mechanisms by which Hemo Pause may improve safety culture, patient engagement, and reduce adverse events.

Funding: Government Support - Non-U.S.

Community-Based Parenteral Anti-Infective Therapy (COPAT) for ESRD Patients

Background: Infections are the leading cause of hospital admissions for patients with ESRD. The majority will need to continue antimicrobial therapy when discharged. Community-based parenteral anti-infective therapy (COPAT) refers to the practice of administering antimicrobial therapy in the outpatient setting. It requires a multidisciplinary and the goals are to improve outcomes, reduce toxicity, drug resistance, and decrease hospital stay. ESRD patients have the advantage that IV antibiotics can be given at their dialysis unit. The downfall is that every outpatient dialysis provider has their own policies for therapy. The majority will need to continue antimicrobial therapy when discharged.

Methods: We conducted a single center, prospective time series study. A convenience sample of 14 nurses and 22 prevalent in-center hemodialysis patients participated. All patients were trained in the administration of Hemo Pause, completed the checklist at every hemodialysis session for 3 months and were free to suggest checklist modifications consistent with quality improvement methodology. The primary outcome was Hemo Pause completion, which was determined weekly using the percentage of checklists in the patient chart with all 17 items assessed. We also measured Hemo Pause acceptability using local patient safety surveys.

Results: There were 799 hemodialysis treatments pre-intervention and 757 post-intervention. The checklist was completed for 556 of 757 (73%) treatments. The most common reasons for non-completion were the availability of nursing staff trained in Hemo Pause and patient admission to hospital. Among hemodialysis nurses, 93% (15/14) agreed that Hemo Pause was easy to use and 79% (11/14) agreed it should be expanded to other patients. Among hemodialysis patients, 73% (16/22) agreed that Hemo Pause made them feel safer and should be expanded to other patients. Negative comments by nurses or patients occurred on 4% (7/200) of survey responses.

Conclusions: A hemodialysis safety checklist (Hemo Pause) was acceptable to both nurses and patients over a 3 month period. Our next step is to spread Hemo Pause locally and conduct a mixed methods study to determine mechanisms by which Hemo Pause may improve safety culture, patient engagement, and reduce adverse events.

Funding: Government Support - Non-U.S.

Improving Emergency Room (ER) to Dialysis Flow in a Busy Inner City ER

Methods: Delays in access to hemodialysis during hospitalization are not uncommon and negatively impact on quality of patient care and lead to avoidable complications and unnecessary hospitalizations. Triple Aim is a sought after goal for health organizations to optimize health system performance. We hoped to target one of the three components which is to improve the experience of care.

Methods: The objective was to ensure initiation of dialysis for all non-emergent patients within four hours of ER triage. We analyzed retrospectively in a 8 week observation period, Electronic Medical Record (EMR) data on all hemodialysis patients >18 years of age presenting to the ER, with emphasis on time from triage to initiation of dialysis (TID). We also analyzed factors contributing to delays in dialysis initiation. Data were collected daily on each patient and tabulated weekly. We instituted two measures to address the obstacles.

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

Underline represents presenting author.
These were i)-educating the ER staff about timeliness of informing the renal team and ii) the second was to institute a track and trigger system to systematically gather detailed data on patient transport metrics such a time to patient pick up from initial contact with the transport office.

**Results:** Baseline data revealed average TID from triage was 8 hours. Two major contributory factors identified were late notification by ER to renal team and delays in transport. By instituting measures targeting these, we were able to achieve being able to provide dialysis within 4 hours of triage in over 80% of our non-urgent hemodialysis patients.

**Conclusions:** We were able to improve the patient experience and care with simple measures. This has a positive impact on patient safety by minimizing late treatments and staff fatigue. Though Triple Aim is a goal at the population and health care delivery level, we believe processes can be implemented at a local level that align with the CMS goals of triple aim. In today’s environment it is incumbent upon us to make efforts to innovate for better patient care and to minimize health care costs.

**SA-PO183**

**Quality Improvement Project in Dialysis: Improving Access to Dialysis for Patients Presenting to the Emergency Room (ER)**

**Nikulkumar Chaudhari,** 1 Bonnie Carnes,2 Cherryll Moore,3 Roshni Uppatallia,1 Parikshith Thakur,1 Naheed Ansari,1 Anjali Acharya.1 1Nephrology, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; 2Nephrology, Atlantic Dialysis, Queens, NY.

**Background:** Hemodialysis patients presenting to the emergency room are a vulnerable patient population. Majority of them have significant comorbid conditions. Delays in evaluation and institution of dialysis are common in busy emergency rooms. We undertook a project to improve quality of patient care as well as the patient experience with a goal to provide timely dialysis.

**Methods:** We analyzed baseline data from electronic medical record (EMR) pertaining to all hemodialysis patients presenting to the ER in a specified 8 week period. After period of data collection we identified a factor that was seen as obstacles in providing timely dialysis. One of them was the time from patient triage to notification of the renal team. We instituted an educational program with the ER staff with focus on the timeliness of informing the renal team, establishing “tria to renal team notification time” of less than 30 minutes as a meaningful metric. Data was collected at pre and post intervention. The objective was to meet this goal >80% of the time over the 2 month intervention period.

**Results:** There was a positive impact on the triage to renal notification time. The percentage of timely notifications as defined, rose to >85% from a baseline of <25% and this effect was sustained over the 8 weeks. Most patient notifications happened within 10 minutes of triage.

**Conclusions:** A simple intervention on educating the ER staff made a significant impact on timely evaluation of dialysis patients presenting to the ER. There was an observable positive impact on patient experience. We view this as a simple first step in optimizing patient care and experience towards a seamless journey through the hospitalization. Simple innovative steps such as this could contribute to cost control by avoiding/minimizing dialysis treatments during off hours. In addition it could help mitigate staff fatigue and treatment errors thus improving patient safety.

**SA-PO184**

**Diagnostic Reference Values for Cerebrospinal Fluid May Not Be Useful in Haemodialysis Patients Suspected of Having Central Nervous System Infection**

**Thomas Oates,** Damien Ashby. Imperial NHS Trust, London, United Kingdom.

**Background:** Invasive investigations in haemodialysis (HD) patients can be associated with complications due to bleeding, and standard diagnostic tests, such as pleural fluid biochemistry, have been shown to be of limited value in this patient group. As a result, we examined the utility of cerebrospinal fluid (CSF) analysis in HD patients suspected of central nervous system (CNS) infection.

**Methods:** We used electronic records to retrospectively examine laboratory data from HD patients who had CSF analysis in a 3 year period. All patients were initially suspected of having a CNS infection due to relevant culture and polymerase chain reaction tests ultimately proved negative for bacterial, mycobacterial, fungal or viral infections in all cases.

**Results:** 30 CSF samples from 29 patients were identified in the study period.

CSF protein concentration was available for 16 samples (median 0.40g/L, range 0.19-1.06g/L, corrected for number of red cells in sample) and paired CSF and plasma glucose concentration was available for 16 samples (median 0.40g/L, range 0.19-1.06g/L, corrected for number of red cells in sample). Additionally, 13 out of 25 samples had a CSF:serum glucose ratio of less than the normal value of 0.6 (see Figure horizontal line) which is also suggestive of CNS infection.

**Conclusions:** CSF biochemistry is frequently used in the diagnosis of CNS infection. Our preliminary results suggest CSF protein and glucose concentrations should be interpreted with caution in HD patients and may not add diagnostic information in suspected CNS infection. We are currently investigating the hypothesis that CSF biochemistry may be influenced by duration of chronic kidney disease and HD vintage.

**Funding:** Clinical Revenue Support.
Cystatin C in Predicting Cardiorenal Syndrome Type 1 and Mortality in Patients with Acutely Decompensated Heart Failure with Preserved Renal Function

Carlos Federico Varela,1 Ivan Constantin,2 Gustavo Cristian Greloni,1 Griselda Bratti,1 German Barrera Hugalde,1 Cesar Belziti,2 Rodolfo Pizarro,2 Guillermo Javier Rosa diez.1 *Nephrology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 2Cardiology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background: Cardiorenal Syndrome type 1 (CRS 1) is defined as a worsening renal function that complicates acutely decompensated heart failure (ADHF). These patients experience higher mortality and morbidity. Serum creatinine (SC) is slow to reflect changes in kidney function. Cystatin C (CysC) has emerged as a novel biomarker with a stronger correlation with cardiovascular disease than SC. The aim of our study was to evaluate CysC in predicting CRS 1 and outcomes in patients admitted with ADHF and preserved renal function.

Methods: We conducted an observational and prospectively study. We included patients above 18-years old with ADHF with preserved renal function defined as a SC below 1.3 mg/dL. We excluded patients with heart valvular disease and acute coronary syndrome. CysC blood samples were collected on admission. We defined CRS 1 as a rise in creatinine by 0.3 mg/dL or more during five days.

Results: 166 patients aging 85 median (IQR 77-89) years old were enrolled. The incidence of CRS 1 was 29.7%, with an in-hospital mortality of 3.1%, and a total mortality (TM) of 24.4%. The median follow-up was 193 days. CysC was significantly higher in patients with CRS 1 compared to those without (1.72±0.58 vs 1.51±0.41; p=0.03) and predict TM but did not predict in-hospital mortality (1.69± vs 1.57±0.48; p=0.58) or readmission (1.47±0.4 vs 1.6±0.5; p=0.58). In the multivariable analysis CysC was an independent predictor of mortality (OR 3.31; IC 1.38-7.93) while SC at admission was not (OR 0.48; IC 0.05-3.48). The area under the receiver-operating characteristic curve of Cys for CRS 1 was 0.60 and for TM was 0.65. The best cutoff value was 1.6 mg/dL for both end points. It had a sensitivity and specificity of 61.2 % and 60.3 % for CRS 1, and 61.5 % and 62 % for TM, respectively.

Conclusions: Above a cut-off value of 1.6 mg/dL, CysC predicts CRS 1 and mortality in patients admitted with ADHF with preserved renal function.

Is Cystatin C a Better Biomarker of AKI in ICU compared to NGAL?

Itir Yegenoglu, Fatih Kamis. Internal Medicine, Kocaeli Univ Medical School, Kocaeli, Izmit, Turkey.

Background: Serum creatinine levels can be affected with many variable factors. We concluded that better bio-marker is needed to recognize AKI as early as possible. We studied Cystatin C (CysC) and Neutrophil Gelatinase Associated Lipocalin (NGAL) in ICU patients to determine which is more predictable.

Methods: Hundred and eighty three (85 male; mean age: 65) critically ill patients with no previous chronic renal failure history were included to this study. Clinical, laboratory evaluations were noted and blood was taken in 48 hours for CysC and NGAL and followed for 7 days, if they meet the RIFLE criteria.

Results: CysC and NGAL values for every stages RIFLE and serum CysC value were significant only for RIFLE-L stages (p<0.05) but not urinary CysC. NGAL in serum and also in urine were significantly different in RIFLE-L,F. Biomarkers were compared when evaluated in urine were significantly different in RIFLE-I,F. Biomarkers were compared when

<table>
<thead>
<tr>
<th>No-AKI (N=122)</th>
<th>1 No-AKI (N=14)</th>
<th>2 No-AKI (N=14)</th>
<th>3 No-AKI (N=15)</th>
<th>4 No-AKI (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-CysC mean± SD</td>
<td>30.42±10.17</td>
<td>7.38±2.58</td>
<td>7.56±0.37</td>
<td>7.91±3.58</td>
</tr>
<tr>
<td>U-CysC</td>
<td>75.68±53.76</td>
<td>69.58±10.50</td>
<td>71.74±15.78</td>
<td>74.05±35.78</td>
</tr>
<tr>
<td>S-NGAL Median(25-75)</td>
<td>17.98±8.72</td>
<td>8.39±3.25</td>
<td>8.74±1.65</td>
<td>9.34±2.56</td>
</tr>
<tr>
<td>U-NGAL Median(25-75)</td>
<td>8.39±3.25</td>
<td>9.34±2.56</td>
<td>9.74±1.65</td>
<td>10.34±2.56</td>
</tr>
</tbody>
</table>

While sNGAL and u NGAL were significantly different between these two groups. Serum CysC level was related to mortality (figure 1)(AUC-ROC 0.68 CI; 0.575-0.733).

Conclusions: In our cohort NGAL obtained in 48 hours is more predictable biomarker than CysC for early AKI diagnosis following 7 days. But CysC levels were fairly predictive for mortality.

The Effect of Point of Care (POC) Creatinine/eGFR Measurement on the Incidence of Contrast-Induced Acute Kidney Injury (CI-AKI) following Primary Percutaneous Coronary Intervention (PPCI) for the Treatment of ST Elevation Myocardial Infarction (STEMI)


Background: Contrast-induced acute kidney injury (CI-AKI) is a predictor of mortality, morbidity and length of hospital stay. During STEMI treatment with primary percutaneous coronary intervention (PPCI) there are a number of predictors of AKI including existing renal dysfunction (eGFR < 60) and contrast volume used.

Methods: A retrospective audit over 6 months at the Essex Cardiothoracic Centre identified 348 patients who had presented with STEMI and had PPCI. These patients formed the standard care control group. Prospectively 131 consecutive patients presenting with STEMI and under-going PPCI had a point of care creatinine measurement (STATSENSOR, Nova Biomedical). A comparison in rates of AKI was made between the two groups.

Results: In the standard care group, 9.7% of patients with normal renal function and 26.6% of patients with impaired renal function developed AKI. When creatinine was measured pre-PPCI, 8% of patients with normal renal function and 16.1% of patients with renal impairment developed AKI; a 39.5% reduction in AKI in those with renal dysfunction in the POC creatinine group. The average contrast volume in the standard care group was 159 ml compared to 117.5ml when renal function was found to be impaired (eGFR < 60) pre-PPCI. 186ml was used on average in the POC group when creatinine was found to be normal.
SA-PO190
Serum Creatinine Variability Predicts Progression to CKD4

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Background: Pre-dialysis patients have high serum creatinine (SC) variability. SC variability is associated with high death rates. We examined the association between SC variability and CKD progression in a large cohort of US veterans with a wide range of baseline eGFR.

Methods: VA patients admitted 10/1999 - 12/2005 with at least 4 months with SC and initial eGFR>30 ml/min/1.73 m² (using CKD-EPI) were selected. Autoregression-based slope was computed for each patient using monthly peak SC. SC variability was root mean-square residual of peak SC readings from the regression line. CKD4-date was the first date when eGFR permanently fell below 30 ml/min/1.73 m². Logistic regression was used to predict CKD4 using: initial eGFR, SC variability, SC slope, age, race, months with SC readings, and comorbidities (DM, CAD, PNE, MI, angina, AKI, COPD, CHF). Kaplan-Meier (KM) analysis was used to examine time from first admission to entry into CKD4, stratified by SC variability quartile and baseline eGFR, and Cox regression was used to adjust survival estimates for the covariates above.

Results: Of 342,066 patients, 36,108 (10.6%) reached CKD4. The logistic model had strong prediction accuracy (c=94) with specificity and sensitivity both 86. SC variability was strongly associated with entry into CKD4 (adjusted OR 3.79 [3.67-3.91], p<0.001). Time to CKD4 differed by level of SC variability in KM (p<0.001; Figure) and Cox (HR 1.34 [1.31-1.36], p<0.001).

Conclusions: SC variability is strongly independently associated with rate of decline in renal function, at all baseline eGFR levels, after accounting for covariates, and is an important risk factor for entry into CKD4.

Funding: Veterans Administration Support

SA-PO191
Assessment of Methods Used to Substitute for Missing Preadmission Creatinine Values in the Diagnosis and Staging of Acute Kidney Injury

Amelie Bernier-Jeant,1 Anatolie Duca,2 Francois Madore,2 Remi Goupil,2 Stephan Troyanov,3 Joscé Bouchard.1 1Nephrology, Hopital du Sacre-Coeur de Montreal, Canada; 2Univ of Calgary, Canada; 3IIBISMED, Univ Mayor de San Simon, School of Medicine, Bolivia; 1Hospital du Sacre-Coeur de Montreal, Canada; 2Univ of California San Diego Medical Center.

Background: Missing preadmission serum creatinine values (SCr) are a common obstacle to the diagnosis and staging of acute kidney injury (AKI). As a workaround, the KDIGO guidelines suggest using a baseline SCr computed from the MDRD formula assuming a baseline estimated glomerular filtration rate (eGFR) of 75 ml/min per 1.73m². We hypothesized that surrogates for preadmission SCr will misclassify AKI incidence and severity when compared to a known preadmission SCr.

Methods: Over a 12-month period, we performed a retrospective single-center study of critically ill patients with known preadmission SCr to identify the most accurate method to estimate baseline SCr for AKI diagnosis and staging (KDIGO criteria). We assessed three surrogate methods: 1) the first hospital admission SCr, 2) the minimal SCr after ICU admission and 3) SCr computed for a eGFR of 75 ml/min per 1.73 m² using MDRD. We hypothesized that surrogates for preadmission SCr will misclassify AKI incidence and severity when compared to a known preadmission SCr.

Results: Of 1001 randomly selected patients, a preadmission SCr was available for 498 and 14 were excluded for requiring acute renal replacement therapy. Median age was 67 (IQR 58-76), 60% were male and 98% were Caucasian or Asian. The median time between SCr measurement and admission was 116 (IQR 78-179) days. AKI incidence according to preadmission SCr was 24.8%. We reported in table 1 the AKI incidence, sensitivity, specificity and kappa values for each surrogate method.

Conclusions: Measuring the POC creatinine of 131 patients presenting with STEMI and undergoing PCI reduces the rates of AKI by 39.5% in those with renal dysfunction. This appears to be mediated in part by a reduction in contrast volume in those patients identified with renal dysfunction (117.5ml) compared to normal renal function (186 ml).

Funding: Pharmaceutical Company Support - Nova Biomedical

SA-PO192
Fluid Balance and Oliguria in Early AKI Diagnosis After Liver Transplant

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Background: AKI is a frequent complication of liver transplant (LT), associated with increased morbidity and mortality. Early diagnosis can translate into secondary preventive measures and improve outcomes. We hypothesized that adjusting Scr for positive fluid balance (FB) and applying urine output(UO) criterion would improve timing of AKI diagnosis. In addition, we investigate whether sequential assessment of urinary biochemistry after LT can improve prediction of early-onset post-operative AKI development.

Methods: In a prospective cohort study, we recorded UO, FB and labs of patients undergoing LT. We assessed urine and blood biochemistry perioperatively (before induction of anesthesia, after portal reperfusion, 6, 18, 24 hours after surgery). AKI diagnosis was based on UO and the scCr KDIGO criterion before and after correcting scr for FB (Scr adjusted), using the formula: ((weight*0.6)/(FB))/weight*0.6).

Results: Fifty-five patients >18 years undergoing LT from Jun13 to Oct14 were included in the analysis. Twenty-seven percent (15) of patients developed AKI based on Scr criterion within 7 days of follow-up (early AKI). By adjusting Scr for fluid balance 38%(21) patients were classified as early AKI. Applying the UO criterion, 43patients were classified exclusively by this criterion as early AKI. All patient showed a decline in FeNa and the FeU after portal reperfusion. Patients developing early AKI had a higher decline and maintained lower levels for 24h. FeNa/FeU values were significantly different 6 hours after surgery in early AKI patients. Patients with early AKI based on both criteria or exclusively by UO had a higher mortality and longer ICU and hospital stay than non-AKI patients.

Conclusions: Applying UO criteria and adjusting Scr for FB can help in the early identification of patients developing AKI after liver transplant. Tubular function assessment could be utilized along with biomarkers of kidney injury to identify patients with increased risk of developing AKI. Standardized approach for early AKI diagnosis in high-risk patients could improve outcomes.

Funding: Other U.S. Government Support

SA-PO193
Renal Angina Index: A Practical Tool to Identify Patients at Increased Risk of Acute Kidney Injury

Rolando Clurio-Del Granado,1 Andrea Pero,1 Josec Bouchard,2 Ravindra L. Mehta,2 1Physician - Hospital de la Princesa, Madrid; 2IIBISMED, Univ Mayor de San Simon, School of Medicine, Bolivia; 2Hospital du Sacre-Coeur de Montreal, Canada; 2Univ of California San Diego Medical Center.

Background: Reliable prediction of acute kidney injury (AKI) has the potential to optimize treatment. Recently Goldstein SL et al. proposed an empiric clinical model of renal angina using patient demographic factors and early signs of injury to identify critically-ill children who would be at higher risk of AKI. We test the hypotheses that in a cohort of adult critically-ill patients, a modified renal angina index (RAI) will identify patients at high risk of developing AKI, and could be related to in-hospital mortality.

Methods: We included 124 consecutive patients admitted to our medical ICU. We measured serum creatinine (sCr) every 24 h for 7 consecutive days after ICU admission. AKI was defined as follows: 1) elevation of sCr >25% at 48h after day 0 (RAI ≥2), 2) sustained sCr ≤50% increase within 48h of surgery (early AKI). By adjusting Scr for fluid balance 38%(21) patients were classified as early AKI. Applying the UO criterion, 43 patients were classified exclusively by this criterion as early AKI. All patient showed a decline in FeNa and the FeU after portal reperfusion. Patients developing early AKI had a higher decline and maintained lower levels for 24h. FeNa/FeU values were significantly different 6 hours after surgery in early AKI patients. Patients with early AKI based on both criteria or exclusively by UO had a higher mortality and longer ICU and hospital stay than non-AKI patients.

Conclusions: Applying UO criteria and adjusting Scr for FB can help in the early identification of patients developing AKI after liver transplant. Tubular function assessment could be utilized along with biomarkers of kidney injury to identify patients with increased risk of developing AKI. Standardized approach for early AKI diagnosis in high-risk patients could improve outcomes.

Funding: Other U.S. Government Support

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

Underline represents presenting author.
Conclusions: The RAI provides a clinically feasible methodology to identify critically-ill patients at high risk of developing AKI before a rise in sCr occurs. This tool would permit the early identification of AKI to initiate preventive and treatment strategies minimizing extension of kidney injury.

SA-PO194

The Renal Angina Index Identifies Patients at High-Risk of Acute Kidney Injury – Analysis from AWARE: A Prospective Multinational Study of AKI in Critically Ill Children Rajat K. Bassi,1,2 Ahmad Kaddourah,3,1 Stuart Goldstein,1,3 1Pediatrics, Center for acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2On behalf of the AWARE Study Investigators, Multinational Pediatric ICU.

Background: We conducted a global, prospective observational study of critically ill children to study the epidemiology of pediatric acute kidney injury (AKI). We analyzed the accumulation of the renal angina index for prediction of AKI and patient outcomes.

Methods: Data from 32 centers (5 continents, data collection for 3 consecutive months in 2014) from children (aged 3 months to 25 years) admitted to a pediatric intensive care unit were analyzed. The renal angina index (RAI) was calculated on the day of admission (Day 0) as previously described. A cut-off of ≥ 8 on Day 0 was used to determine fulfillment of absence of renal angina (RA- vs. RA+). The primary outcome was the prevalence of severe AKI on Day 3, defined by change in serum creatinine from baseline using KDIGO stage 2-3 criteria (Day 3 AKI). Other patient outcomes were assessed at 28 days.

Results: 9.6% (501/5231) of children were RA+ on Day 0. The area-under-curve receiver operating characteristic of the Day 0 RAI for Day 3-AKI was 0.797 (95% confidence interval 0.759-0.836). RA+ was associated with a higher net fluid balance on Day 3 than RA- (p<0.001). Compared to RA-, Day 0 RA+ was associated with prolonged duration of mechanical ventilation, longer length of stay, increased use of extracorporeal therapies, and higher incidence of mortality.

Conclusions: In AWARE, the largest prospective multi-center epidemiologic assessment of AKI in critically ill children, we demonstrate the ability of the renal angina index to identify patients at high risk of AKI, three days in advance. Fulfillment of renal angina early in the ICU course is associated with poor patient outcome.

SA-PO195


Background: The bioelectrical impedance analysis (BIA) is a noninvasive and painless technique to perform and compares body composition. We offer information about membrane cell integrity, volemia and clinical status. We evaluate use of this body composition technique and easy to perform, which is used for determining body composition. Can offer a tool to identify patients at high risk of AKI, three days in advance.

Methods: We conducted a global, prospective observational study of critically ill children to study the epidemiology of pediatric acute kidney injury (AKI). We analyzed the accumulation of the renal angina index for prediction of AKI and patient outcomes.

Results: 9.6% (501/5231) of children were RA+ on Day 0. The area-under-curve receiver operating characteristic of the Day 0 RAI for Day 3-AKI was 0.797 (95% confidence interval 0.759-0.836). RA+ was associated with a higher net fluid balance on Day 3 than RA- (p<0.001). Compared to RA-, Day 0 RA+ was associated with prolonged duration of mechanical ventilation, longer length of stay, increased use of extracorporeal therapies, and higher incidence of mortality.

Conclusions: In AWARE, the largest prospective multi-center epidemiologic assessment of AKI in critically ill children, we demonstrate the ability of the renal angina index to identify patients at high risk of AKI, three days in advance. Fulfillment of renal angina early in the ICU course is associated with poor patient outcome.

SA-PO196

Preoperative Renal Resistive Index Predicts the Risk of Acute Kidney Injury in Patients Undergoing Cardiac Surgery Daniel P. Olsson Hertzberg,1 Ulrik Sartipy,2 Martin Holmznan.1 1Dept of Medicine, Karolinska Inst, Stockholm, Sweden; 2Dept of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska Univ Hospital, Stockholm, Sweden; 3Dept of Molecular Medicine and Surgery, Karolinska Inst, Stockholm, Sweden.

Background: Previous studies have indicated that Renal Resistive Index (RRI), an ultrasound-based measurement, can predict AKI in a variety of settings. To our knowledge, there are no studies investigating the predictive value of preoperative RRI and the risk of AKI in cardiac surgery patients. The aim of this study was to investigate whether an elevated preoperative RRI predicts AKI in a general cardiac surgery population.

Methods: Patients undergoing elective cardiac surgery were included prospectively between September 21, 2014 and April 22, 2015 at the Karolinska University Hospital. RRI was measured before surgery. An elevated RRI was defined as >0.7. The outcome AKI was defined as an absolute increase in post-compared to preoperative serum creatinine by 0.3 mg/dL (≥26.2µmol/L) or a relative increase by >50%. The odds ratio for AKI was calculated by logistic regression in patients with a RRI >0.7 versus those with a RRI <0.7.

Results: 98 patients were included. In patients with a RRI 0.7, 6 (15%) patients developed AKI, compared to 19 (33%) in patients with a RRI >0.7. The mean increase in postoperative serum increase in patients with RRI ≤0.7 was 0.12 mg/dL (11 µmol/L) compared to 0.34 mg/dL (30 µmol/L) in those with RRI >0.7 (P=0.03). The odds ratio for developing AKI in patients with a RRI >0.7 compared to those with a RRI ≤0.7 was 2.76 (95% 1.71-7.71).

Conclusions: We found that patients with an elevated RRI before cardiac surgery had an increased risk of developing AKI postoperatively. RRI might be a valuable tool for identifying patients with an increased risk of developing AKI connected to cardiac surgery.

SA-PO197

Development of a Postoperative Risk Stratification Tool via Bayesian Model Averaging for Acute Kidney Injury After Cardiac Surgery Allison Meisner,1 Kathleen F. Kerr,1 Heather Thiessen Philbrook,2 Francis Perry Wilson,3 Amit X. Garg,2 Michael Shlipak,1 Peter Kavsak,1 Richard P. Whitlock,1 Steven G. Coca,1 Chirag R. Parikh,1 Univ of Washington, Seattle, WA; 2Western Univ, ON, Canada; 3Icahn School of Medicine, New Haven, CT; 1UCSF; 2McMaster Univ, ON, Canada; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Acute kidney injury (AKI) is a frequent complication of cardiac surgery. We sought predictive combinations of biomarkers measured 0-6 hours after surgery, potentially in combination with cardio pulmonary bypass (CPB) time (to account for the degree of insult).

Methods: The primary endpoint was sustained mild AKI, defined as an increase of 50% or more in serum creatinine over preoperative levels lasting at least two days during the hospital stay. Severe AKI were AKI (secondary endpoint) was defined as a serum creatinine increase of 100% or more or dialysis during hospitalization. Data were from a cohort of 1219 adults undergoing cardiac surgery at 6 medical centers; among these, 117 developed sustained mild AKI and 60 developed severe AKI. We considered CPB time and 2 biomarkers as candidate predictors. We used Bayesian Model Averaging (BMA) methods to develop center-adjusted combinations for sustained mild AKI by (1) maximizing the posterior model probability and (2) retaining predictors with posterior variable probabilities above 0.5.

Results: The maximum posterior model probability combination included plasma NT-proBNP, plasma h-FABP and change in serum creatinine; the median probability combination additionally included plasma IL-6. The center-adjusted, optimism-corrected AUCs for these combinations were 0.80 (95% CI: 0.78, 0.88) and 0.81 (0.77, 0.88), respectively, for predicting sustained mild AKI, and were 0.81 (0.77, 0.90) and 0.83 (0.76, 0.90), respectively, for predicting severe AKI. For these data, the BMA methods yielded combinations with predictive capacity comparable to that achieved by standard frequentist methods but with smaller models.

Conclusions: Pending external validation, the identified combinations could be used to identify individuals at high risk of AKI immediately after cardiac surgery and could facilitate clinical trials of renoprotective agents.

Funding: Other NIH Support - RO1HL058757
SA-PO198

Low Pre-Operative Serum Bicarbonate Levels Predict Acute Kidney Injury After Cardiac Surgery 2 Yonsei Univ College of Medicine, Seoul, Korea.

Background: Low serum bicarbonate levels are known to be risk factors for renal function deterioration in chronic kidney injury patients. However, it is not well known whether preoperative low serum bicarbonate levels are associated with the development of acute kidney injury (AKI) in patients who undergo cardiac surgery. Therefore, clinical implications of preoperative serum bicarbonate levels on AKI occurrence after cardiac surgery were evaluated.

Methods: The patients who underwent coronary artery bypass or valve surgery at Yonsei University Health System from January 2013 to December 2014 were enrolled. The patients were categorized into three groups according to pre-operative serum bicarbonate levels (group 1 <23 mEq/L, group 2 23-24 mEq/L, group 3 >24 mEq/L). Multivariate logistic regression analysis was performed to determine the effect of pre-operative serum bicarbonate levels on development of AKI at 48 hours after cardiac surgery.

Results: Among 452 patients, 228 patients (26.1%) developed AKI at 48 hours after cardiac surgery. Incidence of AKI was higher in group 1 (34.6%) than group 2 (26.3%) and group 3 (39.0%) (P < 0.001). The duration of post-operative intensive care unit (ICU) stay was longer in AKI patients (AKI vs. non-AKI, 6.2 vs. 2.7 days, P < 0.001). In addition, post-operative ICU stay was longer in the low pre-operative serum bicarbonate level groups (group 1 4.4 days, group 2 3.6 days, group 3 3.3 days, P < 0.001). In multivariate logistic regression analysis, low pre-operative serum bicarbonate levels were significantly associated with post-operative AKI development even after adjusting for age, sex, hypertension, diabetes mellitus, operation type, hemoglobin, and glomerular filtration rate (group 3 as reference, odds ratio=2.36, 95% confidence interval=1.57-3.54, P < 0.001).

Conclusions: Low serum bicarbonate levels were associated with higher incidence of AKI and prolonged ICU stay. Correction of low serum bicarbonate levels before cardiac surgery may reduce the risk of AKI development.

SA-PO199

Admission Hyperuricemia Increases the Risk of Acute Kidney Injury in Hospitalized Patients 1 Charat Thongprayoon, 2 Stephen B. Erickson. 1 Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 1 Internal Medicine, Bassett Medical Center, Cooperstown, NY.

Background: The association between elevated admission serum uric acid and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of developing AKI in all hospitalized patients with various admission serum uric acid (SUA) levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission SUA available from January 2011 through December 2013 were analyzed in this study. Admission SUA was categorized based on its distribution into six groups (less than 3.4, 3.4 to 4.5, 4.5 to 5.8, 5.8 to 7.6, 7.6 to 9.4, and greater than 9.4 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI of various admission SUA levels using the most common SUA level reference range (5.8 to 7.6 mg/dL) as the reference group.

Results: Of 4,135 patients enrolled, AKI occurred in 263 patients (18%). The incidence of AKI and need for dialysis was increased in patients with higher admission SUA levels. After adjusting for potential confounders, SUA greater than 9.4 mg/dL was associated with an increased risk of developing AKI with odds ratios of 1.79 (95% CI 1.13-2.82). Conversely, admission SUA of less than 3.4 mg/dL and 3.4 to 4.5 mg/dL was associated with decreased risk of developing AKI with odds ratios of 0.38 (95% CI 0.17-0.75) and of 0.50 (95% CI 0.28-0.87) respectively.

Conclusions: Elevated admission SUA was associated with an increased risk for in-hospital AKI.

SA-PO200

Hypoalbuminemia Is a Strong Risk Factor for Acute Kidney Injury Progression in Elderly Patients in Intensive Care Unit 1 Yu Kurata, 2 Keita Hirano, 2 Fumio Omata, 1 Yasuhito Komatsu. 1 2 Div of Nephrology, Mitsui Memorial Hospital, Chiyoda-ku, Tokyo, Japan; 1 2 Div of Nephrology, St. Luke’s International Hospital, Chuo-ku, Tokyo, Japan; 1 Center for Clinical Epidemiology, St. Luke’s International Hospital, Chuo-ku, Tokyo, Japan.

Background: Population aging is a global issue; especially, Japan is experiencing rapid aging, at a faster speed than any other developed country, and those aged 65 or older comprised 25.9% of Japan’s population as of September 2014. Previous studies showed elderly patients are at high risk for developing acute kidney injury (AKI). AKI is also a common clinical syndrome in the ICU setting, but its clinical presentation varies from mild to severe. Predicting whether AKI progress or not is difficult but can guide clinical decision making. The aim of the present study is to elucidate different factors of AKI progression among elderly patients in ICU.

Methods: A retrospective study of patients age 65 and older who developed AKI during ICU stay between January 2004 and September 2013. AKI was defined as increase in serum creatinine (sCr) of ≥1.5 times baseline. The primary outcome was the progression to AKI stage 3 (increase in sCr of 3 times over baseline or need for renal replacement therapy (RRT)) within 14 days after AKI development. Prerenal AKI, postrenal AKI, and AKI Stage 3 at diagnosis of AKI are excluded; prerenal AKI is diagnosed when serum BUN-to-creatinine ratio ≥ 20 and postrenal AKI is diagnosed based on clinical situation.

Results: 418 patients were included. The mean age of 80.6 ± 8.2 years, baseline sCr ≤0.89 ± 0.40 mg/dL, and baseline eGFR 66.1 ± 32.3 ml/min/1.73m2. Among 418 patients, 77 (18.4%) experienced AKI progression and 83 (19.9%) died. Of the 77 patients with AKI progression, 25 (6.0%) patients received RRT. AKI stage 2 at diagnosis (OR=2.33, 95%CI=1.23-4.36), RAS inhibitor use (OR=2.84, 95%CI=1.33-5.93), bacteremia (OR=1.69, 95%CI=0.89-3.14), hypoaalbuminemia (OR=5.10, 95%CI=2.94-9.06) were risk factors for AKI progression.

Conclusions: Hypoalbuminemia is a strong risk factor for AKI progression in older patients in ICU. Further study is needed to evaluate whether correction of hypoaalbuminemia could prevent AKI progression or not.

SA-PO201

Impact of Preexisting Serum Prolaumin in All-Cause Mortality in Community-Acquired and Post-Operative Acute Kidney Injury Patients Yanfang Zhou, 1 Dan Wen, 1 Jingyuan Xie, 1 Xiaonong Chen, 2 Wen Zhang, 3 Nan Chen. 1 Nephrology, Ruijin Hospital, Shanghai, China; 2 Nephrology, Ruijin Hospital; 3 Nephrology, Ruijin Hospital.

Background: To explore the impact of pre-existing prolaumin concentration on all-cause mortality in AKI (acute kidney disease, AKI) patients.

Methods: From 2000 to 2010, 477 patients diagnosed with community-acquired AKI (CA-AKI) and treated in the Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University were enrolled in the CA-AKI group. 138 patients diagnosed with AKI after cardiac operations were enrolled in the post-operative AKI (PO-AKI) group. Data were collected at the time of AKI onset and one year after the discharge.

Results: Patients with CA-AKI were younger than PO-AKI patients. Compared with PO-AKI patients, more patients in CA-AKI group suffered from chronic kidney disease, obesity and hyperlipidemia and less patients with cerebrovascular disease (CVD), anemia, diabetes mellitus, hypertension and so on. Levels of SUA were higher for CA-AKI patients compared with PO-AKI patients. CA-AKI patients had higher frequency of RAS inhibitor use (9.5% vs 4.8%, P=0.048). AKI in CA-AKI group was significantly associated with increased cumulative survival rate of patients in normal PA group (PA>20mg/dL) was higher than that in low PA group (P=0.031). Similarly, in PO-AKI group, normal PA level was associated with a higher survival rate (74.1% vs 47.8%, P=0.019).

Conclusions: A significant difference was detected between CA-AKI group and PO-AKI in general characteristics, comorbidities, laboratory examinations, outcome, and risks. Patients with PA<20mg/dL showed better survival rate.

Funding: Government Support - Non-U.S.

SA-PO202

Usefulness of Serum Ischemia-Modified Albumin Levels to Predict Dialysis Requirement in Patients with Acute Renal Injury Mehmet Uzun, Harun Akar. Internal Medicine, Izmir Tepecik Education and Research Hospital, Turkey.

Background: Ischemia-modified albumin is a promising biomarker for early diagnosis of diseases related with ischemia. Ischemia leads to modification in albumin molecule by reducing its binding to cobalt. The aim of this study was to evaluate the levels of ischemia-modified albumin in patients with acute kidney injury (AKI).

Methods: Levels of serum ischemia-modified albumin were estimated in 51 patients with AKI.

Results: The mean age of 28 female and 23 male patients were 65.39±15.28 and 76.48±12.71, respectively. Levels of IMA were found to be high in 75.5 % of the patients (>400) and were found to be normal in 25.5 % of the patients (<400). Kaplan-Meier survival analysis showed that the survival was not different between IMA groups. Urine amounts were significantly different between IMA groups. The urine volume was lower in patients with higher IMA levels (>400).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 671A
Conclusions: In the present study, the levels of IMA were found to be significantly higher in those who needed hemodialysis treatment. IMA levels do not predict mortality. Taking these results together, serum IMA levels might give an idea about dialysis requirement in patients with AKI. More studies with larger sample groups may help to establish the role of IMA on decisions regarding dialysis initiation.

SA-PO203

**Urinary TIMP-2 and IGFBP7 Elevate Early After Vancomycin Administration in Critically Ill Patients Who Develop AKI**

*Maria Ostermann,*¹ Lui G. Forni,² Lakhmir S. Chawla,² Jing Shi,² Kianoush Banaei-Kashani,² John A. Kellum,⁶ ‘King’s College London, London; ‘Royal Surrey County Hospital, Guildford; ‘George Washington Univ, Washington; ‘Walter Biocience, Carlshbad; ‘Mayo Clinic, Rochester; ‘Univ of Pittsburgh, Pittsburgh.

**Background:** We previously validated a biomarker combination of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) for risk stratification of acute kidney injury (AKI).¹ A cutoff of 0.3 (ng/ml)/1000 for [TIMP-2][IGFBP7] indicated AKI stage 2-3 at least 24h prior to serum creatinine.¹ We also showed that nephrotoxic drug use was common in patients developing AKI and that [TIMP-2][IGFBP7] test could have identified patients earlier. In this sub-analysis of the Sapphire study,¹ we examined the temporal changes in [TIMP-2][IGFBP7] following vancomycin.

**Methods:** We identified patients who received vancomycin and grouped them according to their maximum KDIGO AKI stage within 3 days of 1st dose of vancomycin. We calculated the median daily [TIMP-2][IGFBP7] value from day prior to 1st dose of vancomycin until 5 days after. A bootstrap analysis was used to calculate 1-sided p-values for comparison to their maximum KDIGO AKI stage within 3 days of 1st dose of vancomycin. We calculated the [TIMP-2][IGFBP7] test could have identified patients earlier.

**Conclusions:** In patients with AKI 2-3, median [TIMP-2][IGFBP7] values were significantly elevated on the day of the 1st vancomycin dose and remained elevated for the following 2 days. These 5 days after. A bootstrap analysis was used to calculate 1-sided p-values for comparison to their maximum KDIGO AKI stage within 3 days of 1st dose of vancomycin. We calculated the [TIMP-2][IGFBP7] test could have identified patients earlier. In this sub-analysis of the Sapphire study¹, we examined the temporal changes in [TIMP-2][IGFBP7] following vancomycin.

**Figure 1.** Kinetics of urinary [TIMP-2][IGFBP7] in critically ill patients who received vancomycin.

In patients with AKI 2-3, median [TIMP-2][IGFBP7] values were significantly elevated on the day of the 1st vancomycin dose and remained elevated for the following 2 days. These 5 days after.

Conclusions: In patients with AKI 2-3 after vancomycin administration, urinary [TIMP-2][IGFBP7] was significantly elevated on the first 2 days after the 1st dose. These biomarkers have the potential to improve management in patients receiving vancomycin.

**Funding:** Pharmaceutical Company Support - Astute Medical

SA-PO204

**Peri-Operative Serum IL-33 Concentrations in Matched AKI and Non-AKI Patients Undergoing Cardiac Surgery**

*Charles L. Edelman,*¹ Heather Thiessen Philbrook,² Jay L. Koyner,² Michael Shlipak,² Steven G. Coca,³ Chirag R. Parikh.² ¹Univ Colorado Denver; ²Yale Univ; ³Univ Chicago; ⁴UCSF.

**Background:** Endothelial cell damage and death in the nephron is an early feature of AKI. Damage-associated molecular patterns (DAMPs) are endogenous molecules released by damaged cells including endothelial cells. IL-33, a DAMP, has been shown to be present in blood vessels in the kidney and released into the blood, but not the urine, in cisplatin-induced AKI in mice before the increase in serum creatinine. We sought to determine whether serum IL-33 levels are a biomarker of AKI in humans in a nested case-control study.

**Methods:** Perioperative plasma samples were obtained from patients enrolled in the TRIBE-AKI cohort. 35 cases of AKIN Stage 2 AKI or higher within the first 4 post-op days were matched to 70 controls with no AKI by pre-op GFR, age, sex, site and cohort. Blood samples were available pre-op, day 1 (0-6.6 hours), days 2 and 3. Serum IL-33 was measured by ELISA.

**Results:** The pre and post-operative levels of IL-33 are shown in Table 1. Using a mixed model accounting for the matching in the data, the first post-operative value of IL-33 was significantly different (p=0.005) between cases and controls after adjusting for pre-op values. There was a non-significant trend towards higher IL-33 levels on day 2.

**Conclusions:** While most patients in the TRIBE-AKI Cohort experienced stage 1 AKI when classified by peak serum creatinine increase, one-third of those have duration of AKI of ≥3 days. Elevated urinary kidney injury biomarker within 6 hours of surgery may help in identifying of patients at risk for longer AKI duration, which may serve as a reliable metric for drug development trials.

**Funding:** Other NIH Support - NHLBI

<table>
<thead>
<tr>
<th>Time point</th>
<th>Cases Mean (SD)</th>
<th>Cases Median (P25,P75)</th>
<th>Controls Mean (SD)</th>
<th>Controls Median (P25,P75)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>Actual 1082 (2174)</td>
<td>155 (0.516)</td>
<td>1160 (2214)</td>
<td>58 (0.641)</td>
<td>0.87</td>
</tr>
<tr>
<td>Day 1</td>
<td>Actual 1452(2131)</td>
<td>331 (71,1922)</td>
<td>1172(2094)</td>
<td>72 (0.759)</td>
<td>0.048</td>
</tr>
<tr>
<td>Day 1 Delta from pre</td>
<td>355(926)</td>
<td>0 (-43, 202)</td>
<td>12(759)</td>
<td>-5(-166, 0)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>Actual 1591(2082)</td>
<td>315 (34, 2731)</td>
<td>1272(2236)</td>
<td>158 (0.905)</td>
<td>0.08</td>
</tr>
<tr>
<td>Day 2 Delta from pre</td>
<td>456(1252)</td>
<td>0 (-97, 592)</td>
<td>1111(1069)</td>
<td>0 (-163, 5)</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>Actual 1367(2098)</td>
<td>413 (12, 1391)</td>
<td>1583(2294)</td>
<td>135 (0.1170)</td>
<td>0.38</td>
</tr>
<tr>
<td>Day 3 Delta from pre</td>
<td>282(1402)</td>
<td>0 (-152, 382)</td>
<td>222(190)</td>
<td>0 (-82, 50)</td>
<td></td>
</tr>
</tbody>
</table>

Biomarkers at 0-6 hours

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>AKI Duration in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (No AKI)</td>
<td>n=788</td>
</tr>
<tr>
<td>1-2</td>
<td>n=250</td>
</tr>
<tr>
<td>3-6</td>
<td>n=118</td>
</tr>
<tr>
<td>≥7</td>
<td>n=38</td>
</tr>
<tr>
<td>Urine IL-18 (pg/mL)</td>
<td>9.3 (3.6-27.9)</td>
</tr>
<tr>
<td>Urine NGAL (ng/mL)</td>
<td>8.4 (3.3-32.8)</td>
</tr>
<tr>
<td>Urine KIM-1 (ng/mL)</td>
<td>0.4 (0.1-0.8)</td>
</tr>
<tr>
<td>Urine LFABP (ng/mL)</td>
<td>16.0 (3.3-79.0)</td>
</tr>
<tr>
<td>Urine Albumin (mg/L)</td>
<td>12.5 (6.4-30.8)</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
SA-PO206

Urinary Biomarker Evaluation in Cancer Patients Receiving Cisplatin
Blessy George, 1 Amanda Roque-Atiáno, 2 Cara A. Chang, 3 Nickie L. Johnston, 4 Madeleine Gomez, 5 Lucas Ellison, 6 Xia Wen, 5 Lauren Aleksunes, 1 Daniel Bowles, 1 Cindy L. O’Bryant, 6 Melanie S. Joy. 7 1School of Pharmacy, Rutgers Univ, NJ; 2Schools of Pharmacy and Medicine, Univ of Colorado, CO.

Background: The study explored the time dependency of urinary biomarker changes and correlations between the biomarkers and traditional markers of kidney injury in a cohort of patients receiving cisplatin.

Methods: Urine was obtained at baseline, 2Day and 3Day 10 from patients (n=42) receiving cisplatin (25 mg/m²). Urinary kidney injury molecule-1 (Kim-1), calbindin, beta-2 microglobulin (B2M), clusterin, monocytic chemotactant protein-1 (MCP-1), cystatin C, trefoil factor 3 (TFF3), tissue inhibitor of metalloproteinase 2 (TIMP2), and insulin growth factor binding protein 7 (IGFBP7) were measured by multiplex or ELISA.

Results:

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mean±SEM</th>
<th>1Day</th>
<th>3Day</th>
<th>10Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim-1</td>
<td>0.42±0.1±*</td>
<td>0.77±0.1</td>
<td>0.97±0.2</td>
<td></td>
</tr>
<tr>
<td>Calbindin</td>
<td>59.0±13.8±</td>
<td>70.1±12.2±</td>
<td>544±163</td>
<td></td>
</tr>
<tr>
<td>B2M</td>
<td>144±39.1±</td>
<td>502±71.8±</td>
<td>185±41.5</td>
<td></td>
</tr>
<tr>
<td>Clusterin</td>
<td>42.0±23.9±</td>
<td>27.7±8.5</td>
<td>5.2±9.1±</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.62±0.2±</td>
<td>0.45±0.1</td>
<td>1.0±0.23</td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>39.5±7.7</td>
<td>77.2±22.8</td>
<td>64.9±19.0</td>
<td></td>
</tr>
<tr>
<td>TFF3</td>
<td>865±154±</td>
<td>144±202</td>
<td>1616±264</td>
<td></td>
</tr>
<tr>
<td>TIMP2</td>
<td>2.2±0.5</td>
<td>2.3±0.6</td>
<td>3.2±0.7</td>
<td></td>
</tr>
<tr>
<td>IGFBP7</td>
<td>293±484</td>
<td>2357±514</td>
<td>4658±561</td>
<td></td>
</tr>
<tr>
<td>Albunin</td>
<td>11,038±2067</td>
<td>15,958±2442</td>
<td>24,373±4232</td>
<td></td>
</tr>
</tbody>
</table>

A: baseline vs. Day 3: p<0.05, B: baseline vs. Day 10: p<0.05, C: Day 3 vs. Day 10: p<0.05

The biomarker-GFR correlations were: TFF3 (r: -0.259), B2M (r: -0.2017), Kim-1 (r: -0.1758), MCP-1 (r: -0.1390), cystatin C (r: -0.0935), IGFBP7 (r: -0.0764), clusterin (r: -0.067), calbindin (r: -0.0647), and TIMP2 (r: -0.0619). The biomarker-albumin correlations were: calbindin (r: 0.7813), TFF3 (r: 0.5949), clusterin (r: 0.5869), Kim-1 (r: 0.3166), TIMP2 (r: 0.3016), MCP-1 (r: 0.2340), IGFBP7 (r: 0.2217), cystatin C (r: 0.1375), and B2M (r: 0.1149).

Conclusions: Urinary biomarkers display time dependent increases post cisplatin and exhibit variable degrees of correlation with GFR and urinary albumin. TFF3 had high concordance with both GFR and urinary albumin, which may be a favorable characteristic.

Funding: NIDDK Support

SA-PO207

Prediction of Long-Term Renal Outcomes in AKI Survivors by Urinary Biomarkers
Rei Isshiki, 1 Kent Doi, 1 Maki Sumida, 2 Yoshifumi Hamasaki, 2 Naoki Yahagi, 2 Masaoi Nangaku, 1 Eisei Noiri. 1 1Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; 2Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: Although several epidemiological studies suggested that acute kidney injury (AKI) in tropics with lot of morbidity and mortality. The aim of this study was to (I) evaluate the carbonyl and oxidative stress in these group and their pathogenesis link and (II)identify the risk factors and possible interventions.

Methods: We conducted an observational study examining the association of three urinary biomarkers measured at ICU admission [L-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl- β-D-glucosaminidase (NAG)] with CKD progression after discharge without major adverse kidney events. The study explored the time dependency of urinary biomarker changes in two groups of critically ill patients who frequently suffer from multiple and transient/peristent renal insults. This study was aimed to evaluate whether serial measurement enables to predict AKI progression and recovery in these patients.

Results: Among the enrolled 272 patients, 33 were determined as newly developed AKI after ICU admission, 64 showed worsening of kidney function and 63 recovered from AKI. ROC analysis showed that biomarkers at day 2 showed no significantly additional benefit in predicting these three AKI outcomes compared with those measured at day 1. However, net reclassification improvement (NRI) analysis demonstrated adding AKI biomarkers at day 2 to the clinical model consisted of clinical variables and biomarker at day 1 significantly improved prediction of these AKI outcomes.

Conclusions: Serial measurement of AKI biomarkers involved in clinical models could contribute to prediction of AKI outcomes in a heterogeneous cohort of adult mixed ICU.

SA-PO208

Significance of Serial Measurement of Acute Kidney Biomarker in Intensive Care Unit
Rei Isshiki, 1 Kent Doi, 2 Maki Sumida, 1 Naoki Yahagi, 2 Masaoi Nangaku, 1 Eisei Noiri. 1 Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; 2Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.

Background: AKI biomarkers have been developed with the concept of earlier detection of kidney damage than serum creatinine. However, single time point measurement appears not to provide sufficient information for detecting and predicting AKI in ICU patients who frequently suffer from multiple and transient/peristent renal insults. This study was equipped to evaluate whether serial measurement enables to predict AKI progression and recovery in these patients.

Methods: Serial measurements of AKI biomarkers including plasma and urinary NGAL, urinary L-FABP, and urinary NAG at ICU admission (day 1) and 24 hr after (day 2) were conducted in adult critically ill patients who were treated in a mixed ICU.

Results: Among the enrolled 272 patients, 33 were determined as newly developed AKI after ICU admission, 64 showed worsening of kidney function and 63 recovered from AKI. ROC analysis showed that biomarkers at day 2 showed no significantly additional benefit in predicting these three AKI outcomes compared with those measured at day 1. However, net reclassification improvement (NRI) analysis demonstrated adding AKI biomarkers at day 2 to the clinical model consisted of clinical variables and biomarker at day 1 significantly improved prediction of these AKI outcomes.

Conclusions: Serial measurement of AKI biomarkers involved in clinical models could contribute to prediction of AKI outcomes in a heterogeneous cohort of adult mixed ICU.

SA-PO209

Role of Carbonyl Stress Revisited in Pathogenesis of Tropical Acute Kidney Injury
Pinaki Mukhopadhyay. 1 Nephrology, NRS Medical College, Kolkata, West Bengal, India.

Background: Malaria and snake bite are two common causes of Acute Kidney Injury (AKI) in tropics with lot of morbidity and mortality. The aim of this study was to (I) evaluate the carbonyl and oxidative stress in these group and their pathogenesis link and (II)propose the oxidative stress marker in this AKI.

Methods: All cases of falciparum malaria mediated AKI (FMAKI) (n=50), confirmed by antigen and/or in peripheral blood smear and snake bite mediated AKI(SAKI) (n=58) were included. AKI was calculated as per RIFLE criteria. Demographical, clinical and biochemical data were analysed and were followed from hospitalization to discharge/ death. Oxidative and carbonyl stress markers [advanced oxidation product protein (AOPP), advanced glycation end product (AGE), pentosidine, dityrosine, thiobarbituric acid reactive substance (TBARS) and methyl glyoxal (MG)] were measured consecutively according to standard protocol. Predictive importance was assessed from trend analysis, receiver operated characteristic(ROC) curve analyses and multiple logistic regression with AKI as positive response.

Results: The Oxidative stress index(OSI) of FMAKI patients were 1.89 higher than controls. The TBARS, MG level were 6.49 and 5.56 times higher indicating a significant carbonyl stress in these patients. AOPP level was 2.33 times higher indicating proteins being highly insulted in FMAKI. Similarly in SAKI significantly elevated total oxidant stress with decreased total antioxidant stress leads to net oxidative stress in SAKI patients depicted by increased OSI values (p<0.001). MG was increased by 3.48 times (p<0.001).Only AOPP (p<0.001) and MG (p=0.004) were found to be significantly elevated in expired patients than the survived indicating their predictive power for adverse outcome. At univariate level,
all parameters can differentiate between AKI and the non-AKI group. At multivariate level, methylglyoxal, AOPP and dityrosine appeared to be independent predictor of AKI in snake bite and malaria infected patients (p<0.05).

Conclusions: 1. MG, the carbonyl stress marker along with oxidative stress are significantly raised and possibly linked to the pathogenesis of AKI. 2. MG and AOPP can be used as a surrogate marker in these tropical AKI.

SA-PO210

Prediction of Short-term and Long-term Outcomes of AKI-Based on Plasma NGAL Karina Soto,1,2 Fernando Pereira,1 Liliana Maria Goncalves Cunha,1 Iola Pinto,1 Ana Luisa Papoila,1 Prasad Devarajan,1 Nephrology, Hospital Fernando Fonseca; 1Inst Superior de Engenharia de Lisboa; 2Nova Medical School/FCM, Univ Nova de Lisboa, Portugal; 2Nephrology, Cincinnati Children’s Hospital Medical Center, OH.

Background: We have previously shown a good performance of Plasma NGAL (pNGAL) as an AKI biomarker in emergency settings. Now we investigated a new AKI classification based on pNGAL for prediction of kidney dysfunction at discharge and at the end of follow-up.

Methods: Patients from a previous study at ED were followed for >5y. During the index hospitalization, 21% were AKI (based on Scr), 26% transient azotemia, 51% normal function and 2.4% stable CKD. All patients had Scr and pNGAL measured at 0, 6, 12, 24 and 48H of admission. A new AKI classification based on pNGAL levels (AKI:pNGAL+) defined AKI as pNGAL≥110 ng/mL (cut-off by GAMS). A multivariable logistic and Cox regression models were applied.

Results: Of 599 patients admitted, 97.8% were available at discharge and 54.4% at last follow-up. At admission 42.6% were reclassified as AKI:pNGAL+ whereas only 21.7% were based on Scr. All significant clinical variables were included in multivariable analysis at discharge.

Variables
OR 95% CI
AKI:pNGAL+ 4.2 2.3-7.6
Age 1.1 1.0-1.1
CVD 1.2 1.2-3.2
DM 1.5 1.5-4.0

p<0.001 all unless CVD=0.007

Having pNGAL≥110 at ED corresponded to 4-fold increased odds for eGFR<60 mL/min (p<0.001 ROC-AUC 0.82). The cumulative incidence of CKD showed that most of AKI:pNGAL+ developed CKD at 60 mo (the highest proportion 77%) (figure 1) HR for CKD: 2.4 for patients AKI:pNGAL+ in long-term (p=0.001 ROC AUC 0.74) NRI 56.3 and IDI 0.03.

Conclusions: Patients who were AKI:pNGAL+ had significant lost kidney function at discharge and more than 2-fold risk of developing CKD in long-term evolution. Plasma NGAL is a useful tool for CKD prediction, independent of serum creatinine.

SA-PO211

The Use of Novel Serum and Urinary Biomarkers to Predict the Development of Hepatorenal Syndrome in Patients with Advanced Cirrhosis

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Background: Hepatorenal syndrome (HRS) is associated with high mortality rates in advanced cirrhotic patients without liver transplantation. Prediction of the development of HRS remains difficult.

Methods: We prospectively recruited patients with Child’s B or C cirrhosis and followed them at 2-week intervals 12 weeks or until HRS developed. Serum cystatin C (CysC), serum Neutrophil Gelatinase-Associated Lipocalin (NGAL), serum IL-18, urine kidney injury molecule-1 (KIM-1) and urine liver-type fatty acid binding protein (LFABP) were measured at recruitment (Baseline).

Results: 43 patients were included. 12 developed HRS at 7.3±5.1 weeks from Baseline. pNGAL at recruitment had a higher Baseline level of serum CysC (4.42±0.51 mg/L vs. 1.07±0.50 mg/L, p=0.021), serum NGAL (129.0±68.66 ng/mL vs. 72.84±48.91 ng/mL, p=0.025), serum IL-18 (759.91±477.05 mL/mL vs. 358.13±153.00 mL/mL, p<0.001), urine KIM-1 and LFABP (3.64±3.34 ng/mL vs. 1.18±1.68 ng/mL and 10.17±8.37 ng/mL vs. 3.28±4.20 ng/mL, p=0.023 and 0.035 respectively) when compared to patients who did not develop HRS. The cut-off and positive and negative predictive values for HRS were shown in Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cut-off Value</th>
<th>AUC</th>
<th>95% CI</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline serum Cystatin C (mg/L)</td>
<td>0.899</td>
<td>0.748</td>
<td>0.572-0.924</td>
<td>52.4</td>
<td>90.9</td>
<td>0.021</td>
</tr>
<tr>
<td>Baseline serum NGAL (ng/mL)</td>
<td>90.47</td>
<td>0.756</td>
<td>0.592-0.939</td>
<td>72.7</td>
<td>75.0</td>
<td>0.025</td>
</tr>
<tr>
<td>Baseline serum IL-18 (ng/mL)</td>
<td>442.84</td>
<td>0.858</td>
<td>0.708-1.000</td>
<td>73.3</td>
<td>92.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline urine KIM-1 (ng/mL)</td>
<td>1.499</td>
<td>0.785</td>
<td>0.607-0.963</td>
<td>75.0</td>
<td>84.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Baseline urine LFABP (ng/mL)</td>
<td>3.398</td>
<td>0.765</td>
<td>0.578-0.949</td>
<td>54.5</td>
<td>86.7</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Serum NGAL and IL-18 and urinary KIM-1 at Baseline were significantly associated with the development of HRS (OR 1.017, 95% CI 1.001-1.033, p=0.035; OR 1.007, 95% CI 1.002-1.013, p=0.012; OR 0.963, 95% CI 0.937, p=0.045, respectively)

Conclusions: Serum IL-18 and urinary KIM-1 could serve as biomarkers to predict HRS in patients with advanced cirrhosis.

Funding: Private Foundation Support

SA-PO212

Robust Risk Assessment of Acute Kidney Injury After Acute Myocardial Infarction Using the Novel Biomarker C-Terminal Fragment of Agrin (cAF)

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Background: Acute kidney injury (AKI) complicating acute myocardial infarction (AMI) increases subsequent morbidity and mortality. The objective of this study was to validate c-terminal fragment of agrin (cAF) as a novel AKI biomarker in patients with AMI.

Methods: 403 consecutive patients with AMI were enrolled, samples were collected and presentation for serum (sCAF), urine (uCAF) CAF, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18) and cystatin-C analysis. The presence of AKI was evaluated at 48 hours post admission and at discharge.

Results: The incidence of AKI was 6.7%±14.6% depending on time-point and criteria used and increased across quartiles of uCAF (x<0.001). Both uCAF and sCAF significantly correlated with serum creatinine on admission (r=0.233, p<0.001 & r=0.175, p<0.001), at 48 hours (r=0.263, p<0.001 & r=0.226, p<0.001) and with peak creatinine as well (r=0.317, p<0.001 & r=0.225, p<0.001). The predictive accuracy for AKI of uCAF was good (AUC=0.630, 95%CI 0.552-0.708) and slightly better as that of urine NGAL (AUC=0.616, 95%CI 0.540-0.692), uCAF vs. sCAF (p=0.733), whereas that of sCAF was moderate (AUC=0.587, 95%CI 0.509-0.666). A uCAF value of 1033 pg/mL is suggested to have the best discriminating ability. The sensitivity of uCAF was 37% and the specificity 85% (NPV; 89%; PPV; 30%). Univariate analysis showed a strong association of uCAF with AKI incidence (OR 1.45, 95%CI 1.15-1.82, p=0.002) which remained significant even after adjustment for several confounders (OR 1.35, 95%CI 1.05-1.74).

Conclusions: Urine CAF analysis allows a robust risk stratification of AKI after AMI and thus optimized management in such patients.

Funding: Government Support - Non-U.S.
SA-PO213

At Myeloma Diagnosis, Age and Free Light Chain Level Predict Renal Function and These Factors with Free Light Chain Response Predict Renal Outcome

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1Univ Hospital Birmingham, UK; 2Univ of Birmingham, UK.

Background: Elevated involved immunoglobulin light free chain (FLC) is a major cause of renal impairment (RI) in myeloma. Relationships between presentation and post-induction (PI) renal function and serum FLC levels are not established.

Methods: We used central laboratory data from the MRC Myeloma IX trial which compared biphosphonate and thalidomide-based therapies. Patients were divided into 3 eGFR categories: eGFR ≥60 mL/min, normal renal function; eGFR 30-59 mL/min, mild-moderate RI; eGFR <30 mL/min, severe RI. Linear regression and Logistic regression modelling were used to explore independent determinants of renal function. Results:

- 52.8% had an eGFR ≥60 mL/min; 37.3% had an eGFR 30-59 mL/min and 9.8% had an eGFR <30 mL/min. Median eGFR in patients with involved FLC was significantly lower than those with κFLC (58 [IQR 42-77] vs 63 [IQR 46-80]; P=0.01). Median eGFR for light chain only myeloma (LCO) was also significantly lower than those with IgG and IgA myeloma (49 [IQR 28-78] vs 62 [IQR 47-79] vs 63.5 [IQR 42.2-82.0]; P=0.0001).
- Patients with a difference between involved and uninvolved FLC (dFLC) ≥500 mg/L had a lower eGFR compared to those with dFLC 100-499 mg/L and dFLC <100 mg/L (52 [IQR 35-72] vs 66 [IQR 52.0- 82.6] vs 67 [IQR 54.2-82.0]; P=0.0001). A dFLC level of 700 mg/L was the optimal cut-off value for prediction of severe RI, with an AUC of 0.8.

Conclusions: Age and serum FLC level predict eGFR at presentation and age, presentation eGFR, and serum FLC response predict PI renal outcome.

SA-PO214

Urinary Biomarkers Improve the Prediction and Prognostic Assessment of Acute Kidney Injury in Critically Ill Patients

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Background: Acute kidney injury (AKI) is common in intensive care unit (ICU) patients, and is diagnosed late by serum creatinine. New biomarkers may permit earlier detection and better management.

Methods: All patients admitted to the ICUs of two university hospitals were screened for this prospective cohort study. Clinical information and urine were collected on admission and daily for 7 days. Urine biomarkers analysed were neutrophil gelatinase-associated lipocalin (NGAL), α- and ʌ- glutathione-S-transferases (GSTs), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), creatinine, and albumin. AKI was defined by modified KDIGO criteria, using ICU admission creatinine as reference. Values were compared between those who did or did not develop AKI or 30d adverse outcomes by a clinical score (including age, gender, serum creatinine & urea, urine output) and urine biomarker values on admission. In patients developing AKI, ROC curves were similarly generated for the prediction of clinical outcomes with values obtained at time of AKI diagnosis.

Results:

- 659 patients were enrolled; 181 patients (27%) developed AKI within 7d of ICU admission. AKI stages at diagnosis were: Stg1(n=81,45%), Stg2(n=17,9%), Stg3(n=83,46%).
- Best predictors were KIM-1 and NGAL, and the combination improved the prediction of AKI in the first 48h in ICU (AUC(95% CI): 0.79 (0.72-0.82)).
- A dFLC level of 700 mg/L was the optimal cut-off value for prediction of severe RI, with an AUC 0.8.
- New biomarkers may permit earlier detection and better management.

Conclusion: Age and serum FLC level predict eGFR at presentation and age, presentation eGFR, and serum FLC response predict PI renal outcome.

SA-PO215

Association of Growth Factor Biomarkers with Acute Kidney Injury and Long-Term Mortality in Adults following Cardiac Surgery


TRIBE-AKI Consortium.

Background: Following the structural damage and functional impairment from acute kidney injury (AKI), the kidney undergoes a coordinated process of repair involving regenerative growth factors. We conducted an ancillary analysis of a large, prospective study of adults undergoing cardiac surgery to investigate the utility of epidemical growth factor (EGF) and vascular endothelial growth factor (VEGF) in predicting kidney injury and mortality.

Methods: Patients undergoing cardiac surgery at high risk for AKI were enrolled at six academic centers. AKI was defined as a doubling in serum creatinine from baseline or receiving acute dialysis during the hospital stay. Postoperative plasma levels of EGF, VEGF, and a combination model of the two growth factors were evaluated for association with outcomes of AKI or long-term, all-cause mortality at a mean follow-up of 3 years.

Results:

- First postoperative and peak plasma EGF were not associated with AKI.
- Peak plasma VEGF was independently associated with increased risk of AKI (adjusted odds ratio [OR] 7.4, 95% confidence interval [CI] 1.1-47.9).
- First postoperative EGF was inversely associated with a lower risk of mortality (adjusted HR=0.67; 95% CI: 0.47-0.97).
- First postoperative VEGF was likewise associated with a lower risk of mortality (unadjusted HR=0.36; 95% CI: 0.16-0.82), though the association was attenuated following adjustment (adjusted HR=0.36; 95% CI: 0.15-1.04).

Conclusions: Postoperatively, EGF and VEGF are released in response to AKI, and their concentrations were inversely associated with long-term mortality. These growth factors may serve as biomarkers of long-term outcomes in adults undergoing cardiac surgery.

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SA-PO216

Procalcitonin as a Predictor of AKI in Patients with Sepsis

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Background: Sepsis is a common cause of AKI. Identifying patients at risk for AKI could improve clinical outcomes. Procalcitonin (PCT) reflects accurately the presence of sepsis and its severity. We evaluated the role of PCT as predictor of AKI in septic patients.

Methods: Cross-sectional study of 72 septic patients between January to December 2014. Patients with Scr >1.5 mg/dl before admission, ESRD patients and those with autoimmune comorbidity were excluded. PCT, Scr, urea, and WBC were measured on admission, and at 24 h and 48 h of hospitalization. X2 and t-test were used when appropriate. A ROC curve for PCT value on admission as well as the area under the curve (AUC), the standard AUC error, and sensitivity and specificity of PCT values were determined.

Results:

- Patients' mean age was 50.8 y (18-79); 37 (51.4%) were women. 18 (25%) patients had PCT value at <0.5 ng/mL (negative) and 54 (75%) 0.5 ng/mL (positive) on admission. Forty-two (58.3%) patients developed AKI, 19 (45.2%) KDIGO 1, 12 (28.6%) KDIGO 2, and 11 (26.2%) KDIGO 3. Of the 42 patients who developed AKI, 37 (88.1%) had a positive value of PCT at admission (p<0.01, OR 5.659, 95% CI 1.738 to 18.425).
- The ROC curve for PCT value on admission as well as the area under the curve (AUC), the standard AUC error, and sensitivity and specificity of PCT values were determined.

Conclusions:

- We found a significant association between levels of PCT and AKI and development of AKI in patients with sepsis. A cutoff PCT value of 2.565 ng/mL on admission had the highest validity for predicting AKI with an SE of 61.9%, one SP of 80%, a PPV of 44.52%, and NPV of 56.18%.
Elevated Erythropoietin Concentration in AKI Is Associated with IGFBP-1 Rather Than Hemoglobin
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Background: EPO expression will be increased by hypoxia in the kidney and hypoxic injury plays a crucial role in pathogenesis of AKI. However, little is known about blood EPO levels in critically ill patients complicated with AKI.

Methods: This study prospectively enrolled 98 adult critically ill patients who admitted to the adult ICU. We measured plasma EPO and also measured plasma IGFBP-1 as a hypoxic marker, which is produced mainly by liver, and plasma NGAL and urinary NAG as renal damage biomarkers on ICU admission. This study was conducted to evaluate whether plasma EPO levels in AKI patients was regulated by other factors than anemia.

Results: AKI occurred in 42 (42.9%) patients. Significantly higher plasma EPO in the AKI group was detected compared with the non-AKI group (16.13 [9.87–28.47] mIU/mL, p<0.05). Plasma EPO concentration was strongly and negatively correlated with hemoglobin in the non-AKI group but not in the AKI group.

Conclusions: Plasma EPO had a predictive value for diagnosing AKI but it itself had a limited value for distinguishing prerenal AKI from other causes of AKI.

Predictive Value of Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) to Distinguish Prerenal AKI to Other Causes of AKI
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Background: Plasma Neutrophil gelatinase-associated lipocalin (NGAL) is a promising biomarker for acute kidney injury, but it’s role for distinguishing prerenal AKI from other causes are not well known. The aim of this study was to evaluate the predictive value of plasma NGAL to distinguish prerenal AKI to other causes of AKI.

Methods: We reviewed all NGAL test from December 26, 2011 to February 28, 2015 in Konkuk University Medical center (Seoul, Republic of Korea) and subtract patients who taken factional excretion of sodium (FENa) test at the same time. Patients were first grouped with Acute Kidney Injury Network (AKIN) stages and evaluated it’s diagnostic role for AKI and second divided with prerenal AKI and other causes of AKI.

Results: Total 5814 NGAL test were done from December 26, 2011 to February 28, 2015 in Konkuk University Medical center, and 495 patients taken FENa test at the same time. In AKI group, plasma IGFBP-1 was strongly and positively correlated with plasma EPO. Multiple logistic regression analysis revealed plasma EPO in the AKI group was significantly associated only with plasma IGFBP-1 and complication of diabetes mellitus.

Conclusions: EPO production in AKI was enhanced by not anemia but systemic hypoxic stimuli evaluated by IGFBP-1, indicating unknown independent pathway of renal EPO production in AKI.

Neutrophil/Lymphocyte Ratio for Early Detection of Acute Kidney Injury (AKI) in Patients Admitted to the Emergency Room
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Background: Neutrophil to lymphocyte ratio (NLR) is a readily available biomarker of systemic inflammation. Several studies have provided evidence of an association between elevated NLR and adverse outcomes in a variety of medical and surgical conditions, including CKD. In this study, we evaluated the predictive capacity of single Emergency Room (ER) measurement of NLR for early diagnosis of acute kidney injury (AKI).

Methods: We prospectively studied 294 patients aged 71.6±17. NLWR was measured at presentation to the ER. AKI was defined as a new-onset 1.5-fold or more increase in serum creatinine or a 25% decrease in estimated GFR sustained for at least 3 days despite volume resuscitation. The primary outcome was AKI. Secondary outcome was in-hospital mortality.

Results: 36 patients (12.2%) developed AKI and 26 (9%) died. Mean NLR was significantly higher in AKI compare to non-AKI patients (11.7±15.2 vs 6.45±15.2; p=0.048). A multivariate model adjusted for age, gender, blood pressure, and plasma albumin levels confirmed that NLR is higher in AKI patients (p=0.048). Receiver operating characteristics curve revealed AUC 0.715 (95% CI 0.63-0.8) sensitivity 0.78, specificity 0.65, OR 6.423 (CI, 2.659 to 16.026) for a cutoff value of NLR 5.5. The association between NLR and in hospital mortality was not statistically significant (p = 0.92).

Conclusions: Single ER measurement of NLR can be a useful tool for early diagnosis of AKI. This finding is particularly important in light of the widespread availability and low cost of NLR, especially compared with other biomarkers currently under study in the context of AKI.
in AKI cases, and within 24h of ICU admission in frequency-matched controls. AKI was defined by KDIGO criteria. Longitudinal data from AKI cases were obtained throughout hospital stay. Renal recovery was defined as the ratio of follow-up SCr/baseline SCr £1.5. Urine Klotho was measured by immunoprecipitation-immunoblot. Mixed-effects linear models were constructed to assess longitudinal trends of Klotho in AKI survivors.

Results: Mean (SD) age was 58 (17) years, 62% were men and 75% white. Patients with AKI had higher critical illness scores than controls without AKI. Five (17.2%) patients died and 8 (27.6%) required RRT in the AKI group. Only 3.5% patients died in the control group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 10 [IQR 4–20] vs 28 [14–52] fmol/mg, p = 0.003. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited renal recovery (n=7, ∆+216%, p = 0.05) but not in those that did not (n=7, ∆+8%, p = 0.91), median follow-up 24 days.

Conclusions: uKlotho/Cr is significantly lower in patients with AKI when compared to ICU controls without AKI. uKlotho/Cr recovered only in patients that recovered kidney function. Klotho may serve as a prognostic marker for AKI recovery.

SA-PO221

Biomarkers of Acute Kidney Injury in Children Treated with Cisplatin

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Background: Cisplatin(CisP) causes acute kidney injury(AKI) and may cause chronic kidney disease(CKD). Biomarker(BioM) may allow early AKI diagnosis and treatment. Applying BioM to Long-Term Effects in Child/Adolescent Cancer Treatment(ABLE) is a Canadian study of cancer treatment toxicities, including nephrotoxicity. We study BioM of child CisP treatment for early and late renal outcome prediction. This analysis evaluates neutrophil gelatinase-associated lipocalin(NGAL), kidney injury molecule-1(KIM-1) and serum Cystatin C(CysC) with CisP therapy in the first 1/3 of subjects.

Methods: Ongoing, 8-site, prospective cohort of 150 children receiving CisP. Excluded: severe CKD. Protocol includes 2 “acute” visits[AV] around CisP infusion(pre, post, discharge urine/blood) for serum creatinine(SCr), CysC, urine NGAL, KIM-1. Outcomes: AKI(Kidney Disease Improving Global Outcomes[KDIGO] SCr criteria; AKI by National Cancer Institute(NCI) criteria(based on serum electrolytes).

Results: Data available in 44/60 (mean/SD age 7.4yrs; AV1/AV2 hospital stay 16±27/12±26 days; 55% male). AV1: 11% KDIGO AKI, 46% NCI AKI, 50% with either. AV2: 14% KDIGO AKI, 72% NCI AKI, 75% with either. BioM drop immediately post-CisP (n=25), followed by a rise at discharge.

A similar pattern is seen in AKI and non-AKI groups and when expressing BioM/urine creatinine(not shown).

Conclusions: This is a novel study of AKI BioM excretion in CisP-AKI. NCI-AKI is more common than SCr-AKI. The immediate BioM drop post-CisP may be related to injury protection from high fluid rate and/or urinary alkalization peri-CisP. Our larger sample size will allow to further characterize BioM excretion and evaluate BioM associations with AKI definition and outcomes.

SA-PO222

Elevated Renal Injury Biomarkers Fall Transiently After Stenting in Human Atherosclerotic Renal Artery Stenosis (ARAS)

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Background: ARAS reduces blood flow and perfusion pressures to the post-stenotic kidney (STK), ultimately producing inflammatory injury. The aim of our study was to identify and track renal injury biomarkers for 24 hours and 3 months after combined CT imaging and stent revascularization.

Methods: 12 patients with severe ARAS scheduled for revascularization for clinical indications were enrolled in a 3 day inpatient and restudied 3 months later. All subjects maintained ACE/ARB Rx and fixed Na+ intake, and were compared with Essential Hypertensives(EH) (n=12) undergoing the same biomarkers and imaging studies. Glomerular filtration rate (GFR) was measured by iothalamate clearance, blood flow and perfusion by Multidetector Computerized Tomography (MDCT) and NGAL, MCP-1, IL-10, TNF-α, KIM-1, IGFBP7 and TIMP-2 in renal vein and peripheral blood/IVC samples every 6 hours for 24 hours and after 3 months.

Results: Kidney perfusion, whole kidney blood flow, single kidney isohalometric GFR were reduced in the STKs compared to kidneys from EH and increased after stent revascularization.
date, it is unclear which intrinsic factors trigger the onset of SIRS and associated AKI. We investigated the role of mtDNA during systemic inflammation and AKI and the role of platelets herein.

**Methods:** Human platelets were stimulated with mitochondrial DNA, genomic DNA or unmethylated CpG-enriched oligonucleotides (CpG ODN). Platelet activation was monitored using FACSTM. In a single centre prospective observational study we included 37 patients diagnosed and classified for the onset of SIRS with or without the development of AKI that were admitted to the ICU. As a control we included (n=25) patients after elective major surgery without a diagnosis of either SIRS or AKI. Blood and urine samples were isolated and processed. Free circulating plasma and urinary mtDNA was determined by RT-PCR. Inflammatory mediators and PUF in urine were measured using specific ELISA.

**Results:** Mitochondrial DNA, but not genomic DNA triggered platelet activation. Unmethylated CpG ODN, dose dependently stimulated platelet activation. Compared to ICU-controls, critically ill patients had elevated plasma and urinary mtDNA and proinflammatory cytokines. Compared to SIRS patients without AKI, the patients with AKI displayed elevated levels of urinary PUF indicative of platelet activation.

**Conclusions:** The development of AKI in critically ill patients is associated with platelet activation, possibly triggered by mitochondrial DNA.

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**SA-PO225**

**Invaders in the Night: Sleep Apnea and Sub-Clinical Renal Injury**

**Aaron A. Rampersad,** Shahab Bozorgmehr, 1 Areef Jishani, 1, 2, 4 F. David Weiner, 1, 4 Satish P Ramachandran, 1 Rebecca Bethy, 1, 4 Muna T. Canales, 1, 4 1Univ of Florida, Gainesville, FL; 2Minneapolis VAMC; 3Univ of Minnesota, Minneapolis, MN; 4Malcom-Randall VAMC, Gainesville, FL; 5Univ of California, San Diego, CA.

**Background:** Sleep apnea is common in patients with CKD. We postulated that sleep apnea may cause renal injury through repeated ischemia-reperfusion. The current study correlated overnight changes in urinary excretion of renal injury biomarkers with severity of sleep apnea.

**Methods:** 39 consecutive participants in the SNORE Study, a longitudinal study of sleep apnea and kidney function decline, underwent overnight sleep study and provided spot urine samples before and after sleep. We measured urinary NGAL, L-FABP, KIM-1, and urinary cys-c levels, and correlated differences between AM and PM levels (AM-PM) with severity of sleep apnea or hypoaxia. Sleep apnea was defined by the apnea-hypopnea index (AHI, events/hour); hypoaxia was ≥ 90% time sleep < 90% SaO2 (%TST90). Data were log-transformed to normalize distribution.

**Results:** Patient characteristics: Mean age, 73.6±6.4 years; 90% male; 87% Caucasian, 13% black; BMI 29.4±4.2 kg/m2; MDRD eGFR, 34.3±18.1 ml/min/1.73m2; Median urinary albumin/creatinine ratio, 46 mg/g Cr [IQR 9.3–357 mg/g Cr]. 69% had sleep apnea (AHI≥5); median AHI, 10 [IQR 2–23]; median %TST90, 15 [IQR 3–22] with 34% %TST90≥10%. Higher %TST90 was correlated with higher AM KIM-1 values (r=0.40, p=0.01) and greater increase in urinary KIM-1 (AM-PM) (r=0.32, p=0.04). None of the remaining urinary biomarkers correlated with %TST90. Also, none of the overnight urinary biomarker changes correlated with AHI.

**Conclusions:** The correlation of KIM-1 with hypoaxia suggests that SA may contribute to CKD through ischemic renal injury. Future studies with larger sample size and in non-CKD populations are needed to further test this hypothesis.

**Funding:** Other NIH Support - DK079337 UAB-UCSD O’Brien Center, Veterans Administration Support

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**SA-PO226**

**Body Mass Index and Acute Kidney Injury in Hospitalized Patients**

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**Background:** Acute kidney injury (AKI) is common in hospital settings. The association between AKI and Body Mass Index (BMI) in general hospitalized patients is not well known. This study is to explore the incidence of AKI and the impact of BMI on AKI in hospitalized patients.

**Methods:** This was a single centre, retrospective, case-control study. All patients aged 21 or above under in-hospital care from January to December 2013 were recruited for analysis. Mean age was 62.5 ± 8.4 years; 90% male; 87% Caucasian, 13% black; BMI 29.4±4.2 kg/m2; Median urinary albumin/creatinine ratio, 46 mg/g Cr [IQR 9.3–357 mg/g Cr]. 69% had sleep apnea (AHI≥5); median AHI, 10 [IQR 2–23]; median %TST90, 15 [IQR 3–22] with 34% %TST90≥10%. Higher %TST90 was correlated with higher AM KIM-1 values (r=0.40, p=0.01) and greater increase in urinary KIM-1 (AM-PM) (r=0.32, p=0.04). None of the remaining urinary biomarkers correlated with %TST90. Also, none of the overnight urinary biomarker changes correlated with AHI.

**Conclusions:** The correlation of KIM-1 with hypoaxia suggests that SA may contribute to CKD through ischemic renal injury. Future studies with larger sample size and in non-CKD populations are needed to further test this hypothesis.

**Funding:** Other NIH Support - DK079337 UAB-UCSD O’Brien Center, Veterans Administration Support

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**SA-PO224**

**AKI Development Upon SIRS Is Associated with Platelet Activation, Possibly Triggered by Mitochondrial DNA Derived from Damaged Cells**

**Marcel Jansen,** Wilco P. Pulsksens, 2 Diba Emaa, 1 Sandrine Florquin, 1 Joris J. Roelofs, 1 Jaklleen Leeman, 1 Nephrology, Academic Medical Center, Amsterdam, Netherlands; 2Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

**Background:** Multiple inflammatory pathways are activated by non-infectious agents during Systemic inflammatory response syndrome (SIRS) leading to collateral damage, including the development of acute kidney injury (AKI). Pattern recognition receptors (PRRs) of the innate immune system sense Damage-Associated Molecular Patterns (DAMPs) leading to an immune response. Components of mitochondrion e.g. unmethylated CpG-enriched mitochondrial DNA (mtDNA) that leak upon cell injury, are a source of DAMP. Platelets express several PRRs and play an important role in innate immunity. To
Conclusions: Preliminary results revealed underweight hospitalized patients had increased risks of developing stage 1 AKI. Stage 2 AKI was more commonly seen in patients with BMI <25. BMI status was not associated with the development of severe AKI (stage 3).

SA-PO227

Hypermagnessemia as a Risk Factor for the Mortality in Intensive Care Unit Patients with Acute Kidney Injury. Shumichi Shibazaki, 1 Makoto Araki, 1 Kohel Muira, 1 Daio Inaguma. 2 Dept of Nephrology, Sawa Central Hospital, Chino, Nagano, Japan; 2 Dept of Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan.

Background: We need an easily measured biomarkers predicting for the mortality in acute kidney injury (AKI) because of high mortality rate. Therefore, we paid attention for serum magnesium (sMg) levels which reflects the renal tubular damage, and study the relationship sMg and prognosis in intensive care unit (ICU) patients with AKI.

Methods: A cohort study was conducted by collecting data from January to December 2014 in Nagoya Daini Red Cross Hospital. According to sMg at ICU 1st day, three groups were divided; low Mg group (sMg < 1.8mg/dL), normal Mg group (1.8mg/dL ≤ sMg < 2.6mg/dL), and high Mg group (sMg ≥ 2.6mg/dL). AKI was defined as serum creatinine (sCr) abrupt increase to ≥1.5 times baseline or sCr increase by ≥ 0.3mg/dL.) The primary endpoint was 28 days mortality after ICU admission. The secondary endpoint was the renal replacement therapy (RRT) induction rate, and the transition rate to endpoint was 28 days mortality after ICU admission. The secondary endpoint was the renal replacement therapy (RRT) induction rate, and the transition rate to endpoint was 28 days mortality after ICU admission.

Results: Out of 1614 ICU patients, 200 patients were included. The number of each groups are following; low Mg group was 55, normal Mg group was 115, and high Mg group was 30. The mortality was higher in high Mg group than in other Mg group (p = 0.011). A multivariate analysis identified high Mg group as an independent risk factor for the mortality (p = 0.041). High Mg group had 2.39-fold increased odds of mortality against recovery rate, the renal replacement therapy (RRT) induction rate, and the transition rate to endpoint was 28 days mortality after ICU admission. The secondary endpoint was the renal replacement therapy (RRT) induction rate, and the transition rate to endpoint was 28 days mortality after ICU admission.

Conclusions: Hypermagnessemia is an independent risk factor for the mortality in ICU patients with AKI.

SA-PO228

Gemcitabine-Induced Thrombotic Microangiopathy (TMA): A Report from the French Pharmacovigilance Network. Noemie Jourde-chiche, 1 Florence Daviet, 1 Frank Rouby, 1 Bertrand Gondouin, 1 Marion Sallée, 1 Julie Moussi-Frances, 1 Stéphane Burtry, 1 Pascale Poullin, 1 Bertrand Dussol, 1 Joelle Micallet. 1 Nephrology, Aix-Marseille Univ, Marseille, France; 2 Pharmacology and Pharmacovigilance, Aix-Marseille Univ, Marseille, France; 3 Hemapheresis, Aix-Marseille Univ, Marseille, France.

Background: Gemcitabine is a chemotherapy which use can be limited by renal adverse events, in particular thrombotic microangiopathy (TMA). This study evaluated the occurrence of gemcitabine-induced TMA, and described therapeutic strategies and outcomes.

Methods: All spontaneous reports of TMA attributed to gemcitabine in the French Pharmacovigilance Network database, between January 2000 and May 2015, were reviewed using a standardized questionnaire.

Results: 81 cases of TMA were reported in 48 male (59%) and 33 female (41%), with a median age of 63.5 yrs (range 39-87). Gemcitabine was prescribed for pancreatic (59%), pulmonary (15%), breast (8%), biliary tract (6%), urinary tract (5%), uterine (5%), testicular (1%) or liver (1%) cancers, or T lymphoma (3%). TMA occurred after a median of 7 months (range 0.2-60), and a median cumulative dose of 21.8g (range 1.1-48.6). Main symptoms were hypertension (51%), diffuse edema and/or congestive heart failure (42%), acute renal failure (86%), thrombocytopenia (67%), hemolytic anemia (86%). Median creatinine level was 1.8 mg/dL (range 0.8-17). In 6 patients, renal TMA was biopsy-proven. Renal replacement therapy was required in 10 (12%) patients, plasma exchanges (PEX) were performed in 17 (21%), 8 (10%) received fresh frozen plasma infusions, 9 (11%) corticosteroids, and 3 (4%) eculizumab (after PEX failure). Evolution data were available for 59 (73%) patients, among which the 17 treated with PEX. Hematological and renal remission was achieved in 35% with PEX versus 50% without, hematological remission without renal improvement in 18% with versus 26%, and no improvement was observed in 47% with versus 24% without PEX. Only one patient improved with eculizumab.

Conclusions: Gemcitabine treatment can be associated with TMA and severe renal adverse effects. The benefit of plasma exchange or eculizumab in this setting remains uncertain.

SA-PO229

Contribution of Drugs versus Risk Factors in Drug-Induced Renal Injury. Celina D. Cededa, 1 Linda Awulidi, 1 Etienne Macedo, 1 Dinna Cruz, 2 Stuart Goldstein, 1 Jorge Cerda, 2 David T. Seleowski, 1 Michael Zappitelli, 1 Andrew J.P. Lewington, 1 Ravindra L. Mehta. 1 Nephrology, Univ of California San Diego, San Diego, CA; 2 Nephrology, Univ of Cincinnati, Cincinnati, OH; 3 Nephrology, Albany Medical College, Albany, NY; 4 Nephrology, Univ of Michigan, Ann Arbor, MI; 5 Nephrology, Univ of Montreal, Montreal, QC, Canada; 6 Nephrology, Care Hospital India, Hyderbad, India; 7 Nephrology, St. James’s Univ Hospital, Leeds, London, United Kingdom.

Background: Drug-induced renal injury (DRI) is an increasing cause of acute kidney injury (AKI). Contribution of DRI requires consideration of the drug exposure, the number of drugs involved and underlying or concomitant risk factors (RF). We hypothesized that underlying RF would influence attribution of DRI.

Methods: The drug induced renal injury (DIRECT) study is an ongoing prospective multicenter study evaluating genetic determinants of the drug exposure, the number of drugs involved and underlying or concomitant risk factors (RF). Each enrolled case was adjudicated for causality by two independent nephrologists. We analyzed the first consecutive 86 adult and pediatric AKI cases. We evaluated the percent agreement, kappa statistic, and contribution of each drug (in setting of multidrug injury) and AKI RF.

Results: Adjudicators agreed 87.2% (n = 75) had DRI. For non-DRI cases, causality could not be established because of competing AKI RF. RF contributed to AKI in 86% of adults and 70% of children. Adjudicators disagreed on the percent attribution for each drug in 52%. For DRI cases, inter-rater agreement on percentage attributed to drug 1 was 48% with kappa=0.239 (p=0.001). For non-DRI cases, inter-rater agreement for drug 1 was 81.8% and RF attribution was 90%.

Conclusions: Underlying RF are common in DRI associated AKI. Causality assessment in DRI is complex due to difficulty in determining the attribution of drug and RF. CAT for DRI should incorporate AKI RF and their interaction with drugs. Funding: Private Foundation Support

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

Underline represents presenting author.

679A
SA-PO231

Acute Kidney Injury in Patients with Chronic Kidney Disease: Aetiology and Survival Comparisons to Non-Acute Kidney Injury Chronic Kidney Disease Population Akib Khan.1 James Ritchie;2 Sneeta Sinha.3 Senior House Officer, Imperial NHS Foundation Trust, London, United Kingdom; ‘Renal Medicine, Univ of Manchester, Manchester, United Kingdom; ‘Nephrology, Salford Royal Foundation Trust, Salford, United Kingdom.

Background: AKI, described by an acute (hours to days) fall in kidney function, is associated with significant morbidity and mortality. Poor outcomes exist when AKI is superimposed on CKD, a disease involving structural or functional renal abnormalities in a chronic setting (>3 months). We present a single-centre prospective observational study; retrospectively analysed. We determined the factors surrounding AKI on CKD. Aetiology, length of stay, specialist review and medication data were examined. We compare AKI on CKD patients’ survival to matched non-AKI CKD patients.

Methods: CRISIS database CKD patients matching inclusion criteria treated at Salford Royal Foundation Trust were studied (n=542). A 2.0-3.0 and >3.0 times serum creatinine increase from last measurement was used to define Acute Kidney Injury Network stages 2 (n=17) and 3 (n=10) events respectively. Controls were matched by age, eGFR and blood pressure. Logistic Regression, Cox-Hazard Ratio and Kaplan-Meier Survival Plots were used.

Results: Aetiological factors associated with AKI included sepsis (48.1%), drug-induced (29.6%) and dehydration (25.9%). Septic-AKI had a 1.405 odds ratio (95%CI:0.999-19.936,p=0.801) of death compared to non-septic events. Hazard ratio for death due to AKI on CKD compared to non-AKI CKD was 1.77 (95%CI:0.72-4.33,p=0.207). Kaplan-Meier survival function clearly demonstrates this.

Conclusions: Aetiology of AKI in our patient group was similar to that seen in non-CKD studies. There was a clear trend towards increased all-cause mortality in patients with AKI on CKD in comparison to non-AKI CKD patients. Renal function decline rate following AKI on CKD should be explored in the future.

SA-PO232

Prospective Study of Incidence and Early Detection of Acute Renal Failure in Preterm Babies in a Tertiary Center in South India Indira Agarwal, Nithya Ponmudi, Anil K. Kuruvilla, Vijayakumar Theophilus-Sunder. Pediatric Nephrology, Christian Medical College, Vellore, Tamil Nadu, India; Neonatology, Christian Medical College, Vellore, Tamil Nadu, India; Nephrology, Christian Medical College, Vellore, Tamil Nadu, India.

Background: Preterm babies are at risk for ischemia, hypovolemia and hypotension and thus vulnerable to acute kidney injury (AKI). We aimed to study the incidence and predisposing factors for AKI in preterm babies and to assess the usefulness of urinary NGAL as a predictor of kidney injury.

Methods: Babies born < 32 weeks or 6 weeks were recruited; those with abnormal antenatal renal scans and major congenital anomalies were excluded. Weekly monitoring of urine output, clinical progress, interventions, ventilation, unexpected events and use of nephrotoxic drugs was done. Serum creatinine and urine NGAL was collected at 72 hours of age and weekly thereafter. Descriptive statistics using mean±SD for continuous variables, ANOVA and chi-square test for AKI detection test for categorical variables and Risk factor analysis using log binomial was performed.

Results: Of the 4823 live births, 80 fulfilled inclusion criteria (10.14%). The incidence of AKI was 12.6%. The risk factors included oligosomnia, PDA, nephrotoxic drugs, low Apgar, mechanical ventilation, CPAP and abnormal antenatal scans. Urine NGAL was estimated in 31 babies. It rose earlier and was significantly elevated in those on mechanical ventilation by week 2 while Creatinine rose only by week 3.

SA-PO233

Acute Kidney Injury Electronic Alerts in Primary Care Conor Patrick Moran.1 Ying C. Kuan,2 Patrick Lm Lynch,2 Francis Mccarroll.1 1Dept of Nephrology, Altnagelvin Hospital, Londonderry, United Kingdom; 2Dept of Clinical Chemistry, Altnagelvin Hospital, Londonderry, United Kingdom.

Background: Acute Kidney Injury, (AKI), is common with a variably reported mortality, (15-60%). A UK national audit reported that up to 30% of cases were avoidable and that as much as 43-61% of post-admission AKI experienced an unacceptable delay in recognition. AKI is regarded as the remit of Secondary Care and there have been few studies examining Community Acquired AKI, (CA-AKI). Guidelines have recommended the utilisation of electronic alerts (e-alerts) for AKI in both Primary and Secondary care. We examined the incidence and mortality of CA-AKI.

Methods: We introduced AKI e-alerts with accompanying e-guidance in late October 2014 and prospectively collected data on the patients identified with severe AKI in Primary, Community and Secondary Care. Data collection was carried out for 3 months. The demographics of both cohorts were compared.

Results: Median age, (74.5 years vs. 75 years), gender distribution, (M:F: 48% / 52% vs. 44.5% / 55.5%), and median time to death, (8 days vs. 11 days), were comparable. 44 Alerts were from Primary Care and 77 from Emergency Department. Of the Primary Care Alerts, 20 patients were subsequently admitted. Of those who were not, 3 died within 30 days, (1. Died at 5 days, 2. Died at 8 days, 3. Died at 21 days). Despite this, Community-acquired AKI was associated with a 30-day mortality of 10.7%. Hospital-acquired AKI, (HA-AKI), was associated with a 28.2% 30-day mortality, (p=<0.001). Sub-group analysis showed Primary care alert associated with 13.64% mortality and Primary Care alerts with 9.76%, (p=<0.001). Median Age at Death; CA-AKI 80 years. Median time to death; CA-AKI 5 days, HA-AKI 11 days.

Conclusions: AKI is common and associated with a significant morbidity and mortality. CA-AKI is common opportunities at diagnosis and intervention are often missed with grave
consequences. Appropriate management of CA-AKI could help reduce the economic and physical burden associated with AKI and reduce the long-term burden of CKD. Further work is required to expand the role of AKI e-Alerts in Primary Care.

SA-PO234

Acute Kidney Injury Causes and Outcome: A Single Center Experience from Sudan

Was 13%. AKI causes.

29 patients (42%) experienced recovery of normal renal function; the recorded mortality blood urea levels on admission were 14.7.

SOBA Univ Hospital, Khartoum, Sudan; 2Renal Research Inst, New York, NY; 3Fresenius Medical Care, Bad Homburg, Germany.

Background: Acute kidney injury (AKI) is a challenging problem in Africa—a diverse continent with regards to population and financial and medical resources. There are no reliable statistics about the incidence of AKI in Africa. Based on sporadic regional publications the incidence has been estimated at 150 per million population. In addition to infectious diseases; toxins play a major etiologic role in AKI.

Methods: In this study we analyzed data from Omer Belail Renal Center in Soba University Hospital, Sudan, a tertiary referral center with a catchment area of 3 million citizens. All hemodialysis (HD) patients treated for AKI in the period between 1/1/2013 and 12/31/2014 were included in the study.

Results: Out of 520 hemodialysis patients we identified 69 patients with AKI; 39 (56.5%) were males. The mean/SD age was 40.5±17.4 years. Serum creatinine and blood urea levels on admission were 14.7±6.7 and 245±125 mg/dL, respectively. Serum creatinine and blood urea levels at discharge were 2.5±2.1 and 53±32 mg/dL, respectively. 29 patients (42%) experienced recovery of normal renal function; the recorded mortality was 13%. AKI causes.

Acute tubular necrosis 15 (22.7%)
Obstructive urethropy 10 (14.5%)
Glomerulonephritis 7 (10.5%)
Acute interstitial nephritis 6 (8.7%)
Sepsis 6 (8.7%)
Snake bite 5 (7.2%)
Hair dye poisoning 4 (5.8%)
Hemolytic uremic nephritis 3 (4.3%)
Fluid depletion 1 (1.4%)
Others 12 (17.4%)

Conclusions: AKI has become increasingly prevalent in developing countries, and is associated with severe morbidity and mortality. Many causes of AKI can be prevented by interventions at the individual, community, and regional levels. Efforts should be directed to eradicate causes of AKI, expedite diagnosis, and aggressively manage pre-renal conditions and specific infections.

SA-PO235

Usefulness of Pressepil, Procalcitonin and IL6 as a Biomarkers of Adverse Renal Outcome and Mortality After Cardiac Surgery

Alessandra Brocca, Grazia Maria Virzi, Maria Jimena Mucino-Bermejo, Davide Giavarina, Massimo de Cal, Claudio Ronco. S Bortolo Hospital, Vicenza.

Background: Cardiac surgery (CS) is now possible in increasingly high-risk patients (pts): accurate evaluation of surgical risk is crucial. Mortality and negative impact on distant organs must be evaluated. In a large number of clinical scenarios, biomarkers have been proven to be reliable tools in clinical settings either for single a single biomarker or a biomarker panels. Presepsin has been reported to be useful for stratifying mortality as "add-value" rather than a "unique-predicting" data. Presepsin and IL6 by ELISA assay. A p-value of <0.05 was considered statistically significant.

Methods: Observational single center study includes 122 adult CS pts. Blood samples were collected at the second day after surgery. Pressepil was tested by the PATHFAST Immunanalyzer system, Procalcitonin by BRAHMS PCT sensitive KRYPTOR and IL6 by ELISA assay. A p-value of <0.05 was considered statistically significant.

Results: We observed that Pressepil and IL6 are better predictors of inhospital (AUC=0.831 and 0.819), 30day (AUC=0.723 and 0.785) and global mortality (AUC=0.759 and 0.793) than Procalcitonin (p=0.05). Pts with worse renal outcome (defined as AKI, change on CKD stage or need for CRRT) have significantly higher Presepsin and Procalcitonin levels (p=0.05). IL6 is not significantly different in pts with adverse renal outcome compare whith those without.

Conclusions: Presepsin and IL6 levels correlate with the risk of death better than Procalcitonin. Higher Presepsin and Procalcitonin levels are associated with adverse renal outcomes in this population. It is possible that a combination of these three biomarker in an inflammatory multi-biomarker panel as opposed to a single biomarker should betaken as "add-value" rather than a "unique-predicting" data.

Funding: A rate Foundation Support

SA-PO236

Allopurinol Attenuates Rhabdomyolysis-Induced Acute Kidney Injury: Renal and Muscular Protection


Background: Myoglobinuric acute kidney injury(AKI) is the most severe complication of rhabdomyolysis. Aim: To evaluate the efficacy of allopurinol(Allo) on rhabdomyolysis-induced AKI.

Methods: Male Wistar rats were injected intramuscularly with 5ml/kg body weight(BW) of either 50% glyceral(Gly) or 0.9% saline(S). Five groups were studied: S(n=5), S+Allo(n=6), Gly(n=7), Gly+Allo(n=7), Gly+ivAllo(n=7). S and Gly+Allo rats received Allo(300mg/L) in drinking water 7 days prior to and for 24h after Gly injection.Gly+ivAllo: intravenous Allo(50mg/kg BW) 30’ after Gly injection and 300mg/L in drinking water thereafter.

Results: Gly rats showed markedly reduced glomerular filtration rate(GFR,umilin clearance) associated with renal vasoconstriction,renal tubular damage,increased oxidative stress,apoptosis and inflammation. Allo treatment ameliorated all these alterations. Allo reduced muscular oxidative stress and accelerated its recovery.

Funding: Government Support - Non-U.S.

SA-PO237

Cell Cycle Progression in the Early Phase of Septic Kidney

Daisuke Nakano, Akira Nishiyama. Dept of Pharmacology, Kagawa Univ, Kagawa, Japan.

Background: The recovery of renal function after acute kidney injury (AKI) is likely controlled by proliferation of survived tubular cells in damaged nephrons containing cell death or sloughing. However, recent studies revealed that AKI concomitant with sepsis had significantly less tubular cell death than other forms of AKI, such as ischemic- and drug-induced AKI. It has not been examined whether septic AKI accelerates tubular cell proliferation in the condition with less cell death. In the present study, we examined the time-course changes in tubular cell proliferation after sepsis.

Methods: Lipopolysaccharide (LPS) and cecum ligation and puncture (CLP) model were used to induce sepsis in mice. Cell cycle progression was assessed by intravital imaging of Tg(FucciG1)#596Bsi (Fucci) mice, which express monomeric Kusabira-Orange2 in G1/0 phase. LPS or CLP was used to induce sepsis in mice. Cell cycle progression was assessed by intravital imaging of Tg(FucciG1)#596Bsi (Fucci) mice, which express monomeric Kusabira-Orange2 in G1/0 phase.

Results: Fucci mice (8 weeks of age) showed an increase in Ki67 and bromodeoxyuridine staining were increased only in young mice (Ki67 cell number: 1.5±0.1 fold in LPS mice and 1.0±0.1 fold in CLP mice compared to normal control), not in old mice (Ki67 cell number: 0.8±0.1 fold in LPS mice and 1.0±0.1 fold in CLP mice compared to normal control) at a similar time course observed in Fucci mice. Etoposide, an anti-cancer drug, abolished the cell proliferation after LPS injection in young mice. Importantly, old mice or etoposide-treated young mice showed much worse AKI as compared to young mice.

Conclusions: Prophylactic and therapeutic Allo attenuates Gly-induced AKI by reducing oxidative stress (systemic, muscular and renal),inflammation and apoptosis. It may represent a new therapeutic approach for rhabdomyolysis and myoglobinuric AKI.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO238
Hepcidin Mitigates Endotoxin-Induced AKI
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Background: Sepsis is a common cause of acute kidney injury (AKI). Sepsis-associated inflammation induces hypoferremia and thereby limits iron availability to pathogens. It has been shown that hepcidin-induced degradation of ferroporin and consequent iron restriction are key for this hypoferric state. Since, iron has been implicated in the pathogenesis of both sepsis and AKI, we hypothesized that hepcidin pretreatment would mitigate bacterial endotoxin-induced AKI.

Methods: C57BL/6 were treated with saline or 50 mg of hepcidin, 24 hours prior to LPS (Escherichia coli O111:B4) injection (6.5 mg/kg). Renal function, injury and inflammation markers were examined up to 24 hours post LPS injection. Mouse glomerular endothelial cells were cultured with 100 ng/mL of hepcidin for 6 hours after treating them with and without 1 mg/mL hepcidin for 12 hours.

Results: Kidney function (as measured by serum BUN) significantly declined 2 hours post LPS injection and progressively deteriorated for 24 hours. This was prevented by hepcidin treatment (BUN: 83.55 Vs Hepcidin = 32.33, p < 0.001). Renal injury markers expressed similarly in BUN (NGAL: LPS = 6.74 Vs Hepcidin + LPS = 0.78, p < 0.001). Hepcidin treatment also reduced early systemic TNF alpha production following LPS injection (TNF alpha: 2266 Vs Hepcidin + LPS = 1248, p < 0.01). The ultra-structural morphology of the glomeruli revealed extensive loss of endothelial fenestrae and epithelial mitochondria in LPS treated mice, which was prevented by hepcidin treatment. However, MGEc cultures treated with or without hepcidin up-regulated endothelin gene to similar levels after stimulation with LPS.

Conclusions: Our results demonstrate a novel protective role of hepcidin in endotoxin-mediated AKI, which is largely exerted through down regulation of systemic cytokine production.

Funding: NIDDK Support

SA-PO239
ELK-B Peptide Prevents Renal Histological Damage and Mortality in Septic Mice
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Background: Targeting SR-BI/II and CD36 receptors with L-37pA, an antagonist peptide, reduced multi-organ failure, peritoneal bacterial counts, and increased survival from 6 to 27% in antibiotic-treated mice subjected to cecal ligation and puncture (CLP)-induced sepsis (J Immunol. 2012). We tested ELK-B, a peptide more specific to the CD36 receptor.

Methods: Because the free peptide was toxic, ELK-B was formulated with micellar 1-conjugated oligo-glycrrhop-3-phospholipid. For survival study, animals were randomized into two groups: CLP (N=16) and CLP+ELK-B (15 mg/kg, N=15). A blinded observer administered treatments every 12h until death or until euthanized per protocol. For acute studies, 10 mice/group were subjected to CLP+saline (CLP) or CLP+ELK-B; saline or ELK-B was administered IV 0 and 6h after CLP. 18h post-CLP mice were euthanized for peritoneal lavage, and blood/organs collection. Serum creatinine (Cr) was measured by HPLC, BUN by colorimetry, and AST, ALT by an autoanalyzer. PAS-stained kidney sections were scored for renal tubular damage. Peritoneal bacterial cell counts were expressed per mouse. Caspase-3 IHC was performed on spleens. Data were analyzed by ANOVA and log-rank test.

Results: ELK-B significantly increased survival: all CLP+vehicle mice died by 78h, whereas 31% of ELK-B treated mice were still alive at 7 days. The survival curves did not diverge until 36h. At 18h (before survival curves diverged), ELK-B did not alter Cr (sham, CLP, CLP+ELK-B = 0.017, 0.30, 0.06, and 0.21±0.06 mg/dl; BUN, ALT, AST, ALT by an autoanalyzer. PAS-stained kidney sections were scored for renal tubular damage. Peritoneal bacterial cell counts were expressed per mouse. Caspase-3 IHC was performed on spleens. Data were analyzed by ANOVA and log-rank test.

Conclusions: ELK-B reduced 7 day mortality and 18h renal histological damage after sepsis. However, it did not alter other biochemical outcomes at 18h. This suggests that it may act late in sepsis, perhaps by increasing bacterial killing.

Funding: NIDDK Support

SA-PO240
Renal Ischemic Preconditioning Protects against Septic Acute Kidney Injury via miR-21
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Background: Septic acute kidney injury(AKI) is one of the most common and life-threatening complications in critically ill patients, and there is approved effective treatment. We have shown ischemic preconditioning upregulates miR-21, provides renoprotection against subsequent ischemia reperfusion injury. Here we studied the effects of renal ischemic preconditioning on septic AKI and its mechanisms.

Methods: Bilateral renal pedicles were clamped for 15 min in mice before the induction of septic AKI, and septic AKI was induced by intraperitoneal injection of lipopolysaccharide. The effects of renal ischemic preconditioning on LPS-induced AKI were investigated, including changes of renal function, histology, inflammation and apoptosis in kidneys. The role of miR-21, in renal protection conferred by the ischemic preconditioning was examined using in vivo knockdown of miR-21 and miR-21 signaling pathways were analyzed.

Results: We observed that renal ischemic preconditioning provided morphological and functional renoprotection, characterized by attenuation of renal tubular damage, cell apoptosis, and a reduction in inflammation in circulation. Furthermore, we found that renal ischemic preconditioning significantly upregulated the expression of miR-21 in kidneys, suppressed proinflammatory factor PDD4D expression and NFκB activity, improved renal tubular production. Meanwhile, renal ischemic preconditioning also suppressed the expression of PTEN which is a proapoptotic protein, activating Akt signaling pathway, subsequently increasing the expression of Bcl-2 and inhibiting Caspase-3. A locked nucleic acid-modified anti-miR-21, given before renal ischemic preconditioning, knocked down miR-21 effectively, and upregulated its target effector PTEN expression, resulting in increase of apoptosis, exacerbated LPS-induced AKI.

Conclusions: Our findings demonstrate that renal ischemic preconditioning protects against LPS-induced AKI, and miR-21 coordinates its downstream signaling to reducing cell apoptosis and circulatory inflammation, contributing torenal protection.

SA-PO241
Remote Ischemic Preconditioning Protects against Contrast-Induced Nephropathy via Renalase Induced by TNFα/FnbB Pathway
Feng Wang, Zeyuan Lu, Jiangyong Yin, Guangyuan Zhang, Niansong Wang. Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People’s Hospital, Shanghai, China.

Background: Renalase is a flavin adenine dinucleotide-dependent amine oxidase which has recently been suggested to be a renoprotective molecule. Herein we suggested that renalase expression induced by circulatory TNF-α which was evoked by remote ischemic preconditioning (rIPC) play a key role in contrast-induced nephropathy(CIN) protection.

Methods: CIN model was setup by ioversol intravenous injection to SD rats. Limbs ischemic preconditioning was carried out 24 hours before CIN induction. TNF-α blocking, NF-Kβ blocking, HIF blocking and renalase blocking were performed respectively. TNF-α administration was also performed as rIPC mimic. Renal injury, kidney oxidative stress, renal function, renal expression, and circulating TNF-α after IPC were assessed. HK2 exposure to TNF-α and its blocker were studied and renalase expression was assessed.

Results: Reduced tubular injury, decreased oxidative stress and improved renal function were observed in CIN rats following rIPC. The therapeutic effects could be neutralized by renalase blocking. Renalase expression was significantly up-regulated after rIPC. rIPC induced renalase expression could be abolished by TNF-α blocking or NF-Kβ blocking but not HIF blocking. Up-regulated renalase triggered by TNF-α could also be blocked by NF-Kβ both in vivo and in vitro.

Conclusions: Renalase expression which mediated by TNFα/FnbB pathway played an essential role in renoprotection of rIPC for CIN.

Funding: Government Support - Non-U.S.

SA-PO242
DNA Methylation in Cisplatin-Induced Acute Kidney Injury
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Background: DNA methylation is a major epigenetic modification, which plays an important role in regulating gene transcription without changing primary nucleotide sequence. DNA methylation has been implicated in major diseases, such as cancer. However, the changes of DNA methylation in kidney diseases, such as cisplatin-induced nephrotoxicity, remain unclear.

Methods: We determined the global DNA methylation changes in cisplatin-induced AKI by reduced representation bisulfitie sequencing (RRBS) using kidney cortex from mice treated with cisplatin. We also established proximal tubule-specific Dnm1t1 (PT-DNMT1) knockout mice to determine the role of DNA methylation in cisplatin-induced AKI. Results: Totally 1.5 and 1.9 millions of CpG sites were analyzed in the control and cisplatin treated kidney samples, respectively. Compared with control, cisplatin-treated samples showed aberrant DNA methylation changes, resulting in the identification of 236 differentially methylated regions (DMRs). Further analysis identified 15 genes that contained DMRs at 5‘ end regulatory promoter region or 5‘ UTR. To determine the pathological role of DNA methylation, we established the PT-DNMT1 model, in which the DNA methyltransferase 1 gene was specifically deleted from kidney proximal tubules. Compared with wide type mice, PT-DNMT1 knockout mice showed higher necritic tubular damage at 4 day after cisplatin injection. However, mice did not show the difference between wide type and knockout mice, serum creatinine was increased in knockout mice treated with cisplatin.

Conclusions: Cisplatin induced significant changes in DNA methylation in kidney tissues, which may contribute to gene regulation and related kidney injury.

Funding: NIDDK Support, Veterans Administration Support
Blockade of KCa3.1 Potassium Channels Protects against Cisplatin-Induced Acute Kidney Injury

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Background: Anti-tumor efficacy of cisplatin chemotherapy is mainly limited by its toxicity to normal tissues, particularly the kidney toxicity. Tubular apoptotic cell death significantly contributes to the pathogenesis of cisplatin-induced acute kidney injury (AKI). KCa3.1, a calcium-activated potassium channel, has been reported to participate in cell apoptosis. However, the involvement of KCa3.1 in cisplatin-induced AKI is unknown.

Methods: We examined KCa3.1 mediates cisplatin-induced tubular apoptotic cell death in vitro, as well as the development of cisplatin-induced AKI in KCa3.1- and pharmacological blockade mouse models in vivo.

Results: Cisplatin treatment triggered an early induction in KCa3.1 expression, which is associated with apoptotic cell death in HK-2 cells, as well as with the development of renal tubular damage and cell apoptosis in mice. By treating with highly selective blocker TRAM-34, we found KCa3.1 inhibition suppressed cisplatin-induced apoptotic cell death in HK-2 cells. In the in vivo study, KCa3.1 deficiency reduced renal function loss, renal tubular damage and apoptotic marker caspase-3 induction in kidneys after cisplatin administration in KCa3.1-/- mice. Pharmacological blockade of KCa3.1 by TRAM-34 similarly attenuated cisplatin-induced AKI in mice. Furthermore, we dissected the underlying mechanisms in which KCa3.1 blocking reduces cisplatin-induced apoptosis. We found KCa3.1 inhibition attenuated the cytochrome c release and the increase of intrinsic apoptotic mediator Bax. Bax mimotope exposure was delayed for 4 or more hours after cisplatin treatment. We also found KCa3.1 blocking inhibited cisplatin-induced the increase of ER stress mediator caspase-12, which is independent of calcium-dependent protease m-calpain activation.

Conclusions: Blockade of KCa3.1 protects against cisplatin-induced AKI through the attenuation of tubular apoptosis by interfering with intrinsic apoptotic and ER stress-related mediators, and that provides a potential target for the prevention of cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

Bax Mimotope Therapy: Effective Treatment for Ischemic Acute Kidney Injury (AKI)

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Background: Ischemic AKI causes renal cell death partly by Bax-mediated apoptosis. Recent studies show that Bax requires the chaperone nucleosomophilin (NPM) for mitochondrial targeting and apoptosis. We propose that a mimotope that interferes with Bax-NPM interaction is an effective treatment for ischemic AKI.

Methods: To assess mimotope efficacy, 2 mg control or therapeutic Bax mimotope was administered by a single tail vein injection in 6-week old B6 mice either before or after renal ischemia caused by 2 min of bilateral renal pedicle clamping, an insult that produces severe AKI. BUN/Cr, histologic injury score, caspase 3 activity, Bax activation and Bax-NPM interaction were compared in each experimental group at the above time points (n = 8 each group).

Results: Compared to control, Bax mimotope administration 15 min before or 15 min, 1.2 or 3 hr after ischemia significantly improved renal function. No protection was observed if Bax mimotope exposure was delayed for 4 or more hours after ischemia. Although 12% of controls died of AKI, only 2% of animals died in the Bax mimotope groups. Despite equivalent Bax activation in both groups, the Bax mimotope improved histologic injury score, reduced caspase 3 activation and decreased Bax-NPM interaction as assessed by co-immunoprecipitation.

Conclusions: Selective interference of Bax-NPM interaction with a Bax mimotope within several hours of acute ischemia improves survival, significantly reduces the severity of AKI (lower BUN and Cr), decreases histologic injury score and inhibits Bax-mediated apoptosis downstream of Bax activation.

Funding: NIDDK Support

Role of AMPK in Aristolochic Acid-Induced Acute Kidney Injury

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Background: Experimental aristolochic acid nephropathy (AAN) is a pertinent model of tubulo-interstitial nephritis characterized by an early phase of acute kidney injury (AKI) followed by chronic inflammation and fibrosis (CKD). AMPK has been previously reported to be involved in the regulation of renal fibrosis. This study was conducted to determine the role of AMPK in renal outcomes and its involvement in the AKI-to-CKD transition.

Methods: C57BL/6J male mice were randomly subjected to i.p. injection of either sterile saline solution, AA, AA+AICAR (the specific AMPK activator) for 4 days. Mice were then euthanized either at day 5 or day 20.

Results: AA-treated mice displayed loss of renal function, as reflected by significant increases in plasma creatinine level and proteinuria at days 5 and 20. In addition, impairment of tubular function was associated by the expression of markers of renal oxidative stress, inflammation and fibrosis.

Conclusion: Mixed results were obtained in terms of AMPK activation in AA-induced AKI.

Funding: Government Support - Non-U.S.

Nrf2 Activation in Tubular Cells Prevents Progression of AKI to CKD

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Background: Acute kidney injury (AKI) is one of the major risk factors for chronic kidney disease (CKD). Reactive oxygen species are generated by ischemia-reperfusion injury (IRI) during transition of AKI to CKD, and oxidative stress contributes to defects of renal tubular cells. Nrf2 is a master transcription factor for cellular defense against oxidative stress. In an E3 ubiquitin ligase Keap1 knockdown mutant (KD) and tubular-specific Keap1-null mutant (TKO) mice were used for genetic activation of Nrf2. A Keap1 inhibitor CDDO-Im was used for pharmacological activation of Nrf2.

Results: Remaining tubular areas at 14 days after IRI were 64%, 51% and 34% in KD, TKO and wild-type mice, respectively compared with their contralateral kidneys. Genetic Nrf2 activation treatment after IRI to wild type mice also protected against tubular defects (CDDO-Im, 63%). Nrf2-irrelevant antioxidant defenses (Nqo1, Hmox1, Gclc, Gclm, and Srxn1) were transiently up-regulated in 3-6 hours after IRI in wild-type mice, while both genetic and pharmacological activation of Nrf2 maintained expression of these genes at high levels throughout the observation period.

Conclusions: Activation of Nrf2 alleviates IRI-induced tubular loss through enhancing the antioxidant response system. Nrf2 inducers are one of prospective therapeutic candidates for preventing AKI-to-CKD transition.


Acute Kidney Injury in the Rat Is Prevented by Pirfenidone

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Background: Pirfenidone (PFN) is an orally active small molecule which acts mainly through an anti-fibrotic effect, but also possesses antioxidant and anti-inflammatory properties.

This study was designed to evaluate the effect of the prophylactic treatment with PFN on acute kidney injury (AKI) due to bilateral renal ischemia (IR) in the rat. We studied this group of rats: 1) sham operated, (S) 21 rats undergone 20 min of ischemia and 24-h of reperfusion and, 3) rats treated with PFN (700 mg/kg), 24-h before ischemia (IR/PFN). Serum creatinine, creatinine clearance (CrCl) protein excretion, urinary levels of Hsp72 (UHsp72V) and nitrates and nitrites (UNO2/NO3V) were assessed. Mean arterial pressure (MAP) and renal blood flow (RBF) were recorded 24-h after surgery. Tubular injury (TI) was evaluated in fixed kidneys by counting the cast number and the number of injured tubules per field.

Results: As expected, the IR group showed a reduction in CrCl (IR 0.2 ± 0.4 vs. S 0.7 ± 0.6, p<0.05), urinary output (IR 20.9 ± 5 vs. S 32.7 ±19.3 ml/day; p<0.05), RBF (IR 1.08 ± 0.37 vs. S 1.53±0.17 ml/min/100 g BW; p<0.05), and a significant increase in UHsp72V assessed by Western blot. Extensive TI was evidenced by histological analysis. These alterations were associated with a decrease in UNO2/NO3V (IR 3.1±1.3 vs. S 5.4±2.5 mmol/24h; p<0.05). In contrast, IR+PFN group showed restoration of CrCl (1.33±0.4 mmol/100g BW; p<0.05), urinary output (47.5 ± 5.7 ml/day; p<0.05), RBF (1.51±0.15 ml/min/100g weight; p<0.05). The levels of urinary Hsp72 were undetectable or very low and the histological signs of TI were significantly reduced. Interestingly, UNO2/NO3V was completely recovered (7.05±0.78 mmol/24h; p<0.05).

Conclusions: Our results revealed that pre-treatment with PFN prevents AKI in the rat.

Part of its renoprotective effects seems to be related with the restoration of NO production. These findings suggest that PFN could be a promising tool in the prevention of AKI.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.
HDAC8 Plays a Critical Role in the Epigenetic Activation of Fibroblasts and the Pathogenesis of Renal Fibrosis

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Background: The development of renal fibrosis is associated with changes in the expression of approximately 10% of the genome, suggesting widespread transcriptional dysregulation. Nonetheless, the roles of critical epigenetic pathways in disease progression remain poorly understood. Here, we examine the biological and therapeutic importance of histone deacetylases (HDACs) in the function of fibroblasts and the pathogenesis of renal fibrosis.

Methods: Renal fibrosis was modeled in vitro by treatment of NRK-49F fibroblasts with the pro-fibrotic cytokine TGF-β and in vivo in mice by unilateral ureteral obstruction (UUO). The role of HDAC proteins was assessed by treatment with the broad spectrum HDAC inhibitor Trichostatin A (TSA) and the HDAC-specific inhibitor PCI-34051. The translational relevance of these findings was assessed in patients who underwent a nephrectomy following UPJ obstruction.

Results: UUO leads to a 6.1-fold increase in HDAC8 expression that localizes specifically to myofibroblasts. In NRK-49F cells, treatment with PCI-34051 promotes myofibroblast differentiation and apoptosis, but suppresses proliferation and matrix synthesis. These findings extend to the injured kidney in vivo, where HDAC inhibition results in a 41.6% decrease in COL1A1 and a 61.6% decrease in α-SMA. Furthermore, there is a 77.9% decrease in the interstitial proliferative response, a 43.0% decrease in myofibroblast number, and a 31.1% decrease in renal fibrosis. Finally, the development of renal fibrosis in patient with obstructive urologic disease is associated with a 32.1% increase in the number of HDAC8-positive cells.

Conclusions: Together, these findings demonstrate that HDAC8 plays a critical role in regulating fibroblast activation. Treatment with HDAC inhibitors is also an effective therapeutic approach to reverse the epigenetic changes associated with the pathogenesis of renal fibrosis. Finally, since an increase in HDAC8 expression occurs in patients during disease progression, HDAC8-targeted therapies have therapeutic potential for the treatment of chronic kidney disease.

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Reciprocal Effects of HDAC1 and HDAC2 Deletion on Renal Ischemia-Reperfusion Injury

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Background: Histone/protein deacetylase proteins (HDACs) have been implicated in renal ischemia-reperfusion injury (IRI). HDACs 1 and 2 are highly homologous Class I HDACs thought to have similar function.

Methods: This study included wild type C57BL/6 (B6) and inducible HDAC1- or HDAC2 gene deleted mice (HDAC1KO and HDAC2KO). Renal-specific or extra-renal gene deletion of the HDACs thought to have similar function.

Results: HDAC1KO mice had impaired renal IRI tolerance compared to controls with higher BUN levels (p<0.01; Figure 1A) and increased fibrosis post-injury. HDAC2KO mice had improved early renal function (p=0.01; Figure 1B) and decreased fibrosis (p<0.01) compared to controls and tolerated extended periods of ischemia. In transplant models, renal-specific HDAC2KO mice had superior IRI tolerance with less renal impairment (p<0.01) and decreased fibrosis (p=0.01) compared to extra-renal HDAC2KO and controls. After transplantation with 18 hours of cold ischemia, HDAC2KO donor kidneys had improved BUN (p=0.02) and survival compared to controls.

Conclusions: HDAC1 and 2 have reciprocal effects on murine renal IRI tolerance, with HDAC1 deletion increasing vulnerability and HDAC2 deletion providing protection. The effect of HDAC2 deletion is profound, is intrinsic to the kidney, and extends to cold ischemia and renal transplantation.

Funding: NIDDK Support

Renoprotective Effect of Long Acting Thiorodoxin by Modulating Oxidative Stress and Macrophage Migration Inhibitory Factor against Rhabdomyolysis-Associated Acute Kidney Injury

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Background: Rhabdomyolysis-associated acute kidney injury (AKI) is a serious life-threatening condition. As such, more effective strategies are needed for its prevention and treatment. Although thiorodoxin-1 (Trx) possesses superior biological activities, such as anti-oxidative and anti-inflammatory effect via the modulating macrophage migration inhibitory factor (MIF), its short blood retention limits the therapeutic application. To overcome this, we engineered a long acting Trx by genetically fused with human serum albumin (HSA-Trx), and examined its renoprotective effect against glycerol-induced AKI.

Methods: HSA-Trx was prepared by using Pichia expression system. The mouse model of rhabdomyolysis-associated AKI was induced by the administration of a 50% glycerol solution.

Results: An intravenous HSA-Trx pre-treatment attenuated the glycerol-induced decline in renal function, compared to a PBS, HSA or Trx alone. HSA-Trx caused a reduction in the tubular injuries and in the number of apoptosis-positive tubular cells. Renal superoxide, 8-hydroxy deoxyguanosine, nitrotyrosine and the plasma Cys34-cysteinylated albumin were clearly suppressed by the HSA-Trx treatment. Prior to decreasing TNF-α and IL-6, HSA-Trx suppressed an increase of plasma MIF level. In LLC-PK1 cells, HSA-Trx decreased the level of reactive oxygen species and lactate dehydrogenase release induced by myoglobin. HSA-Trx treatment resulted in a threefold increase in the survival of lethal glycerol-treated mice. The post-administration of HSA-Trx at 1 and 3 hr after glycerol injection exerted a significant renoprotective effect.

Conclusions: HSA-Trx, a long acting Trx, has potential for use in the prevention and treatment of rhabdomyolysis-associated AKI via its extended effects of modulating oxidative stress and MIF.

Selective Endothelin-A Receptor Antagonism Prevents the Progression of Acute Kidney Injury to Chronic Kidney Disease

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Background: AKI is common and associated with significant morbidity and mortality. AKI often progresses to CKD and endothelin-1 (ET-1) contributes to this. We hypothesized that therapeutic administration of selective ET-A receptor antagonist would protect from the transition of AKI to CKD.

Methods: 28 FVB mice underwent prolonged (50min) unilateral ischemia-reperfusion injury (IRI) with 28d recovery. 14 mice received daily selective ET-A receptor antagonism (fractional excretion of ET-1: IRI vs. control and for IRI 28d). We assessed blood pressure (BP) via telemetry, vascular function, renal injury and measures of the ET system.

Results: Systolic BP increased by ~5mmHg after IRI and was associated with vascular dysfunction in both resistance and conduit vessels. Sitaarten partially prevented both of these. At 28d after IRI kidney weight was reduced (~55%) and associated with significant macrophage infiltration and fibrosis compared to the contralateral control kidney. Mice treated with sitaxentan had normal kidney weight, reduced macrophage infiltration and less renal injury. IRI vs. IRI kidney vs. IRI kidney with sitaxentan: F30/stain/high power field: 2.5±0.2 vs.0.8±0.0%; picrosirius red stain/high power field: 8.6±0.48 vs.3.1%. For both macrophage infiltration and fibrosis, p<0.05 for IRI vs. control and for IRI vs. IRI with sitaxentan, p=3.0; control vs. IRI with sitaxentan. Furthermore, an up-regulation of both the ET-A (28-fold) and ET-B (2-fold) receptors as well as pre-pro-ET-1 (10-fold) mRNA was seen in both the cortex and medulla of the IRI kidney relative to control. With sitaxentan treatment ET-A receptor and pre-pro-ET-1 mRNA remained similar to baseline levels. Finally, renal ET-1 production increased following IRI and this was prevented by ET-A receptor antagonism (fractional excretion of ET-1: IRI vs. IRI with sitaxentan: 47%±16%, p<0.05).

Conclusions: In an in vivo model of AKI progressing to CKD, ET-A receptor antagonism reduced BP and vascular dysfunction and prevented progression of renal injury and ET system activation after AKI. Therefore, selective ET-A receptor antagonism offers a potentially novel therapy for AKI. Translational studies are now warranted.

Inhibition of Vascular Adhesion Protein-1 Suppresses Neutrophil Infiltration and Preserves Renal Function in the Rat Model of Renal Ischemia–Reperfusion Injury

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Background: Vascular adhesion protein-1 (VAP-1) is an adhesion expressed in endothelial cells. With its unique properties as an ectoenzyme which catalyzes oxidative deamination of primary amines, VAP-1 plays a critical role in leukocyte trafficking. In light of a growing body of evidence that VAP-1 controls inflammation in various organs, such as the liver and the lung, we examined the effect of VAP-1 inhibition in the rat model of renal ischemia–reperfusion injury.

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

Underline represents presenting author.
**Methods:** Rats were subjected to left renal ischemia for 45 min after right nephrectomy, followed by 24 h of reperfusion. A specific VAP-1 inhibitor, RTU-1096 (R-Tech Ueno, Tokyo, Japan), or vehicle was administered to rats since 7 days before the surgery (mixed with feed, 40 mg/kg/day).

**Results:** Immunofluorescence studies suggested that VAP-1 is expressed not only in endothelial cells of capillaries but also in interstitial cells of non-endothelial lineage. In vitro, higher mRNA expression of VAP-1 was confirmed in cultured pericytes. In vivo, VAP-1 enzyme activity in the whole kidney was unaffected by the surgery, but following VAP-1 inhibition by RTU-1096 (0.9:0.1 vs. 7.0:1.3 pmol/mg protein/min), renal function was significantly improved as compared to the vehicle group (0.5±0.1 vs. 69.1±13.95 mg/dl, Cr: 1.4±0.1 vs. 2.5±0.02 mg/dl; P<0.01), which was accompanied by amelioration in histological tubular injury and decreased KIM-1 mRNA levels. Immunohistochemical analysis revealed a significantly decreased number of neutrophils in the cortical interstitium in IRI mice (3.1±1.3 vs. 9.2±2.2 mmHg) than in Sham operated mice (7.5 mmHg) when compared to Sham operated mice (9.5±4.2 mmHg).

**Conclusions:** We found that mean Pf was higher in PU mice (48.9±1.2 mmHg) than in Sham group mice (220 pg/ml in RP and 734 ± 16 pg/ml in RA group, respectively). Histology by PAS staining showed that all AKI mice had a significant increase in renal tubular necrosis (2.3± ± 0.1%, 2.2± ± 0.1% and 8.9± ± 1.3% for normal, Sham-operated and PU mice, respectively). Thus, IL233 cytokine attenuates kidney inflammation to protect from IRI.

**Funding:** NIDDK Support

**SA-PO255**

**Vagus Nerve Stimulation (VNS) Protects Kidneys from Ischemia-Reperfusion Injury Through Alpha 7 Nicotinic Acetylcholine Receptor (α7nAChR) Expressing Splenocytes**

**Background:** The nervous and immune systems interact in complex ways to maintain homeostasis and respond to stress or injury. The inflammatory reflex referred to as the cholinergic anti-inflammatory pathway (CAP) modulates innate and adaptive immunity, and modulation of the reflex by VNS is effective in inflammatory disease models. The effect of VNS on AKI has never been examined. Experimental activation of vagal efferent fibers suppresses inflammation in a manner that depends on α7nAChR in the CAP. However, the site of the essential α7nAChR was not established.

**Methods:** We applied electrical VNS (5 Hz, 50μA for 10 min) 24 hr prior to kidney IRI and assessed kidney injury by evaluating plasma creatinine (PCr, mg/dl), kidney-1 mRNA expression and histology (H&E). The effect of VNS on IRI was assessed by: a) prior splenectomy and b) adoptive transfer of splenocytes from VNS-stimulated mice to recipient mice subjected to IRI.

**Results:** VNS applied 24 hr prior to IRI markedly attenuated IRI. VNS reduced the IRI-induced increase in PCR by 65% (P<0.01) and Kim-1 mRNA expression in whole kidney by >70% (P<0.01). H&E- and stained sections confirmed the functional data. When splenectomy was performed 7 d before VNS and IRI, the protection by VNS was abolished. Adoptive transfer of splenocytes from VNS-treated mice to recipient mice subjected to IRI provided greater protection than splenocytes from mice who received sham VNS stimulation (PCr: 0.41 and 1.54 (P<0.001) for VNS- and sham-VNS-treated splenocytes, respectively). To evaluate the role of α7nAChR, VNS was initiated 24 hr prior to IRI in α7nAChR knock out (α7KO) and WT mice. Compared to the protective effect of VNS on IRI in WT mice, no protection was observed in α7KO mice. In addition, recipient mice were protected (PCR) if IRI if they received splenocytes from VNS-treated WT mice (0.41) but not from VNS-treated α7KO mice (1.57; P<0.01).

**Conclusions:** VNS-induced protection from IRI is consistent with activation of the CAP.

**SA-PO256**

**Elevations of Intraglomerular Pressure Exacerbate Ischemia Reperfusion Injury-Induced Acute Kidney Injury**

**Background:** The physiological and pathophysiological mechanisms of renal ischemia reperfusion (IR)-induced acute renal injury (AKI) are complex and have not been elucidated. We sought to determine whether intraglomerular hydrostatic pressure (Pg) during the ischemic phase plays a critical role in IR-induced AKI.

**Methods:** We created two transgenic zebrafish models of Kim-1 overexpression in nephrons employing the cd17 promoter. One model utilized a constitutive active promoter while the other utilized a tamoxifen-induced Cre-ERT2 recombinase to express Kim-1 in nephrons in a temporally-controlled manner. The role of mTOR signaling was evaluated using a specific mTOR inhibitor, Rapamycin. Zebrafish GFP was determined using the elimination rate of fluorescein-labeled dextran.

**Results:** Kim-1 was markedly upregulated after gentamicin-induced kidney injury and had conserved phagocytic activity in zebrafish. Both constitutive and tamoxifen-induced expression of Kim-1 in zebrafish kidney tubules resulted in shedding of the tubule brush border, reduced GFR, pericardial edema and increased mortality rate. Kim-1-induced kidney injury was associated with inhibition of growth of adult fish. Kim-1 expression led to mTOR pathway activation, and inhibition of this pathway with rapamycin increased survival. mTOR pathway inhibition in Kim-1 overexpressing transgenic mice also significantly reduced serum creatinine, proteinuria, tubular injury and kidney inflammation.

**Conclusions:** Persistent Kim-1 expression resulted in chronic kidney damage and growth impairment in zebrafish. Kim-1-mediated kidneys tubular injury was mediated by mTOR pathway activation. This observation in zebrafish prediction the role of the mTOR pathway and therapeutic efficacy of rapamycin to protect the mouse kidneys against Kim-1-mediated kidney injury and fibrosis.

**Funding:** NIDDK Support

**SA-PO254**

**Treg and ILC2 Contribute to IL233 (a Novel Fusion Cytokine)-Mediated Protection in AKI**

**Background:** Inflammation is an early event in AKI and studies have shown regulatory T cell (Treg)-mediated protection in inflammation driven injuries. Since we found that intraglomerular pressure (Pg) may be a novel therapeutic target for AKI, we explored the zebrafish model for investigating the role of Pg. Pg was measured with servo-nulling method during ischemia. Pf was used as an index of Pg. Elevations of Pg in ischemia and 24 hours of reperfusion (IRI)-induced acute renal injury (AKI) are complex and have not been elucidated.

**Methods:** A specific VAP-1 inhibitor, RTU-1096 (R-Tech Ueno, Tokyo, Japan), or vehicle was administered to rats since 7 days before the surgery (mixed with feed, 40 mg/kg/day).

**Results:** Immunofluorescence studies suggested that VAP-1 is expressed not only in endothelial capillaries but also in interstitial cells of non-endothelial lineage. In vitro, higher mRNA expression of VAP-1 was confirmed in cultured pericytes. In vivo, VAP-1 enzyme activity in the whole kidney was unaffected by the surgery, but following VAP-1 inhibition by RTU-1096 (0.9:0.1 vs. 7.0:1.3 pmol/mg protein/min), renal function was significantly improved as compared to the vehicle group (0.5±0.1 vs. 69.1±13.95 mg/dl, Cr: 1.4±0.1 vs. 2.5±0.02 mg/dl; P<0.01), which was accompanied by amelioration in histological tubular injury and decreased KIM-1 mRNA levels. Immunohistochemical analysis revealed a significantly decreased number of neutrophils in the cortical interstitium in IRI mice (3.1±1.3 vs. 9.2±2.2 mmHg) than in Sham operated mice (7.5 mmHg) when compared to Sham operated mice (9.5±4.2 mmHg).

**Conclusions:** We found that mean Pf was higher in PU mice (48.9±1.2 mmHg) than in Sham group mice (220 pg/ml in RP and 734 ± 16 pg/ml in RA group, respectively). Histology by PAS staining showed that all AKI mice had a significant increase in renal tubular necrosis (2.3± ± 0.1%, 2.2± ± 0.1% and 8.9± ± 1.3% for normal, Sham-operated and PU mice, respectively). Thus, IL233 cytokine attenuates kidney inflammation to protect from IRI.

**Funding:** NIDDK Support
GFR in Conscious Mice After Sepsis: Role of Tubuloglomerular Feedback

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Background: Reabsorption of glomerular filtrate by the tubules is an energy-intensive process. During sepsis the ability of the tubules to meet this energy demand may be impaired. To prevent renal salt wasting during sepsis it is hypothesized that activation of tubuloglomerular feedback reduces GFR and subsequently the metabolic demand on the tubules. "acute renal success". Mice without tubuloglomerular feedback should maintain higher levels of GFR. In conscious mice we detected early changes in GFR using a novel transcutaneous measurement of a fluorescent filtration marker. Because adenosine 1a receptor (A1AR) signaling is required for tubuloglomerular feedback we directly measured GFR following sepsis in A1AR knockout mice.

Methods: Sepsis was induced in male A1Ar knockout mice and littermate controls by cecal ligation and puncture. GFR was monitored in awake mice for five hours by transcutaneous measurement of a fluorescent filtration marker. Because adenosine 1a receptor (A1AR) signaling is required for tubuloglomerular feedback, unexpectedly, GFR begins to decrease earlier after sepsis suggesting impaired autoregulation. The sudden decrease in GFR in WT mice at two hours after induction of sepsis does not occur in A1AR KO mice. Tubuloglomerular feedback modestly supports, not suppresses, GFR in the first hour following sepsis, and only later acts to suppress GFR.

Results: The baseline GFR was similar in A1AR WT and KO mice. In WT mice, GFR was stable during the first hour following induction of sepsis. GFR slowly declined over hour two, and then fell rapidly to <10% of normal and remained low for five hours. In contrast, the GFR was lower in KO mice than in WT mice in the first hour following sepsis (p=0.0226), then fell gradually to 27% of normal, with a smaller decrease observed after two hours compared to WT mice (p=0.0286).

Conclusions: In mice lacking tubuloglomerular feedback, unexpectedly, GFR begins to decrease earlier after sepsis suggesting impaired autoregulation. The sudden decrease in GFR in WT mice at two hours after induction of sepsis does not occur in A1AR KO mice. Tubuloglomerular feedback modestly supports, not suppresses, GFR in the first hour following sepsis, and only later acts to suppress GFR.

Funding: NIDDK Support

SA-PO258

Renal Functional Reserve May Be Inferred from Variation of Renal Resistive Index: Preliminary Evidence

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Background: The increase of glomerular filtration rate(GFR)after a protein load represents the renal functional reserve(RFR).Mechanical abdominal stress(MAS),through the compression of renal arteries and the consequent reduction of renal blood flow,can activate the autoregulation mechanism to maintain glomerular perfusion.Both phenomena are related to the afferent vasodilation,which can be displayed by the drop of renal resistive index(RI)measured by color Doppler. We hypothesized that the variation of RI during MAS may predict the RFR.

Methods: In 15 healthy volunteers,MAS was performed through the application of a saline bag on abdominal wall. According to the performed dose-response curve,we used bags which weigh 10% of subject’s BW.We recorded RI in mesorenal interlobar arteries each min for the 10 min of MAS.The RI reduction was defined by the difference between baseline RI and the lowest RI reached during MAS and expressed as percentage reduction(pDRI).

RFR was measured through a standardized protein loading test.Spearman’s correlation was applied to evaluate if pDRI correlates with RFR.

Results: We enrolled 9 M and 6 F with a median of 30(24-75) yrs old,The median baseline CrCl was 99.2(70.3-132.8)ml/min/1.73m2. The RFR ranged between 11.55% and 134.66% with a median value of 38.55%. The median baseline RI was 0.600(0.50-0.67) while pDRI ranged between 13.35% and 29.23% with a median value of 20%. The correlation between pDRI and RFR was r=0.16 (p=0.01). According to physiology, RFR and pDRI may not be directly proportional; indeed, while ranges of RFR may widely broaden,pDRI should reach a plateau value. For this reason, we analyzed the linear regression model between pDRI and logarithm[ln] of RFR. According to this model, we found that an increase in pDRI was associated to an increase in the ln of RFR(coef0.10,p=0.001,95%CI:0.06,0.15,R2=0.66).

Conclusions: Our results suggest that the variation of RI during MAS is an indirect measure of RFR,putting the bases for the development of a stress test that could be used for a rapid screen of RFR before potentially nephrotoxic procedures.

Funding: Veterans Administration Support

SA-PO259

5-Aminolevulinic Acid Attenuates Rhabdomyolysis-Induced Acute Kidney Injury in Mice

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Background: Rhabdomyolysis often occurs after severe skeletal muscle injury, and high mortality have been reported with the acute kidney injury (AKI) that develops subsequently. Thus, the establishment of effective prevention and treatment is a pressing problem. 5-Aminolevulinic acid (ALA) is the naturally occurring metabolic precursor of heme, and serves as protein material related to energy production. Previous study demonstrated that ALA has the potential to prevent cisplatin-induced AKI via the induction of heme oxygenase (HO-1), and prevention of tubular apoptosis. We hypothesize that ALA plays a protective role by induction of the induction of HO-1 and anti-apoptotic pathway in rhabdomyolysis-induced AKI.

Methods: Male C57BL/6 mice were used. Rhabdomyolysis-induced AKI was induced by intramuscular injection of glycercol (50%) 5 ml/kg bw. ALA (30 mg/kg) was administered at 24 hr before or 24 hr after glycercol administration. These mice were sacrificed at 72 h after glycercol injection, and the blood and renal tissues were harvested. In vitro experiment, human proximal tubule cells were stimulated by 100 μM hemin to induce apoptosis. Cells were incubated for 24 h with or without 1 μM ALA. Apoptotic cells were examined by TUNEL staining and caspase-3 expression.

Results: In vivo experiments, serum creatinine, blood urea nitrogen and urine NGAL excretion were increased in glycercol-injected group compared with saline-injected control group. ALA significantly reduced these changes in both pre and post treatment. ALA also ameliorated glycercol-induced morphological tubular damages. HO-1 level was increased in glycercol-injected group and further up-regulated by ALA treatment. ALA significantly attenuated macrophage infiltration and pro-inflammatory cytokine (IL-1β and TNFα) expression. In vitro experiments, TUNEL-positive cells and caspase-3 expression were increased by hemin and were significantly reduced by ALA co-treatment.

Conclusions: ALA has renoprotective effects in glycercol-injected AKI. ALA is already used for tumor diagnosis in human. So the safety of the drug is proved in clinical use. ALA treatment may be a new therapeutic target in rhabdomyolysis-induced AKI.

SA-PO260

Ferroptosis as a Cause of Proximal Tubule Injury

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Background: ‘Ferroptosis’ has recently been described as a form of iron-dependent, lipid peroxidation-mediated cell death with a distinct injury pattern relative to other forms of necrosis and there is evidence that it contributes to AKI in vivo.(PNAS 111:16835,2014, Nat. Cell Biol. 16:1180,2014). Here, we have refined approaches to study ferroptosis in freshly isolated proximal tubules (PT) and assessed new agents being developed to ameliorate it.

Methods: Freshly isolated rabbit (R) and mouse (M) PT were treated with either tert-butylhydroperoxide (tBHP, 5 mM) or hydroxquinoline + ferrous ammonium sulphate (HQ+Fe,10 μM each) followed by incubation for 120 min, then measurement of LDH release, malondialdehyde (MDA) production, mitochondrial membrane potential, and GSH.

Results: tBHP and HQ+Fe induced progressive LDH release that was more severe in M PTs (R0: R60'-35.5 ± 6.8%, R120'-51.4 ± 9.6%; M60'-72.1 ± 2.6%, M120'- 87.4 ± 3.25%). These changes were accompanied by 5 fold increases of MDA levels and GSH depletion. LDH release and MDA production were iron and NAPHA oxidase (Nox)-dependent since they were blocked by deferoxamine or the Nox1/4 inhibitor GKT 137831. Feri, the prototypical ferroptotic inducer, did not target that phase of injury. Ferrostatins were not effective against acute cell killing and energetic deficits induced by hypoxia/reoxygenation, indicating that the benefit seen during in vivo ischemia/reperfusion does not target that phase of injury.

Conclusions: Ferroptosis is strongly expressed in fully differentiated PTs, is suppressed by both newly developed ferrostatins and the classical lipophilic antioxidant, DPPD, and is an injury process that can be targeted to alleviate AKI.

Funding: Veterans Administration Support

SA-PO261

Identification and Characterization of IGFBP7 and TIMP2 Expression in Human Proximal and Distal Tubule Cells

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Background: IGFBP7 and TIMP2 have been identified as biomarkers for Acute Kidney Injury (AKI), but little is known regarding any role in the pathogenesis of the disease. To study this question we established primary cell culture models of human proximal and distal tubule epithelial cells.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: The cortex of human kidneys were dissociated and viable cells cultured. Proximal and distal tubule epithelial cells (PTECs and DTECs) were isolated with antibodies against CD163 and CD227 using the Dynabead pan-mouse IgG system. Isolated cells were cultured on transwell supports and characterized by immunoblot and immunofluorescence.

Results: CD163 isolated cells were positive for the PTEC markers Gamma Glutamyl Transpeptidase and Aquaporin-1. CD227 isolated cells were negative for GGT and AQP1 but positive for the distal tubule markers CD227 and E-cadherin. Microscopy demonstrated that both PTECs and DTECs formed tight junction monolayers with a low percentage of cells in cycle as identified by Ki-67. Analysis of conditioned media demonstrated that both cell types secreted high GGBP7 and TIMP2. Importantly, we identified a preferential expression of IGFBP7 in PTECs and of TIMP2 in DTECs. Furthermore, we discovered evidence suggesting that TIMP2 is primarily secreted across the apical surface, while the majority of GGBP7 is secreted across the basolateral surface. Despite this, we also found that some PTECs and some GGBP7 can be secreted apically, primarily in PTECs.

Conclusions: We have developed human cell culture model systems of PTECs and DTECs for the cellular/molecular analysis of AKI. We confirmed that IGBP7 and TIMP2 can be expressed and secreted by these cells, and we have identified differential expression and secretion of these proteins across cell types and spatially within cells. These systems and knowledge will now allow for investigation of the potential role of these biomarkers in the molecular etiology of AKI.

Funding: Pharmaceutical Company Support - Astute Medical

SA-PO262

Klotho and S100A8/A9 as Discriminative Markers Between Pre-Renal and Intrinsic AKI

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Background: Early detection and accurate differentiation of the cause of acute kidney injury (AKI) is of prognostic significance for patients. However, to date, there are few reliable biomarkers for the discrimination of pre-renal and intrinsic AKI. The purpose of this study was to determine whether AKI is associated with an altered level of klotho and the expression of S100A8/A9 in serum; 3361.11 ± 101.96 ng/ml; P = 0.003 in urine). Serum and urinary NGAL showed no difference between pre-renal and intrinsic AKI group. The model of renal IRI was induced by the release of bilateral renal pedicle clamping for 60 min. Mice were subjected to renal LR and treated with DNAse1 or saline (5 mg/kg). All animals were euthanized 72 hr after first IF injection. We also performed a proof of concept cross-sectional study to measure serum and urinary biomarkers in 77 hospitalized patients with established AKI.

Results: Compared with intrinsic AKI group, pre-renal AKI group caused a marked depression of urinary klotho level (13.21 ± 17.32 vs. 72.97 ± 17.96 pg/ml; P = 0.002). In addition, intrinsic AKI group caused a marked elevation of S100A8/A9 level than those of pre-renal AKI group (2629.97 ± 598.05 ng/ml vs. 685.09 ± 111.85 ng/ml; P = 0.002 in serum; 1361.11 ± 230.86 ng/ml vs. 741.72 ± 101.96 ng/ml; P = 0.003 in urine). Serum and urinary NGAL showed no difference between pre-renal and intrinsic AKI group. The proof of concept study with hospitalized AKI patients also demonstrated decreased urinary klotho in pre-renal AKI patients and increased urinary S100A8/A9 concentrations in their urine samples.

Conclusions: The attenuation of urinary klotho and increment of urinary S100A8/A9 may contribute to discriminate the pre-renal AKI and intrinsic AKI.

Funding: Pharmaceutical Company Support - Fresenius Medical Care Korea

SA-PO263

Release of Extra Cellular DNA Contributes to Renal Ischemia Reperfusion Injury Through Platelet Activation and Formation of Neutrophil Extracellular Traps

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Background: There have been considerable growth in older population and age-related kidney disease in the world. It was demonstrated that the impairment in the potentiality to repair and regenerate of renal resident cells is a hallmark of biological processes associated with aging. However, the impact of senescence of bone marrow derived cells (BMDC) on kidney injury is not known. Here, we investigated the role of senescence of BMDC in the development and progression of ischemic acute kidney injury (AKI).

Methods: Seven wk-old female mice were sublethally irradiated and reconstituted with bone marrow from 12-mo-old (old-to-young, old BMT) or 7-wk-old (young to young, young BMT) mice. Then we performed renal ischemia reperfusion injury (IRI) in old or young BMT mice, and functional, histological kidney damage and inflammation were compared.

Results: The Y chromosome was detected in peripheral blood of BMT mice indicating successful reconstitution of female mice with male bone marrow. Although the population of intracellular DNA in splenocytes from old and old BMT mice was significantly different, old BMT mice showed less renal functional deterioration and histological damage after IRI. This was associated with less infiltration of F4/80 macrophages and lower level of tissue cytokine (IL-12). In vitro study with BMDCs also revealed that LPS-induced cytokine productions (IFN-γ, MCP-1 and IL-10) were significantly suppressed in old BM cells than young BM cells.

Conclusions: Our data shows that senescence of BMDC could affect susceptibility and response to renal ischemic injury possibly via immune modulatory effect. A better understanding of these processes could help to develop new strategies that are specifically tailored for treatment of the elderly population.

Funding: Non-U.S.

SA-PO265

Optimal Transplantation Timing of Mesenchymal Stem Cell in Rat Model of Renal Ischemia Reperfusion Injury

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Background: It is optimal timing to transplant MSCs in IRI before kidney injury is not known. Here, we investigated the role of senescence of BMDC in the development and progression of ischemic acute kidney injury (AKI).

Methods: The serum creatinine level peaked at 24h of reflow (470.6 ±1066 pg/ml, P<0.05) and NGAL peaked at 12h(767.1±106 pg/ml, P<0.05). The highest expression of inflammatory factor was in 1h and 4h groups, and the lowest was in 1h and 4h groups. In vitro, there was lower cell apoptosis and higher proliferation in 1h and 0h groups compared with other groups. Significant kidney function and histological damage improvement was observed after the treatment of MSCs in 1h and 4h groups. Meanwhile, the expression of proinflammatory factor significantly decreased in 1h and 0h groups compared with other point time groups and control group. In addition, we also observed more obvious inhibition of renal tubular cell apoptosis and promotion of proliferation in 1h and 0h groups compared with other groups. Consistent with the improvement above, the viability of implanted MSCs also increased in 1h and 0h groups.

Conclusions: MSCs transplantation 1h before reperfusion or immediately after reperfusion protects from I/R injury. It is the optimal timing to transplant MSCs in IRI before the inflammatory response is established.

Funding: Government Support - Non-U.S.

SA-PO266

Renal Protective Role of Par1 in Acute Kidney Injury

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Background: Par1 has been shown to be involved in the development of renal injury. However, the role of Par1 in acute kidney injury has not been well elucidated.

Methods: We stimulated platelets with necrotic renal cells in presence of absence of deoxyribozonuclease 1 (DNase1). Platelet activation and platelet-leukocyte formation were measured by FACS. We stimulated granulocytes with activated platelets and measured DNA release – indicative of NET formation. Vicious versa we stimulated platelets with NETs and measured platelet activation, resulting in tissue damage. It has been shown that platelet inhibition protects from I/R. How platelets are activated upon renal I/R is not entirely clear. In this study we investigate renal cell death, extracellular DNA release and neutrophil extracellular traps (NETs) as potential triggers for platelet activation and renal I/R injury.

Results: We stimulated platelets with necrotic renal cells in presence or absence of DNAse1 reduced platelet activation. Activated platelets generated NETs in vitro and, vice versa, NETs stimulated platelet activation ex vivo. Mice subjected to renal I/R showed a significant increase of extracellular DNA and PF4 levels in the circulation. Treatment with DNase1 improved renal functional outcomes. Pretreatment with DNase1 reduced renal swelling and inflammation. Treatment with DNase1 resulted in a trend towards fewer NETs and granulocytes in tissue.

Conclusions: Both DNA from necrotic kidney cells and NETs activate platelets, which in turn cause further NET formation, leading to a vicious triad in the pathogenesis of I/R injury. Treatment with DNase1 may have therapeutic benefits in the context of renal I/R injury.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
are functionally redundant on kinase assays. We have identified a role for Par1α/b in glomerular and proximal tubular development in mice associated with downregulation of Notch signaling. We hypothesized that Par1α/b would contribute to renal epithelial repair in the setting of acute kidney injury.

Methods: Expression of Par1α/b and Notch signaling was examined using western blotting and immunofluorescence in models of tubular injury and human kidney tissue (leftover from clinically indicated renal biopsy). Proximal tubular injury was induced by in wild-type(WT) and Par1α knockout mice by injecting cisplatin (30mg/kg, ip) or folic acid (250 mg/kg, ip). The degree of histological damage was assessed by light microscopy. Par1α/b migration was studied using developing mouse kidney and comparison with normal adult human kidney.

Background: Heat shock protein beta-1 (HSPB1, also known as HSP27) is a small heat shock protein involved in various cellular processes and reported to protect cells against oxidative and chemical stress. Autophagy protects cells from many types of stress and is thought to play a key role in preventing stress in acute kidney injury (AKI). However, little is known about the role of HSPB1 in autophagy and apoptosis in the pathogenesis of AKI.

Methods: We used a rat ischemia/reperfusion AKI model and cultured renal tubular cells as an in vitro model. To elucidate the regulation of HSPB1, we evaluated the promoter activity and expression of HSPB1 in normal rat kidney (NRK)-52E cells in the presence of H2O2. To examine the regulation of autophagy by HSPB1, we established NRK-light chain 3 (NRK-LC3) cells that were stably transfected with a fusion protein of green fluorescent protein and LC3.

Results: The results of immunohistological examination showed that HSPB1 was expressed in proximal tubule cells after AKI. Real-time quantitative reverse transcription-polymerase chain reaction and western blot analysis showed that HSPB1 mRNA and protein expression were upregulated 6–72 h and 12–72 h, respectively, after ischemia/reperfusion injury. HSPB1 promoter activity as well as mRNA and protein expression indicated dose-dependent induction by H2O2. HSPB1 overexpression-induced autophagy in NRK-3LC3 cells under normoxic conditions was confirmed with confocal microscopy, which revealed the presence of LC3-positive granules. Furthermore, H2O2-induced autophagy was inhibited by the transfection of small interfering RNAs for HSPB1. Overexpression of HSPB1 reduced BAX activation and H2O2-induced apoptosis, as measured by caspase 3 activity and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling assay.

Conclusions: These results indicate that HSPB1 upregulation plays a role in the pathophysiology of AKI.

SA-PO268


Background: Cisplatin, a commonly used chemotherapeutic for the treatment of many solid cancers is known to induce acute kidney injury (AKI) in 30% of patients. Patients that develop cisplatin-induced kidney toxicity must either have the dose severely reduced or be switched to an alternative therapy to prevent long-term renal damage. In many cases the alternative therapy may be less effective at treating the tumor. Due to cisplatin’s complex nephrotoxicity, development of new agents remains a challenge. Currently there are no FDA approved drugs for the protection of cisplatin-induced AKI. The standard mouse model of cisplatin-induced AKI is a single high dose of cisplatin (10-30 mg/kg), and animals are sacrificed 72h after injection. This model does not accurately represent the clinical dosing regimen, which involves repeated dosing of cisplatin.

Methods: In this study we compared the standard single dose model to a new multiple dose model where mice received lower doses of cisplatin once a week for 4 weeks. We measured and compared indicators of kidney function (KIM-1, NGAL, BUN, and Serum Creatinine). We also measured markers of inflammation (IL-6, IL-1β, TNFα, MCP-1). Indicators of apoptosis and cell death were measured as well as indicators of fibrosis (i.e. TGF-β, CTGF, BMP-7, and Sirtus Red staining).

Results: In comparing the results of the single and multiple dose models, BUN values were similar, suggesting a comparable loss of kidney function. However, KIM-1 and NGAL were reduced by roughly 10-fold and 100-fold, respectively. Inflammation was also decreased in this model with TNFα, IL6 and IL1-β reduced by 4, 10 and 5-fold, respectively. Fibrosis was nearly non-existent in the single dose model; however, the multiple dosing model showed a significant increase in fibrosis. Also, expression of PAI-1, a marker of fibrosis was significantly increased in the multiple dosing model compared to the single dose model.

SA-PO269


Background: Heat shock protein beta-1 (HSPB1, also known as HSP27) is a small heat shock protein involved in various cellular processes and reported to protect cells against oxidative and chemical stress. Autophagy protects cells from many types of stress and is thought to play a key role in preventing stress in acute kidney injury (AKI). However, little is known about the role of HSPB1 in autophagy and apoptosis in the pathogenesis of AKI.

Methods: We used a rat ischemia/reperfusion AKI model and cultured renal tubular cells as an in vitro model. To elucidate the regulation of HSPB1, we established NRK-light chain 3 (NRK-LC3) cells that were stably transfected with a fusion protein of green fluorescent protein and LC3.

Results: The results of immunohistological examination showed that HSPB1 was expressed in proximal tubule cells after AKI. Real-time quantitative reverse transcription-polymerase chain reaction and western blot analysis showed that HSPB1 mRNA and protein expression were upregulated 6–72 h and 12–72 h, respectively, after ischemia/reperfusion injury. HSPB1 promoter activity as well as mRNA and protein expression indicated dose-dependent induction by H2O2. HSPB1 overexpression-induced autophagy in NRK-3LC3 cells under normoxic conditions was confirmed with confocal microscopy, which revealed the presence of LC3-positive granules. Furthermore, H2O2-induced autophagy was inhibited by the transfection of small interfering RNAs for HSPB1. Overexpression of HSPB1 reduced BAX activation and H2O2-induced apoptosis, as measured by caspase 3 activity and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick end labeling assay.

Conclusions: These results indicate that HSPB1 upregulation plays a role in the pathophysiology of AKI.

SA-PO270

The Protective Role of Doxycycline for Cisplatin-Induced AKI by Its Anti-Inflammatory and Anti-Oxidative Effects Tetsuya Nakagawa,1 Yutaka Kakizoe,1 Yoshikazu Miyasato,1 Teruhiko Mizamato,1 Manabu Hayata,1 Yuichiro Izumi,1 Takashige Kawaiura,2 Taku Miyoshi,1 Masataki Adachi,1 Kenichiro Kitamura,2 Masashi Mukoyama.1 Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan;1 Internal Medicine III, Univ of Yamanashi Faculty of Medicine, Yamanashi, Japan.

Background: Cisplatin (CDDP) is a chemotherapeutic drug widely used for the treatment of solid tumors. However, its nephrotoxicity is the major dose-limiting factor. Doxycycline (Dox) is a tetracycline antibiotic commonly used in a variety of infections, but several other properties have been suggested such as an anticancer effect or the inhibition of matrix metalloproteinase (MMP). In this study, we investigated whether Dox exerts the protective effects on CDDP-induced acute kidney injury(AKI).

Methods: Ten-week-old male C57BL/6J mice were divided into following four groups: 1) Control, 2) Dox (2mg/ml in drinking water), 3) CDDP (25 mg/kg, intraperitoneally) and 4) CDDP+DOX. After 7 days pretreatment with Dox, CDDP was administrated, and animals are sacrificed 72h after injection. Protective effects on CDDP-induced acute kidney injury(AKI).

Results: No apparent adverse effects were observed in Dox group. Dox did not affect mRNA expression of transporters for CDDP (OCT-1, OCT-2 and MATE1) in the renal tubules. CDDP caused severe tubular damages along with elevated BUN and Cr levels. It also increased mRNA expression of inflammatory and profibrotic molecules, together with enhanced oxidative stress in the kidney. Dox alleviated significantly those detrimental changes (Cr: Control, 0.13±0.01; Dox, 0.13±0.03; CDDP, 1.04±0.20 and CDDP+Dox, 0.30±0.12 mg/dL). Moreover, Dox suppressed the activities of MMP-2 and 9 as well as serine proteases, which were enhanced by CDDP in the kidney tissue.

Conclusions: Dox mitigated CDDP-induced AKI through its pleiotropic effects, i.e., anti-inflammatory, anti-oxidative, and anti-fibrotic factors. Our results suggest that Dox could become a new strategy for the prevention of CDDP-induced nephrotoxicity in humans.

Funding: Government Support - Non-U.S.
Methods: For in vivo study, male C57BL/6 mice were given a single intraperitoneal injection of cisplatin. In vitro, the cisplatin-resistant proximal tubular cells (RPTC) were incubated with cisplatin. To determine the role of heat shock factor 1 (HSF1), HSF1 was knocked down by stable transfection of specific siRNAs.

Results: In RPTC, cisplatin induced a rapid expression of HSF1 and specific heat shock proteins, including Hsp70, Hsp27, and Crystallin-αB. The expression of these proteins was transient and decreased at late time points of cisplatin treatment. Similar changes were verified in kidney tissues following cisplatin injection, whereas Hsp90 did not change significantly. Knockdown of HSF1 decreased Crystallin-αB expression and pro-RPTC apoptosis. Interestingly, p38 activation was enhanced in these cells. Moreover, inhibition of p38 with SB203580 markedly inhibited cisplatin-induced apoptosis in HSF1-knockdown cells.

Conclusions: Induction of HSF1 is a cytoprotective response during cisplatin nephrotoxicity. Crystallin-αB appears to be a key heat shock protein induced by HSF1 for its protective effect. Heat shock response may regulate or co-operate with other signaling pathways, such as p38, to regulate tubular cell apoptosis.

Funding: NIDDK Support, Veterans Administration Support

SA-PO274

The Effect of the Cytoplasmic Domain of Tissue Factor in Contributing to Renal Ischemic Reperfusion Injury Is Both Protease Activated Receptor-1 (PAR-1) and Strain Dependent

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Background: The cytoplasmic domain of tissue factor plays a role in cell signaling and regulation of apoptosis and inflammation. It may do so by regulating protein tyrosine phosphorylation and via modulating protease activated receptor signaling. Previously we have shown that mice on a mixed genetic background deficient (MGB) in the cytoplasmic domain of tissue factor (TFcyt) mice developed severe renal injury. They have increased cytokine and PAR-1 expression, which contributed to the importance of increased PAR-1 signaling and the strain background of the mice.

Methods: Mice WT or TFcyt/deltact on MGB or mice backcrossed onto C57BL/6 mice background underwent 2.5 min bilateral warm ischemia and 24 reperfusion. Renal function was assessed by serum creatinine and renal injury was further assessed by histology and expression of inflammatory mediators form renal tissue. The role of PAR-1 was assessed using the inhibitor SCH79797.

Results: TFcyt/deltact mice on the MGB developed more severe injury at 24 than WT on a similar genetic background. These mice developed greater PAR-1 mRNA expression and treatment of these mice with the PAR-1 inhibitor reduced injury similar to PAR-1 deficient mice. In contrast the effect of TF cytoplasmic depletion was not seen in mice on C57BL/6 background. These mice had similar PAR-1 induction to that observed in WT C57BL/6. WT mice with a MGB had lesser renal injury and lower basal PAR-1 expression than WT C57BL/6 mice. TFcyt/deltact mice on MGB having similar basal PAR-1 expression and much greater inducible PAR-1 expression (5 fold compared to 2.8 fold for WT). TFcyt/deltact on a C57BL6 background had similar renal injury and PAR-1 induction to WT mice.

Conclusions: The cytoplasmic domain of TF may contribute to renal IR injury by regulating PAR-1 expression. The role of the TF cytoplasmic domain in regulating renal injury is genetic background dependent.

SA-PO275

Protective Effects of Endonuclease Inhibitors on Cisplatin-Induced Acute Kidney Injury

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Background: Cisplatin is one of the most commonly used and the most nephrotoxic anticancer drugs. Acute kidney injury induced by cisplatin cannot be overcome and may lead to chronic kidney failure. Our previous studies showed that genetic inactivation of two kidney apoptotic endonucleases, DNase I and EndoG, was partially protective against tubular epithelial cell death induced by cisplatin. Until very recently, pharmacologically meaningful inhibitors of the endonucleases, which would be non-toxic and effective in vivo, were not available.

Methods: This study was aimed to determine if the two new endonuclease inhibitors recently identified by us, IG-17 (1,3-polyethylen-bis-aminoguanidine hydrochloride) for DNase I and PNR-382 (5,8-(1H-2-naphthyl)-5-methoxy-1H-indol-3-yl(ethylen)-2-thioxoimidazoline-4(1H,5H)-dione) for EndoG, could ameliorate cisplatin toxicity to kidney tubular epithelial cells in vitro and in vivo.

Results: In vitro experiments using NRK-52E cells showed that the compounds are able to suppress endonuclease activity inside the cells provide partial protection against cisplatin toxicity measured using LDH release assay and TUNEL, and are non-toxic at the used concentrations. The inhibitors were found to markedly suppress the total-body endonuclease activity in mice at the dose of 5 mg/kg administered subcutaneously; and were non-toxic up to 25 mg/kg as measured using 14 blood plasma markers of organ toxicities.

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Underline represents presenting author.

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Conclusions: Importantly, cisplatin-induced kidney injury was functionally (creatinine) and structurally (acute tubular necrosis, TUNEL) reduced by the administration of the inhibitors (5 mg/kg) in mice suggesting their potential therapeutic value.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

SA-PO276

Involvement of CYLD as a Regulatory Factor in Fibrotic Response of Ischemic AKI Kidney and Hypoxic HK-2 Cells

Background: The effect of oxygen and hypothermic therapy on the prevention of acute kidney injury (AKI) is an important risk factor of chronic kidney disease (CKD). We investigated the role of microRNA-17 (miR-17) regulation in kidney against damage in ischemia-reperfusion injury.

Methods: Renal ischemia-reperfusion was induced in C57 mice by bilateral clamping for 36° C body temperature. Prior treatment was given to six groups in different ways. The left kidneys were used for control. After a catheter was placed in a bladder, oxygen was cooled for hypothermic therapy before the induction of acute kidney injury. The kidneys were extracted after the induction of acute kidney injury with clamping. Gross examination of both kidneys during the clamping and after the extraction was performed. Results: Gross examination of kidneys demonstrated less ischemic changes of kidneys treated with oxygen or hypothermic oxygen during and after the induction of acute kidney injury. As shown in Figure 1, right kidneys that received oxygen therapy or hypothermic oxygen showed less ischemic changes on gross examination during the clamping and after extraction.

Oxygen therapy

Control

Hypothermic oxygen

Figure 1

Conclusions: This pilot study shows novel methods for the prevention and treatment of acute kidney injury. Further study is necessary to investigate the effects of catheter oxygen and hypothermic therapy in the prevention and treatment of acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO273

MicroRNA-17 Is Induced via P53 to Protect against Renal Ischemia-Reperfusion Injury by Targeting Death Receptor 6

Background: MicroRNA-17 (miR-17) regulates cell survival and proliferation pathways by acting as a deubiquitinating enzyme. Recent studies have revealed that CYLD could play a pathological role in regulating pathways by acting as a deubiquitinating enzyme. Recent studies have revealed that CYLD could play a pathological role in regulating fibrosis. It is well-documented that tissue fibrosis is common hallmark of chronic kidney disease (CKD), and CKD progresses toward end-stage renal disease through renal fibrosis. However, the molecular pathogenesis of renal fibrosis is not fully understood yet. In this study, we elucidated the roles of CYLD in renal fibrosis by using in vivo and in vitro models.

Methods: We generated model mice of ischemia/reperfusion (I/R)-induced acute kidney injury (AKI) and hypoxic human kidney (HK)-2 cells. CYLD protein expression was markedly decreased (0.4-fold) in a time-dependent manner. Interestingly, fibrosis gene expression (PAI-1: 12-fold, CTGF: 2.5-fold, COL1A1: 4-fold) was significantly increased in response to the treatment on the development of fibrosis, neither treatment (at doses demonstrated to be effective in more mild injury models) showed effect in the vitro model. Broad anti-inflammatory suppression by dexamethasone attenuated fibrotic gene expression. We speculate that the natural course of renal demise after UIRI is very robust and highly likely to require a multi-target approach. Whether some combination of the therapies tested here could have efficacy in this model remains to be determined.

Funding: Government Support - Non-U.S.

SA-PO278

Effect of Oxygen and Hypothermic Therapy on the Prevention of Acute Kidney Injury

Background: There is no effective therapy for acute kidney injury. The effect of oxygen, hypothermic therapy delivered through urinary tract on the treatment of acute kidney injury has not been known. This pilot study was performed as a proof of concept of a catheter-based oxygen and hypothermic oxygen therapy in preventing and treating acute kidney injury.

Methods: Rats (n=6) were used for the experiment. Three rats were used to compare oxygen therapy and control. The other three rats were used to compare hypothermic oxygen therapy and control. Oxygen was cooled for hypothermic oxygen therapy before it was delivered to the kidney. Right kidneys treated receive oxygen or hypothermic oxygen therapy and left kidneys were used for control. After a catheter was placed in a bladder, oxygen (or cooled oxygen) was delivered to the right kidney from the bladder through the catheter for five minutes for pretreatment before clamping. Both right and left renal arteries were clamped for 30-45 mins to induce acute kidney injury. Only right kidneys continued to receive oxygen or hypothermic oxygen during the clamping of renal arteries. The kidneys were extracted after the induction of acute kidney injury with clamping. Gross examination of both kidneys during the clamping and after the extraction was performed. Results: Gross examination of kidneys demonstrated less ischemic changes of kidneys treated with oxygen or hypothermic oxygen during and after the induction of acute kidney injury. As shown in Figure 1, right kidneys that received oxygen therapy or hypothermic oxygen showed less ischemic changes on gross examination during the clamping and after extraction.

Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

SA-PO279

The Effect of Oxygen and Hypothermic Therapy on the Prevention of Acute Kidney Injury

Background: Ischemic acute kidney injury (AKI) is an important risk factor of chronic kidney disease (CKD). We optimized a mouse model of AKI to CKD by unilateral ischemia-reperfusion (UIRI) with development of renal fibrosis. To validate this model for use in therapeutic intervention studies, 3 experimental treatments were tested: administration of 1) recombinant human CCN3 (CCN2/CTGF antagonist), 2) TGFβ1 neutralizing antibody (ID11) or 3) dexamethasone (corticosteroid).

Methods: Male C57Bl/6 mice underwent 21 min of unilateral ischemia-reperfusion (UIRI) at 36° C body temperature. 8 treatment groups (n=4/group, ip) were included: dexamethasone (10 mg/kg, daily), vehicle (PBS, daily), rCCN3 (5 μg/kg, daily), vehicle (PBS, daily), antibody to TGFβ1 (0.5 mg/kg, every other day), vehicle (PBS, every other day), an untreated UIRI group and a sham group. Three weeks after UIRI renal fibrotic outcome was determined by gene expression analysis (qPCR) of collagen I, TGFβ, CTGF, CCN3, PAI-1 and TNF-α.

Results: UIRI induced a ~40% reduction in renal mass. Treatment with rCCN3, anti-TGFβ or dexamethasone did not attenuate this reduction. UIRI induces significant upregulation of the fibrosis-related genes. rCCN3 treatment had no effect on gene expression. Anti-TGFβ antibody treatment induced significantly less upregulation of TGFβ1 and CCN3 gene expression, however, vehicle also reduced TGFβ expression. Dexamethasome treatment induced significantly less upregulation of collagen I and CCN2/ CTGF gene expression and a trend towards higher CCN3 upregulation.

Conclusions: Despite the earlier proven benefits of TGFβ1 antagonism and CCN3 treatment in the development of fibrosis, neither treatment (at doses demonstrated to be effective in more mild injury models) showed effect in the vitro model. Broad anti-inflammatory suppression by dexamethasone attenuated fibrotic gene expression. We speculate that the natural course of renal demise after UIRI is very robust and highly likely to require a multi-target approach. Whether some combination of the therapies tested here could have efficacy in this model remains to be determined.

Funding: Government Support - Non-U.S.
SA-PO280

Proximal Tubule-Derived CSF-1 Mediates Expansion and Polarization of Renal Macrophages/Dendritic Cells and Recovery in Acute Kidney Injury

Yinpeng Wang, Bing Yao, Raymond C. Harris, Ming-Zhi Zhang. Medicine, Vanderbilt Univ, Nashville, TN.

Background: Colony-stimulating factor-1 (CSF-1)-mediated renal macrophage expansion and polarization play an essential role in recovery from acute kidney injury in ischemia/reperfusion (IR)-injury and selective apoptotic proximal tubule injury in transgenic mice expressing the human diphtheria toxin receptor (DTR) and exposed to DT (DTR-AKI). In the kidney, a major site of CSF-1 production is in proximal tubular epithelial cells.

Methods: Male DTR mice with CSF-1-/- (wild-type) or with γ-GT-Cre-CSF-1+/- (CSF-1 KO in renal proximal tubule) were used for DTR-AKI and for IR injury (30 min of ischemia and contralateral nephrectomy).

Results: CSF-1 expression in the proximal tubule and its deletion in CSF-1 KO mice were confirmed with immunostaining. Six days after DTR-AKI, activation of the CSF-1 receptor (p-c-fms) was markedly attenuated in both renal tubules and interstitial cells, including macrophages (F4/80 and p-c-fms dual positive cells). Flow cytometry and qPCR indicated fewer renal macrophages/dendritic cells and reduced mRNA levels of M2 phenotype markers (CD206, IL-4Rα, TGF-β and 15-LOX) in CSF-1 KO mice 6 days after DT injection. Although selective proximal tubule CSF-1 deletion did not affect the severity of kidney injury, it delayed renal functional recovery, in association with increased oxidative stress, increased secondary necrosis (HMGB1 expression) and severe tubulointerstitial fibrosis, with increased Picro-sirus red staining of fibillary collagen and increased profibrotic and fibrotic components (α-SMA, CTGF, Fbronectin, collagen I and IV). Selective proximal tubule CSF-1 depletion also led to delayed functional recovery after IR injury, with decreased mRNA levels of M2 phenotype markers in isolated renal macrophages/dendritic cells and more severe renal fibrosis. In both IR injury and DTR-AKI, selective proximal CSF-1 deletion had minimal effects on the expression of M1 phenotype markers.

Conclusions: These studies demonstrate that proximal tubule is a major source of CSF-1 that mediates the expansion and polarization of renal macrophages/dendritic cells that play an essential role in recovery following AKI.

Funding: NIDDK Support

SA-PO281

Ablation of Myo-Inositol Oxidase Protects against Cisplatin-Induced Acute Kidney Injury by Inhibiting p53 Activation

Rajesh K. Dutta, Yashpal S. Kanwar. Dept of Pathology, Northwestern Univ, Chicago, IL.

Background: MIOX is a renal tubular enzyme. Its role in the pathogenesis of diabetic nephropathy is currently being investigated. Conceivably, it modulates redox imbalance and apoptosis in tubular cells in diabetes via modulation of glucuronate-xylulose (G-X) pathway. However, its role in acute kidney injury (AKI) is unknown.

Methods: In this study we used both MIOX-over-expressing transgenic and MIOX null mice to elucidate its role in a model of cisplatin induced AKI.

Results: We observed severe cisplatin-induced proximal tubular injury in MIOX transgenic and protection in null mice compared to wild type mice. In transgenic mice an increased serum creatinine and urea levels, caspases-3 activity and tubular apoptosis along with marked deterioration of tubular morphology was observed. Renal injury was remarkably less in null mice compared to wild type mice. Cisplatin treatment led to p53 activation in wild type and MIOX transgenic mice, whereas minimal p53 activation was observed in MIOX null mice. Likewise, we noted that cisplatin induces mTOR pathway in both wild type and MIOX transgenic mice while such an effect was not observed in MIOX null mice. Treatment with mTOR inhibitor, rapamycin, prevented cisplatin-induced MIOX expression, p53 activation and deterioration of tubular morphology in control mice. In vitro studies revealed significantly high levels of ROS generation, caspases-3 activity and apoptosis in MIOX over-expressing cells compared to control cells transfected with empty vector following cisplatin treatment.

Conceivably, this was attributed to the accentuated induction of G-X-pathway and its associated myriad enzyme system.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO284
Allopurinol Protects against Rhabdomyolysis and Acute Kidney Injury Induced by a Membrane Protein (Lp25) from Pathogenic Leptospires
Antonio C. Seguro,1 Daniele Canale,1 Patricia A. Abru,2 Denize Monariz,2 Tatiana B. Gotti,2 Larissa R. Matos,2 Thales de Brito,2 Pedro H F Gois,1 Antonio J. Magalhã,1 1Nephrology, Hospital das Clínicas FMUSP, São Paulo, Brazil; 2Lab. de Bacteriologia, Inst Butantan, São Paulo, Brazil.

Background: Acute kidney injury (AKI) in leptospirosis is frequently nonoliguric, hypo or normokalemia. Higher serum potassium levels, elevated creatinine phosphokinase (CPK) associated with maximum serum creatinine level were observed in non-survivor patients suggesting that rhabdomyolysis contributes to more severe AKI in leptospirosis. Previous study from our group demonstrated that Lp25, a protein membrane from pathogenic Leptospires, was responsible for hyperkalemia AKI induced by rhabdomyolysis in guinea pigs. Recent studies suggest that Allopurinol (Allo) protects individuals from exercise-induced rhabdomyolysis. The aim of this study was to evaluate the effect of Allo on guinea pigs injected with Lp25.

Methods: Three groups of guinea pigs were studied: 1. Sham (phosphate-buffered solution); 2. Lp25-3-L: Lp25+Allo. One mL of PBS and Lp25 (400μg of Lp25/mL) were intraperitoneally injected for 4 days. Lp25+Allo received Allo (300mg/Kg) in drinking water during this time. On the 5th day, animals were placed in metabolic cages for 12 hours urine collection. We measured urinary volume (Ur V/12h), creatinine clearance (ml/min/100gBW), serum potassium (mEq/L), CPK (U/L), uric acid (mg/dL), phosphate (mg/dL). Data are mean±SEM.

Results: Lp25 induced hyperkalemia, rhabdomyolysis (elevated CPK, uric acid, phosphate) and oliguric AKI. Allo ameliorated CPK, serum potassium, CPK and uric acid.

<table>
<thead>
<tr>
<th></th>
<th>Cr Cl</th>
<th>Ur V</th>
<th>K (mEq/L)</th>
<th>CPK (U/L)</th>
<th>Uric acid (mg/dL)</th>
<th>Phosphate (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=7)</td>
<td>1.18±0.18</td>
<td>25L±3.1</td>
<td>4.8±0.3</td>
<td>897.2±77</td>
<td>108.0±0.19</td>
<td>6.9±0.3</td>
</tr>
<tr>
<td>Lp25 (n=8)</td>
<td>0.48±0.05</td>
<td>11.1±1.8</td>
<td>6.8±0.5</td>
<td>2852±495</td>
<td>4.15±0.48</td>
<td>9.3±0.6</td>
</tr>
<tr>
<td>Lp25+Allo (n=6)</td>
<td>0.91±0.14</td>
<td>17.0±3.7</td>
<td>5.1±0.6</td>
<td>1331±374</td>
<td>0.47±0.004</td>
<td>8.4±0.5</td>
</tr>
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*p<0.05, **p<0.01 vs. Sham; p<0.05, **p<0.001 vs. Lp25

Conclusions: These data demonstrate that Allo ameliorates rhabdomyolysis and AKI induced by Lp25 in guinea pigs. This may represent a new therapeutic approach for AKI in patients with leptospirosis.

SA-PO285
Conventional Autophagy Regulates the Degradation of AQP2 in Hypokalemia
Wan-Young Kim,1 Sun-ah Nam,1 Yumi Kim,1 Arum Choi,1 Yong kyun Kim,2 Jin Kim.1 1Anatomy and Cell Death Disease Research Center, The Catholic Univ of Korea, Seoul, Korea; 2Internal Medicine and Cell Death Disease Research Center, The Catholic Univ of Korea, Bucheon, Korea.

Background: Autophagy is a catabolic pathway utilized to maintain a balance among the synthesis, degradation, and recycling of cellular components, thereby playing a role in homeostasis. Abundance of AQP2 is regulated through balance between production by tration and removal by degradation. Although AQP2 degradation is supposed to be occurred via lysosomal or proteasomal degradation, the precise mechanisms still remain unknown. It has been known that prolonged hypokalemia causes vasopressin-resistant polyuria and induces autophagy especially in principal cells (PC) of collecting duct.

Methods: To investigate the role of autophagy in the degradation of AQP2, we generated AQP2-cre;Atg7-/- mice, in which Aqp7, an essential gene for mammalian autophagy, was selectively inactivated in PCs. Hypokalemia was induced by K-depleted diet for 2 weeks.

Results: In control AQP2-cre;Aqp7+/- mice, the distribution pattern of AQP2 was not different from AQP2+/- mice. Immunolabeling of pS261-AQP2 was localized mostly subapical and cytoplasmic in appearance in the PCs. In contrast to pS261-AQP2, immunolabeling of pS256-AQP2 was localized mainly at the apical plasma membrane and subapical domains. In hypokalemia Aqp7+/- mice, the abundance of pS261-AQP2 was significantly reduced and redistributed to intracellular vesicles, and co-localized with LC3-positive vacuoles. In hypokalemia Aqp7+/- mice, there was a decrease of conversion of LC3-I to LC3-II and a marked accumulation of p62 selectively in PCs. Rab9 protein, an essential molecule for alternative autophagy pathway, and Rab9-positive vacuoles were markedly increased. Interestingly, pS261-AQP2 was distributed throughout the cytoplasm and not co-localized with Rab9 or LC3-positive vacuoles in the PCs of AQP2-cre;Aqp7+/- mice. There was no difference in localization of pS256-AQP2 at the plasma membrane from each genotype.

Conclusions: These results suggest that down regulation of AQP2 in hypokalemia could in part be caused by degradation of pS261-AQP2 in PCs through a LC3/Atg7-dependent conventional autophagy pathway.

Funding: Government Support - Non-U.S.

SA-PO286
Early Autophagy Precedes Angiotensin II-Induced Podocyte Apoptosis
Tae-Sun Ha. Pediatrics, Chungbuk National Univ, Cheongiu, Chungbuk, Korea.

Background: Autophagy is a highly regulated catabolic process that is involved in the turnover of unwanted cellular materials, on the other hand, apoptosis removes damaged or unwanted cells. Therefore, autophagy and apoptosis constitute the two processes through which injured/aged cells or organelles are eliminated. Angiotensin II (Ang II) induces apoptosis in the podocytes in vitro and in vivo. However, the relationship between autophagy and apoptosis in Ang II-induced podocytes is not elucidated and the role of Ang II-induced autophagy in podocyte survival remains unclear. We investigated the sequential relationship between autophagy and apoptosis in Ang II-induced podocytes.

Methods: Podocytes were cultured in media in various concentrations of Ang II and at different incubation times. The changes of podocyte autophagy and apoptosis were observed by electron microscopy, confocal imaging, Western blotting, and FACS assay according to the presence of Ang II. Results: Ang II-treated podocytes showed an increase in autophagosomes compared with control cells at early phase in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine, an inhibitor of PI3-kinase class III. Ang II enhanced podocyte expression of autophagic proteins such as LC3-II and beclin-1. Ang5 siRNA further reduced the expression of LC3-II and cleaved caspase-3 suppressed by Ang II at 12 hrs. However, Ang5 siRNA did not affect the expression of Ang5, LC3-II, and cleaved caspase-3 in the presence of Ang II at 24 hrs. Thereafter, Ang II induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS assays. LC294002 and Ang5 siRNA further increased podocyte apoptosis induced by Ang II. Therefore, high concentrations of Ang II induced apoptosis, while autophagy response decreased, which implicated that autophagy preceded apoptosis for cytoprotection in angiotensin II-induced podocyte injury.

Conclusions: We suggest that Ang II induced autophagy in mouse podocytes prior to apoptosis as an early adaptive cytoprotective mechanism for podocyte survival after Ang II treatment and the imbalance between autophagy and apoptosis causes podocyte injury.

Funding: Government Support - Non-U.S.

SA-PO287
Emodin Amediates Cisplatin-Induced Renal Tubular Cell Apoptosis Through Activation of Autophagy
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Background: Autophagy plays a key role in regulating cell survival. Emodin can activate the cisplatin-related protective autophagy pathway, thus explored the effects and mechanisms of emodin on cisplatin-induced apoptosis in NRK-52E cells by activation of autophagy.

Methods: NRK-52E cells were treated with cisplatin with or without emodin, cell morphology and expressions of cleaved Caspase-3 and autophagy makers LC3-II, and LC3-I were detected by fluorescence microscopy. The level of LC3 was tested after treated with Bafilomycin A1 and mTOR inhibitor rapamycin. Besides, morphological changes of apoptotic cells were observed and cell death was evaluated by FACS analysis. Finally, AMPK/mTOR signaling pathway related proteins were detected. Further, changes of cell morphology and the level of cleaved Caspase-3 were detected after the addition of compound C, which is an AMPK inhibitor.

Results: Emodin improved cisplatin-induced cell shape change, cell viability and caspase 3 cleavage. This protective effect of emodin was associated with increased LC3 conversion and occurrence of RFP-LC3 punctate structures. Further studies revealed that the suppressive effect of emodin on cisplatin-induced apoptosis could be abolished by suppression of autophagosome bafilomycin A1 and mimicked by activation of autophagy with rapamycin. Additionally, AMPK/mTOR signaling pathway was important for the induction of autophagy and inhibition of apoptosis.

Conclusions: Induction of autophagy could be an important mechanism by which emodin protected renal tubular cells against cisplatin-induced cell injury, and the potentially protective effect of emodin-induced autophagy may be attributed to the activation of AMPK and inhibiting mTOR signaling pathway. Emodin may have a therapeutic potential in the prevention of cisplatin-induced nephrotoxicity.

Funding: Government Support - Non-U.S.

SA-PO288
Autophagy in Renal Tubular Epithelial Cells Plays a Protective Role in Renal Fibrosis
Yong Kwon Kim,1 Sun-Ah Nam,2 Wan-Young Kim,2 Arum Choi,2 Yumi Kim,2 Ho Cheol Song,1 Jin Kim.2 1Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; 2Dept of Anatomy and Cell Death Disease Research Center, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.

Background: Renal tubulointerstitial fibrosis (TIF) is the final common pathway of various renal injuries. Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell death or proliferation. Recent studies reported that autophagy has protective role in renal TIF. However, the mechanism of autophagy...
regulating fibrosis is not fully understood. In this study, we investigated the proposed mechanisms of autophagy in renal TIF induced by UUO by using conditional knockout mice in which Atg7 is genetically ablated specifically in tubular epithelial cell (TEC).

**Methods:** Atg7-flanked mice were crossed with Ksp-Cre mice to generate TEC-specific Atg7 knockout mice (Atg7$^{−/−}$Ksp-Cre’). Unilateral ureteral obstruction (UUO) was performed. We examined the expression of epithelial-mesenchymal transition (EMT) markers. The expression of TGF-β, plasminogen activator inhibitor 1 (PAI-1) and p62 as markers of autophagy were examined. We determined apoptosis and proliferation of TECs with the expression of TGF-β, PAI-1 and p62 during renal TIF. Autophagy also regulates apoptosis and proliferation of TECs in mice with TEC-specific Atg7 deletion after UUO. TEC-specific Atg7 deletion enhanced renal TIF after UUO. TEC-specific Atg7 deletion increase expression of TGF-β, PAI-1 and p62 during renal TIF. Autophagy also regulates apoptosis and proliferation of TECs through the expression of c-Myc as a regulator of cell apoptosis and proliferation.

**Results:** In vitro, TGF-β treatment induced autophagy. In vivo, TEC-specific Atg7 deletion enhanced renal TIF after UUO. TEC-specific Atg7 deletion increase expression of TGF-β and enhance tubular EMT (decrease E-cadherin and increase α-smooth muscle antibody and vimentin) after UUO. In electron microscopy, TEC-specific Atg7 deletion results in ultrastructural alterations of TEC after UUO. TEC-specific Atg7 deletion increase expression of PAI-1, P62 after UUO. TEC-specific Atg7 deletion enhanced apoptosis and proliferation of TECs after UUO. The expression of c-Myc was significantly increased mice with TEC-specific Atg7 deletion after UUO.

**Conclusions:** Our data suggest that autophagy regulate expression through TGF-β, PAI-1 and P62 during renal TIF. Autophagy also regulates apoptosis and proliferation of TECs in mice with TEC-specific Atg7 deletion after UUO.

SA-PO289
Partial De-Differentiation of Parietal Epithelial Cells Caused by Reduced Expression of Sirt1 and Concomitant Increased Expression of p21 and CD133 in Diabetic Nephropathy Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. Keio Univ.

**Background:** We have previously reported the role of proximal tubular Sirt1 in diabetic nephropathy (DN). Parietal epithelial cells (PECs) and their cellular metabolism reportedly play a pivotal role in kidney. Sirt1 is a key energy sensor, whereas DN disrupts energy metabolism.

**Methods:** Thus, we examined the effect of Sirt1 expression in PECs on DN.

**Results:** In two DN murine models including streptozotocin-treated and db/db mice, expression of Sirt1 in proximal tubules and PECs was decreased at 8 weeks after the onset of DN, corresponding to the early stage of DN. Sirt1 expression was also downregulated in podocytes at 24 weeks. We further investigated the changes in PECs at 8 weeks. No change was found in the number of PECs. The morphology of all PECs showed hypertrophy, and some PECs contained autophagic vesicles, especially in the periphery or the border of the plasma membrane at basal lateral sides.

**Conclusions:** Partial de-differentiation of PECs could be related to loss/decay of variants APOL1 mRNA or to some extent defects in protein translation/decay. Since HIV AN occurs in APOL1 variants only, presence of APOL1 variants seems to be critical to sustain HIV-induced podocyte injury.

SA-PO290
APOL1 Variants are Critical to Induce Vitamin D Receptor (VDR) Down Regulation in Dedifferentiated Podocytes Shabirul Haque, Xqian Lan, Amrita Kaur Chawla, Riva Lederman, Rabani Bharara, Ramachandra prasanna Bongu, Ashwani Malhotra, Pravin C. Singhal, Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; 2Medicine, Ramhanh Health Care Campus, Haifa, Israel.

**Background:** APOL1 variants have been reported to contribute to higher prevalence of kidney diseases in African Americans. APOL1 gene is known to contribute to kidney cell injury but the mechanisms involved are not clear. Interestingly, renal biopsy specimens in kidney disease patients with APOL1 variants displayed lower podocyte expression of VDR compared with APOL1 homozygotes. However, the involved mechanism for lower APOL1 expression in these patients is not clear. Gene sequence alterations/mutations hamper either mRNA transcription defect or defects in protein translation. We hypothesized that mutation in APOL1 would lead to modulation of protein expression in podocytes.

**Methods:** Protein blots of human podocytes (HPs) stably expressing vector, APOL1G0, APOL1G1 and APOL1G2 were probed for APOL1 and reprogrammed for acina. RNAs were extracted with HPs expressing VDR, G0, G1 and G2 and CDNA were amplified with APOL1 specific primer. 293 T cells were transfected with equal amount of plasmids (vector, G0, G1 and G2) for 48 hours. Protein blots were probed for APOL1 and reprogrammed for acina. To evaluate stability/decay rate of APOL1 mRNA, APOL1/APOL1 variants expressing HPs were pulsed with actinomycinD and RNAs were harvested at different time points (0, 0.5, 1.0, 3.0, 8.0, and 24 hours) by Trizol method.

**Results:** APOL1 variants (G1/G2) expressing HPs displayed lower expression of APOL1 when compared APOLIG0. 293 T cells also displayed lower expression of G1 and G2. However, there was no difference in mRNA expression in APOL1G0 and APOL1G1/G2 expressing cells. Stability/decay kinetic assay revealed that variants (G1 and G2) of APOL1 mRNA decayed in an accelerated mode (more than 35%) during ½ to 24 hours after actinomycin D exposure.

**Conclusions:** These results suggest that APOL1 variants protein instability may be related to loss/decay of variant APOL1 mRNA or to some extent defects in protein translation/decay.

**Funding:** NIDDK Support

SA-PO291
Post-Transcriptional and Post-Translation Status of APOL1 (G0) and Its Variants (G1and G2) in Podocytes and 293T Cells Post-Transcriptional and Post-Translation Status of APOL1 (G0) and Its Variants (G1and G2) in Podocytes, 293T Cells, and Human and rabbit Podocytes Xinlian Yan, Gauri P. Patil, Pravin C. Singhal, Amrita Kaur Chawla, Ashwani Malhotra, Karl Leon Skorecki, Pravin C. Singhal. 1Medicine, Hofstra North Shore LIJ Medical School, Great Neck, NY; 2Medicine, Ramhanh Health Care Campus, Haifa, Israel.

**Background:** APOL1 gene variants have been reported to contribute to higher prevalence of kidney diseases in African Americans. APOL1 gene is known to contribute to kidney cell injury but the mechanisms involved are not clear. Interestingly, renal biopsy specimens in kidney disease patients with APOL1 variants displayed lower podocyte expression of VDR compared with APOL1 homozygotes. However, the involved mechanism for lower APOL1 expression in these patients is not clear. Gene sequence alterations/mutations hamper either mRNA transcription defect or defects in protein translation. We hypothesized that mutation in APOL1 would lead to modulation of protein expression in podocytes.

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**Results:** APOL1 variants (G1/G2) expressing HPs displayed lower expression of APOL1 when compared APOLIG0. 293 T cells also displayed lower expression of G1 and G2. However, there was no difference in mRNA expression in APOL1G0 and APOL1G1/G2 expressing cells. Stability/decay kinetic assay revealed that variants (G1 and G2) of APOL1 mRNA decayed in an accelerated mode (more than 35%) during ½ to 24 hours after actinomycin D exposure.

**Conclusions:** These results suggest that APOL1 variants protein instability may be related to loss/decay of variant APOL1 mRNA or to some extent defects in protein translation/decay.

**Funding:** NIDDK Support

SA-PO292

**Background:** Dysregulated growth and loss of podocytes are important features of HIV-associated nephropathy (HIVAN). In a recent report, HIV induced programmed cell death in T cells has been implicated to pyroptosis as a consequence to inflammation formation. We hypothesized HIV would also be promoting podocyte loss through the induction of pyroptosis. We evaluated the role of HIV in podocyte NOD-like receptor family, pyrin domain containing (NLRP) 3 protein complexes (inflammasomes) formation both in vitro and in vivo.

**Methods:** Renal cortical sections of control and TG6 (HIVAN) mice (n=4) were labeled with inflammasome molecular markers (IMMs; NLRLP3, ASC, cleaved caspase-1 and IL-1β). Protein blots of renal tissues of control and TG6 mice were also probed for IMMs and actin (n=11). Protein blots of empty vector (EV) - and NL-3 (HIV)-transduced human podocytes (HPs) were probed for IMMs and actin (n=4). EV/HPs and HIV/HPs were evaluated for pyroptosis by PI staining under a fluorescence microscope as well as by FACS analysis. Effect of Tempol (SOD mimetic), caspase-1 inhibitors, and glyburide (an inhibitor of K-eflux inhibitor was evaluated on HIV induced podocyte pyroptosis by morphologic assay and FACS analysis.

**Results:** Renal cortical sections of HIV-transgenic mice (TG6) displayed increased podocyte expression IMMs. Renal tissues of TG6 mice also displayed enhanced mRNA

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

Underline represents presenting author.
expressions as well as protein expressions of IMM. Serum from Tg26 mice showed higher levels of IL-1β. HIV promoted pyroptosis in podocytes in a dose as well as time dependent manner. Since caspase-1 inhibitor not only attenuated podocyte expressions of caspase-1 and IL-1β in addition to protection against pyroptosis; this would confirm that HIV induced podocyte injury was mediated by caspase-1 activated complexes. Interestingly, HIV-induced podocyte pyroptosis could be partially inhibited by tempol as well as by glyburide.

Conclusions: These findings indicate that generation of reactive oxygen species and potassium efflux contributed to HIV-induced pyroptosis in podocytes.

SA-PO293

Urinary Cytochrome C (Cyto C) Detects Subliminal Injury and Correlates with Apoptosis in Acute (AKI) and Acute on Chronic Kidney Disease (A-CKD)

Methods: In male Sprague Dawley rats (i) adeno-CKD was induced by diet supplementation with 0.025% adenine, days (d) 0 to 28 and monitored until d56 (n=8). On d56, AKI was induced in rats by a sub nephrotoxic (2mg/kg; n=8) or nephrototoxic (4mg/kg; n=8) cisplatin (Cis) dose and monitored until d91 (n=8 in matched controls). (ii) Aristolochic-acid nephropathy (AAN) was induced by AA-1 (0.2%km/g) ip for five days and monitored for d21 (n=6) or d42 (n=6) then driven 2mg/kg (n=6) or 4mg/kg (n=6) Cis and monitored to d28 and d49 respectively. Cyto C was measured by ELISA. Tubulointerstitial damage (TID) and TUNEL were quantified on d63.

Results: Cyto C levels increased in subliminal AAN (d1 to d7) and adeno-CKD (d3 to 21) without change in sCr, but increased in both CKD groups after 2mg/kg and 4mg/kg Cis dose in controls. In AAN, Cyto C levels increased progressively (d22 to d28) after inducing controls given 4mg/kg whereas Cyto C was lower after Cis on d42 to d49. Regardless of Cis dose, Cyto C increased in controls and adeno-CKD. A-CKD rats displayed diffuse medullary and cortical TID with positive TUNEL staining while injury in CKD alone was largely in outer medulla. In ANN peak Cyto C, 72 hours post Cis, correlated significantly with outer medullary TID and cortical apoptosis (R=0.85 and 0.86 respectively; p<0.01). In adeno fed rats, Cyto Correlated only with medullary apoptosis (R=0.79**). sCr correlated only with severe diffuse cortical TID (R=0.94*) (P<0.05).

Conclusions: Cyto C detected subliminal injury and correlated strongly with outer medullary apoptosis in A-CKD, which alone did not increase sCr. Cyto C is a useful biomarker for early detection of apoptotic kidney injury.

SA-PO294

Assessment of Graphene Toxicity to Kidney Tubular Epithelial Cells and Cell Spheroids Using DNase Activity Probe

Methods: Non-modified graphene (50 μg/ml) exposed with cultured rat kidney tubular epithelial NRK-52E cells induced TUNEL-type DNA fragmentation usually associated with cytoxicity. Ramon spectroscopy showed the TUNEL-positive cells have significantly higher graphene content than TUNEL-negative cells. DNase activity was quantified in live cells using the oligonucleotide-based NIFR probe. Quantitative immunocytochemistry (qICC) was then used to measure apoptotic DNases such as caspase-activated DNase (CAD), endonuclease G (EndoG), and DNase I, and the marker of oxidative stress, heme oxygenase-1 (HO-1).

Results: The NIFR fluorescence and all of the above qICC markers were induced in NRK-52E cells by graphene exposure. In addition, a 50% colocalization of HO-1 with DNase activity was observed suggesting a possible link between oxidative stress and the DNases. Furthermore, we developed kidney spheroids (mini-kidneys) model by culturing NRK-52E cells using 3D hanging drop method, and tested the graphene toxicity in this model by measuring the DNase activity using the NIFR probe. The result showed a strong dose-dependent increase of DNase activity induced by graphene.

Conclusions: Measuring of DNase activity by using NIFR probe in combination with TUNEL assay and qICC are appropriate tools for assessment of graphene toxicity. Funding: NIDDK Support, Other U.S. Government Support, Veterans Administration Support

SA-PO295

Identification of a Novel Bidirectional Regulatory Mechanism Involving AKT/B-Catenin and Anillin That Drives Podocyte Proliferation

Methods: Mutations of the F-actin binding protein Anillin (ANLN) have been shown to cause familial Fanconi anemia (FA). ANLN is a suspected modulation of phosphoinositol-3 kinase (PI-3K) signaling, specific interactions with PI-3K pathway intermediates and the role of these interactions in the pathogenesis of FS is remains unknown.

Results: siRNA-mediated gene knockdown studies, immunoblot and proliferation assays were performed by in vitro methods in conditionally immortalized human podocytes (CHP) to examine the effects of ANLN depletion on PI-3K pathway signaling in podocytes. CHP lines stably expressing GiFP-vector control or GiFP-ANLNKD were established via lentiviral transduction to characterize the effects of ANLN overexpression on PI-3K signaling in podocytes.

Conclusions: We evaluated the effect of ANLN overexpression and targeted ANLN knockdown (KD) on AKT activation in podocytes. Additionally, we explored the effects of pharmacologic inhibition of AKT on ANLN expression in podocytes. Finally, we examined the role of AKT-mediated activation of β-Catenin via the direct phosphorylation of serine 552 in podocyte ANLN expression. We determined that ANLN overexpression significantly attenuated AKT activation. Conversely, ANLN KD significantly enhanced AKT activation and upregulated AKT-mediated phosphorylation/activation of β-Catenin at serine 552. Pharmacologic inhibition of AKT also inhibited basal podocyte proliferation. Finally, we demonstrated that pharmacologic inhibition and targeted gene knock down of β-Catenin significantly attenuated podocyte ANLN expression.

Conclusions: These findings elucidate a novel mechanism of reciprocal regulation involving AKT/β-Catenin signaling and ANLN which may provide valuable insights into the role of ANLN in the pathogenesis of FS and other proliferative podopathies.
response to stress and survival, and is a target of mTORC2 and an upstream activator of mTORC1. mTORC1 is the master regulator of autophagy and metabolism. mTORC1 and 2 are also implicated in the regulation of cytoketosis and cell motility.

**Methods:** Using conditionally immortalized proximal tubular epithelial cells (PTECs) and podocytes originating from cystinosis patients and healthy donors, we performed biochemical and microscopic analysis of phosphorylation and activation of protein kinases in response to various stimuli.

**Results:** Phosphorylation of Akt1 and 2 was increased in cystinosis podocytes and PTEC in response to nutrient/growth factor replenishment and wounding of cellular monolayer. In podocytes, such increased phosphorylation, was associated with altered cytoketosis, disturbed focal adhesion sites and increased motility. Treatment with specific Akt inhibitor demonstrated a prominent decrease of motility and Akt phosphorylation. mTORC1 activation in response to nutrient replenishment was delayed in cystinosis PTECs accompanied with abnormal subcellular distribution of the kinase complex, as revealed by antibody staining of mTOR.

**Conclusions:** We demonstrate that cystinosis dysfunction is associated with disturbed signalling of protein kinases mTORC1 and Akt1 and 2.

**Funding:** Private Foundation Support

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**SA-PO298**

**Intestinal Pericytes Decrease in Aged Mouse Kidneys**

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**Background:** With increasing age, the kidney undergoes characteristic changes in the glomerular and tubulo-interstitial compartments, which are ultimately accompanied by a reduced kidney function. Studies have shown age-related loss of perivascular cells. Normal perivascular cell tone, function and survival depend on neighboring pericytes. Pericyte detachment leads to vascular damage, which can be accompanied by their differentiation to fibroblasts and myofibroblasts, a state that favors matrix production. Here we aim to determine the impact of age on pericyte populations.

**Methods:** To better understand the fate of pericytes in the aged kidney, 27-month-old mice were studied. Picrosirius red staining was performed to evaluate kidney fibrosis. Histological sections were stained against endothelial antigen CD31 together with pericyte markers PDGFRα and NG2. Additionally, immunoreactivity of myofibroblast marker αSMA was assessed together with pericytes.

**Results:** Compared to 3 month-old young adult mice, aged kidneys showed a substantial decrease in capillaries, identified by CD31 staining, in both cortex and medulla. This was accompanied by a marked decrease in surrounding NG2+/PDGFRα+ pericytes. This decrease was more pronounced in the medulla. Capillaries devoid of pericytes were typically dilated and podocytes originating from cystinosis patients and healthy donors, we performed biochemical and microscopic analysis of phosphorylation and activation of protein kinases in response to various stimuli. In podocytes, such increased phosphorylation, was associated with altered cytoketosis, disturbed focal adhesion sites and increased motility. Treatment with specific Akt inhibitor demonstrated a prominent decrease of motility and Akt phosphorylation. mTORC1 activation in response to nutrient replenishment was delayed in cystinosis PTECs accompanied with abnormal subcellular distribution of the kinase complex, as revealed by antibody staining of mTOR.

**Conclusions:** We demonstrate that cystinosis dysfunction is associated with disturbed signalling of protein kinases mTORC1 and Akt1 and 2.

**Funding:** Private Foundation Support

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**SA-PO299**

**Interactions of Urotensin II and Mitophagy in Diabetic Nephropathy and Its Implications on Drug Design**

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**Background:** Urotensin II (UII), an important vasoactive neuropeptide, and the processes of mitophagy have been considered as possible therapeutic targets for treating diabetic nephropathy (DN). The present study is to determine the interaction between UII and the process of mitophagy under the setting of DN.

**Methods:** Immunohistochemistry and western blot analysis were conducted on the protein extracts harvested from the kidney tissues of DN mice that were induced eighteen weeks after the injection of streptozotocin. For in-vitro cell experiment, HK-2 cells were cultured and treated with different concentrations of UII (10⁻³-10⁻⁷ mol/L) for 12 h and 3-MA treatment was used as a negative control. The cell protein extracts were then analyzed by western blot. For immunohistochemistry and western blot analysis, BNIP3 was used as a marker for mitophagy.

**Results:** Immunohistochemistry and western blot analysis showed that the expressions of UII and BNIP3, marker of mitophagy, are upregulated for DN kidney compared to that of controls. In-vitro cell experiment results also demonstrate UII can upregulate BNIP3. Further data indicates that UII expression is positively associated with the expression of BNIP3.

**Conclusions:** Our results indicate that UII expression can upregulate mitophagy in DN. Past studies already demonstrate that mitophagy can have a therapeutic role in DN. Our results carry the implications that UII and its effect on the process of mitophagy presents potential therapeutic implications for DN.

**Funding:** Government Support - Non-U.S.

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**SA-PO300**

**Reduction in CTGF Leads to Increased Proliferation Through Influences on Claudin-1 and Extracellular Matrix Protein Spondin 2**

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**Background:** Accumulation of extracellular matrix is a characteristic feature of diabetic kidney disease. We have recently demonstrated that connective tissue growth factor (CTGF) mediate influences in extracellular matrix production, proteinuria and scarring in mice. In addition, CTGF may have anti-proliferative properties. In specific human neoplasm (breast, colon), increased CTGF have been linked to reduced proliferation, improved response to therapy and prognosis but data is not consistent. On the other hand, metastatic melanoma progression correlates with CTGF levels and inhibition of CTGF reduces invasion and metastasis.

**Methods:** To define a possible role for CTGF in proliferation, embryonic fibroblasts (MEF) generated from wild-type and a previously reported CTGF knock mouse line were studied. Expression array (Illumina) was used to identify changes in gene expression in MEF with CTGF expression was validated by Immunoblotting. Inhibition of MAPK (SP600126, SB203580 and U0126) were used to assess role of MAPK in glucose-mediated CTGF expression by cultured MEF.

**Results:** CTGF gene disruption lead to enhanced proliferation (3-fold) in CTGF knockout cells compared with wildtype cells. Reduced CTGF led to 50% decreased expression of the gene for the extracellular protein, procollagen 4, alpha 2 (Col4a2; confirmed at protein level)) in association with 2.8-fold increased expression of claudin-1, a member of the tight junction proteins. In addition, there was a 3.2-fold increased expression of spondin-2 and a 1.6-fold increased expression of Secreted protein, acidic and rich in cysteine-like 1 (SPARC1). Immunoblotting confirmed the observation for claudin-1. Glucose induced CTGF expression (2-3 fold) was attenuated by inhibitors of p38MAPK and JNK, but unaffected by inhibition of ERK (p42/44 MAPK).

**Conclusions:** In MEF, targeted gene disruption of CTGF led to increased proliferation and altered matrix protein linked to increased expression of claudin 1 and other extracellular protein. Secondly, glucose-induced CTGF level is mediated by MAPK (p38 and JNK). Targeted alteration in CTGF along with one or more of these extracellular protein may offer new approaches to manage glomerulosclerosis.

**Funding:** Private Foundation Support, Clinical Research Support

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**SA-PO301**

**miR21 Upregulates YY1 to Increase Renal Cell Apoptosis in Diabetes**

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**Background:** The regulation of miRNAs in response to hyperglycemia that contributes to the pathogenesis of kidney disease has been underscored.

**Methods:** In the current study, we investigated the role of miR21 in regulation of cells apoptosis in human renal proximal tubular cells (HK2) cells exposed to high glucose and in type II diabetes mouse model.

**Results:** Cells pretreated with either miR21 inhibitor or antisense before exposed to HG resulted in decrease YY1 expression and decrease cleavage of caspase 3. Nuclear extracts from HK2 cells exposed to high glucose for 48hrs showed increase in binding of YY1 to the YY1 promoter element in nuclear extracts of cells EMSA. On the other hand, pretreatment with miR21 inhibitor or antisense significantly decrease the binding of miR21 to YY1 in nuclear extracts of cells grown in NG or treated with HG. The DNA-protein complexes were significantly decreased in the presence of the YY1 antibody, indicating that YY1 is indeed a component of these complexes. Transfected the cells with promoter/reporter construct of miR21 showed significant increase in miR21 promoter activity in cells exposed to HG while cells pretreated with miR21 inhibitor reverse the effect of HG. In addition, significant increase in the percentage of TUNEL-positive tubular cells stained in the kidney sections of db/db mice compared to kidney sections of the wild type mice. Quantitation of miR21 by real-time PCR showed significant increase miR21 levels in kidney of diabetic mice (db/db) compared to kidneys from wild type mice. Immunostaining analysis of miR21 showed that majority of miR21 staining within the tubular cells and glomerular compartments.

**Conclusions:** In summary, expose renal cells to HG and increase hyperglycemia in kidney of diabetic mice resulted in significant increase in miR21. Increase binding of YY1 to miR21 under HG condition suggesting the important role of miR21 in regulating YY1 to increase cell apoptosis. The data provide a novel role of miR21 as a target for controlling renal cell death that induced by hyperglycemia during diabetic nephropathy.

**Funding:** Veterans Administration Support

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**SA-PO302**

**The Role of miR-302 and Let7 in Macrophage Polarization**

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**Background:** Recent advances in the pathogenicity of renal injury highlighted the critical role of the immune system in the onset and resolution of disease. Monocytes canto differentiate along two pathways: pro-inflammatory (M1) due to the secretion of cytokines such as IL-6 and a pro-resolution attributable to the secretion of cytokines such as IL-10. Bane/Fet et al. have suggested that the ratio of M1 and M2 macrophages is controlled
interplay between two micro RNAs, miR302 and Let7. We have recently shown that the silencing targets of miR302 and Let7 are the TGFβ type II and type I receptors respectively and hypothesize that this circuitry plays a critical role in macrophage differentiation.

Methods: The pro-resolving lipid mediator, conjugated linoleic acid (CLA), inhibits the acquisition of a pro-inflammatory macrophage phenotype by priming monocytes towards an anti-inflammatory phenotype. To identify pathways associated with this phenotype we performed proteomic analysis of THP-1 cells treated with CLA. Exosomes were isolated from urine samples taken from patients with renal injury and analyzed for miRNA expression. Renal cells were transduced with miR302 and let7 virus. TGFβ receptor expression and signaling was analyzed by western blot. Additionally, THP-1 cells were co-transduced with miR302 and let7 and their effects on macrophage differentiation as assessed for expression of CD68 and CD206.

Results: Bioinformatic and Western blot analysis revealed enrichment of the TGFβ signaling pathway in THP-1 cells treated with CLA. miR302 expression was increased in the urine of patients compared to controls. Cells transduced with miR302 and Let7 displayed low levels of expression of the TGFβ type II and type 1 receptors respectively and dampened Smad3 phosphorylation. miR302 and let7 prevented renal epithelial cell dedifferentiation. THP-1 cells transduced with both miRs demonstrated similarly enhanced plasticity. Manipulation of this circuitry results in enhanced cell plasticity. In vitro studies suggest that this results in the generation of pro-resolution cellular phenotypes in both resident cells and macrophages.

SA-PO303
Dopamine D2 Receptor Regulates Wnt3/-β-Catenin Signaling and Apoptosis in Human Renal Proximal Tubule Cells
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Background: Dopamine D2 receptor (D2R) in the kidney has a direct role in regulating renal tubulointerstitial injury and, blood pressure. Some common single nucleotide polymorphisms (D2R SNPs) with a frequency of 5% have been identified in the human D2R gene and are associated with decreased D2R expression and function.

Methods: We measured apoptosis and activation of Wnt3/-β-catenin signaling pathway in human renal proximal tubule cells (RPTC) carrying these D2R SNPs (RPTC-D2R SNPs), and in RPTC carrying wild type (RPTC-D2R WT).

Results: RPTC-D2R SNPs showed increased apoptosis compared with RPTC-D2R WT (1.0% vs 0.8%; P<0.05; protein: 133±4% vs 100±0.3%; P<0.05). RPTC-D2R SNPs showed activated Wnt3/-β-catenin signaling pathway demonstrated by decreased β-catenin phosphorylation (64±4% vs 100±0%; P<0.05) and increased expression of downstream pro-apoptotic factors Bax (136±4% vs 100±0%; P<0.05) and FasL (12±5% vs 11±0%; P<0.05). Silencing D2R in RPTC-D2R WT increased Wnt3/-β-catenin phosphorylation and increased expression of Bax and FasL. In contrast treatment of RPTC-D2R WT with a D2R agonist (quinpirole, 1µM, 24h) or transfection of RPTC-D2R SNPs with a D2R inhibitor (Rho327; which restored D2R expression decreased Wnt3/-β-catenin phosphorylation and decreased β-catenin phosphorylation and increased Bax and FasL expression. Moreover Wnt3/-β-catenin silencing in RPTC-D2R SNPs increased β-catenin phosphorylation (132±5% vs 100±0%; P<0.05), decreased Bax (68±2.5% vs 100±0%; P<0.05) and FasL (70±5% vs 100±0%; P<0.05) expression and reduced the number of apoptotic cells (6±1.0% vs 12±0.9%; TUNEL positive cells, P<0.01).

Conclusions: D2R protect cells from apoptosis by regulating the Wnt3/-β-catenin pathway. These results may have clinical relevance for subjects bearing D2R SNPs.

SA-PO304
Effect of Omega-3 Fatty Acids on Nrf-2 Expression and Its Regulation in Cyclosporine Induced Rat Model
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Background: Cyclosporine (CsA)-induced kidney injury is characterized by kidney dysfunction with inflammatory cell infiltrations, apoptosis, and fibrosis. Although Nrfa2 regulates antioxidant and anti-inflammatory process in kidney injury model, it is not clear omega-3 fatty acid (FA) role on Nrf-2 expression. The aim of this study is to investigate whether omega-3 FA (300 mg/kg/day) treatment attenuates the renal injury and improve Nrf-2 expression and release of HMGB1 from the cells. Both pharmacologic inhibition and siRNA-mediated knock-down of HMBG1 led to reduced cell viability as determined by MTT assay.

Results: Following exposure to a high salt diet, pharmacologic inhibition of HMBG1 resulted in more severe kidney damage as assessed by the percentage outer medullary area with tubular dilatation and protein casts, when compared with vehicle-treated rats. Inhibition of HMBG1 was associated with a significant increase in tubular cell apoptosis in comparison to vehicle treatment on TUNEL staining. Also, inhibition of HMBG1 led to significantly higher urinary albumin excretion and blood pressure at day 21 compared with vehicle treatment. Exposure of NRK52E cells to hyperosmotic medium resulted in increased expression of Nrf-2 and related inflammation and fibrosis. The expression of Nrf-2 was decreased in CsA-treated rats but Nrf-2 activation related with urinary albumin excretion and blood pressure at day 21 compared with vehicle treatment.

Conclusions: HMBG1 plays an important role in renal tubulointerstitial cell survival during hypertensive stress.

SA-PO305
KIM-1-Mediated Phagocytosis Defines a New Mechanistic Paradigm for Kidney Epithelial Cells, which Involves Autophagy and Anti-Inflammatory Antigen Presentation
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Background: The expression of kidney injury molecule-1 (KIM-1), the protein most upregulated during proximal tubular epithelial cell apoptosis (PTC) and transition of PTCs into senescent phenotypes. The processing of phagocytosed cells to the lysosome can determine the immunogenicity of antigens derived from the phagosomal cargo. Here we compare the phagocytic processing of KIM-1-expressing PTCs to that of professional phagocytes and establish distinct mechanisms.

Methods: LLC-PK1 cells expressing KIM-1 were exposed to apoptotic cells. LC3 localization to the phagosome, phagosome acidification and degradation were measured by live cell imaging, phagosome isolation and western blotting. NADPH oxidase (NOX) activity was blocked with diphenyleneiodonium and reactive oxygen species (ROS) were measured with fluorescent probes. MHC presentation was measured in primary PTCs directly using specific antibodies by flow cytometry. Functional implications were determined by activation of CD4+ and CD8+ T cells.

Results: KIM-1 binds to and induces phagocytosis of apoptotic cells within ~5-30 min, similar to professional phagocytes. Following uptake, however, PTCs process phagosomes more slowly than professional phagocytes, with delayed phagosome acidification and degradation (4-12 hrs v 1-2 hrs). Mechanistically, PTCs do not upregulate NOX-induced production of ROS, a process necessary for efficient acidification and degradation of the phagosome. LC3 associated phagocytosis (LAP), an important NOX-dependent feature of professional phagocytic function, is not observed in PTCs. PTCs instead induce canonical autophagy to clear phagocytosed debris. Delayed phagosomal processing and increased autophagy result in increased PTC antigen presentation and decreased T cell activation.

Conclusions: Autophagy plays a critical role in KIM-1-mediated phagocytosis in PTCs, distinguishing the epithelial cell process from the mechanism used by professional phagocytes. The PTC has evolved a distinct process which leads to anti-inflammatory antigen presentation which is beneficial in acute kidney injury.

Funding: NIDDK Support
SA-PO307

A apoptotic cells activate AMPK and inhibit proximal tubular cell (PTC) growth without change in intracellular energy stores


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Background: Apoptosis plays an indispensable role in the maintenance and development of tissues. We have shown that receptor-mediated recognition of apoptotic target cells by viable kidney PTCs inhibits the proliferation and survival of these viable PTCs. Here, we examined the effect of apoptotic target cells on PTC cell growth (cell size during G1 phase of cell cycle).

Methods: We used BUMPT cells, a conditionally immortalized PTC line, as responder cells. BUMPT cells, induced to undergo apoptosis in several ways, were used as apoptotic targets. Autophagy is the process by which cells remove and recycle unwanted structures, contributing to intracellular homeostasis and energy production. Cardiac autophagy activation led to decreased activity of its downstream target, ribosomal protein S7 kinase (p70S6K) and concomitant inhibition of cell growth. Importantly, these events occurred without detectable change in intracellular levels of AMP, ADP, or ATP. Inhibition of AMPK, either pharmacologically by compound C or molecularly by shRNA, diminished the effects of apoptotic targets, and largely restored p70S6K activity and cell size to normal levels. Autophagic targets also inhibited Akt, a second signaling pathway regulating cell growth. Expression of a constitutively active Akt construct partially relieved cell growth inhibition, but was less effective than inhibition of AMPK. Inhibition of cell growth by apoptotic targets was dependent on physical interaction between apoptotic targets and PTCs, but independent of phagocytosis.

Conclusions: We conclude that receptor-mediated recognition of apoptotic targets mimics the effects of intracellular energy depletion, activating AMPK and inhibiting PTC cell growth. By acting as sentinels of environmental change, apoptotic death may enable nearby viable cells, especially non-migratory epithelial cells, to monitor and adapt to local stresses.

Funding: Clinical Revenue Support

SA-PO308

The Effect of Uremia on Cardiac Autophagy

William White, Steven Michael Harwood, Petros Andrikopoulos, Muhammad M. Yaqoob.


Background: Autophagy is the process by which cells remove and recycle unwanted structures, contributing to intracellular homeostasis and energy production. Cardiac autophagy has a role in maintaining heart protection and ventricular remodeling, and decreasing autophagy is central to aging. Evidence suggests these processes are disorderd in CKD. We have previously demonstrated that autophagy may be down-regulated at a transcriptional level in uremic hearts, and now present data concerning cardiac autophagic-protein expression (LC3, p62) and senescence marker p53 in models of uremia.

Methods: In Vitro Rat cardiac myoblast cells (H9C2) were cultured in the presence of indoxyl sulphate (IS) to simulate a uremic milieu, for 24 or 48 hrs. In Vitro, to mimic nephrogenic glucocorticoid, PTCs were exposed to albumin. Autophagy was assessed in tissue samples from mice and primary PTCs. Steady state LC3-II, an autophagy marker was quantified by immunoblot. Autophagosomes (APs) were visualized in cell culture using fluorescent markers and in renal cortical tissue using immunohistochemistry. Mitochondrial morphology and colocalization with autophagosomes were imaged using confocal microscopy. Reactive oxygen species production was measured using a 2',7'-dichlorofluorescin diacetate assay.

Results: Exposure to excess albumin induced defective autophagy and mitophagy in vitro. In renal cortices, proteinuria decreased both the number of LC3-II positive APs and the amount of LC3-II detected in cell lysates. Albumin-exposed cells accumulated damaged mitochondria with altered mitochondrial function and morphology. Albumin exposure caused mitochondrial dysfunction as evidenced by decreased oxygen consumption rate from coupled ATP production. Increasing albumin exposure time caused an increase in ROS production.

Conclusions: Dysfunctional autophagy caused by proteinuria likely contributes to tubular cell toxicity leading to renal progression.

Funding: NIDDK Support, Private Foundation Support

SA-PO309

Decorin Potentially Alleviates TGF-β1 Induced Podocyte Injury by Inactivating mTORC1 and Increasing Autophagy

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Background: TGF-β1 is the major factor mediating podocyte injury during mesangial proliferative glomerulonephritis (MsPGN), manifested by decreased autophagy, cytoskeleton relaxation and increased apoptosis. Decorin (DCN), mainly secreted by mesangial cells (MCs) in glomeruli, is a natural antagonist of TGF-β1 and has been shown to protect against cell death induced by TGF-β1 (DCN2A). This study aims to investigate the possibility of any possible differences between DCN2A expression, VC and CVD in a CKD population.

Methods: DCN2A expression was determined in epigastic arteries (n=43) from patients with end-stage renal disease (ESRD) undergoing living donor renal transplantation (RTX). All arteries were scored for degree of calcification in percent. Coronary artery calcification (CAC) score was also obtained.

Results: The arterial expression of DCN2A was significantly associated with VC (p=0.01, p=0.04), CVD (p=0.0002), CAC score (p=0.008, p=0.5) and diabetes mellitus (p=0.05). In addition, arterial DCN2A expression was associated with MGP (p=0.007, p=0.4) and RUX2 (p=0.046, p=0.3) expression in artery, both of which are involved in osteogenic transformation of vascular smooth muscle cells.

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

Underline represents presenting author.

697A

SA-PO310

Albumin Endocytosis in the Proximal Tubule Causes Accumulation of Dysfunctional Mitochondria


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Background: Proteinuria is a major risk factor for chronic kidney disease progression. Furthermore, exposure of proximal tubular epithelial cells (PTEC) to excess albumin promotes tubular atrophy and fibrosis, key predictors of progressive organ dysfunction. The mechanism by which protein exposure causes tubular cell injury is unclear. We hypothesize that albumin endocytosis causes tubular cell injury by inhibiting autophagy, including mitophagy, resulting in an accumulation of dysfunctional mitochondrial leading to enhanced ROS production, mitochondrial and cellular injury.

Methods: The effect of proteinuria was examined both in vivo and in vitro experiments. Proteinuria was induced in mice by injection of a sheep nephrotic serum that causes acute immune-complex glomerulonephritis with massive proteinuria by 24-48 hrs. In Vitro, to mimic nephrogenic glucocorticoid, PTECs were exposed to albumin. Autophagy was assessed in tissue samples from mice and primary PTECs. Steady state LC3-II, an autophagy marker was quantified by immunoblot. Autophagosomes (APs) were visualized in cell culture using fluorescent markers and in renal cortical tissue using immunohistochemistry. Mitochondrial respiration was measured in primary cells. Mitochondrial morphology and colocalization with autophagosomes were imaged using confocal microscopy. Reactive oxygen species production was measured using a 2',7'-dichlorofluorescin diacetate assay.

Results: Exposure to excess albumin induced defective autophagy and mitophagy in vitro. In renal cortices, proteinuria decreased both the number of LC3-II positive APs and the amount of LC3-II detected in cell lysates. Albumin-exposed cells accumulated damaged mitochondria with altered mitochondrial function and morphology. Albumin exposure caused mitochondrial dysfunction as evidenced by decreased oxygen consumption rate from coupled ATP production. Increasing albumin exposure time caused an increase in ROS production.

Conclusions: Dysfunctional autophagy caused by proteinuria likely contributes to tubular cell toxicity leading to renal progression.

Funding: Government Support - Non-U.S.
Background: The inflammasome may be superior to targeting apoptosis. Caspase-1, but not of caspase-3, ameliorates diabetic podocyte injury. Markers of inflammasome activation (Nlrp3, caspase-1 cleavage) are reduced by 80%. Then, we inject BSA intraperitoneally in these RTN1-A knockdown tubular cell-specific RTN1-A shRNA knockdown mice, in which RTN1-A expression was reduced by 80%. These data suggest that RTN1-A mediated HSA-induced ER stress and apoptosis in tubular cells of RTN1-A knockdown mice and their control littermates to generate albumin overload mouse model. Mice with BSA injection developed significantly increased proteinuria in both knockdown and wild-type mice. However, RTN1-A knockdown mice developed less tubulointerstitial injury than wild-type mice. Also, there was less apoptosis and lower expression of ER-stress markers in tubular cells of RTN1-A knockdown mice than wild-type mice.

Conclusions: These data suggest that RTN1-A likely mediates proteinuria-induced tubular cell injury and progression of kidney disease through ER stress and apoptosis.

Funding: NIDDK Support

SA-PO314

Endothelial Autophagy Is Essential for Vascular Lipid Homeostasis
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Background: Cardiovascular disease is one of the common complications in chronic kidney diseases. It is known that autophagy plays a critical role in the course of kidney diseases. The resulting cardiovascular diseases are presumably regulated by autophagy. However the physiological role of autophagy in the vascular endothelial cells remains poorly understood.

Methods: Using human umbilical vein endothelial cells (HUVECs), induction of autophagy by ox-LDL, and uptake and transcytosis of LDL are analyzed. To inhibit autophagy pharmacologically, chloroquine is used. The essential autophagy gene, Atg7 shRNA-mediated knockdown are performed to inhibit autophagy genetically. To assess an acute and chronic in vivo model of lipid exposure, we generated endothelial specific Atg7 knockout in ApoE deficient mice (Atg7/−/Apoe KO).

Results: Ox-LDL induced autophagosome formation in HUVECs. Moreover, native or ox-LDL appeared to be engulfed within autophagosomes by live cell imaging and electron microscopy. Atg7 knockout or pharmacological inhibition of autophagy resulted in higher accumulation of intracellular LDL, suggesting that in vascular endothelial cells, autophagy is one of the degradation machinery of excess lipids. As an acute model of lipid exposure in vivo, Atg7/−/Apoe mice showed longer retention of ox-LDL within the retina after infusion of Dil-ox-LDL. In a chronic model of lipid excess, we analyzed atherosclerosis in Atg7/−/Apoe KO mice. Atg7/−/Apoe KO mice demonstrated markedly increased atherosclerosis.

Conclusions: In endothelial cells, autophagy appears to play a critical role in regulating excess intracellular lipids. Moreover, in both acute and chronic in vivo model, endothelial autophagy is essential to attenuate LDL accumulation within endothelial layer. Prevention of the decline in autophagy flux accompanied by kidney diseases pharmacologically might be beneficial to treat atherosclerotic diseases.

Funding: Private Foundation Support

SA-PO316

Targeted Mutations at the p66 Locus Antagonize Stem Cell Aging and Delay Expression of Senescent Phenotypes in Diabetic Kidneys
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Background: Senescence has important implications for the biologic function of tissue stem cells, which maintain tissue homeostasis by replacement of old or dying cells and via the repair of tissue injury. The p66 longevity gene plays a key role in the activation of gene programs that induce senescent and apoptotic phenotypes. We hypothesize gene base strategies targeting p66 will delay or prevent stem cell senescence and premature aging phenotypes in diabetic kidneys.

Methods: Mesenchymal stem cells (MSCs) were isolated from kidneys of p66 KO mouse (p66 KO-MSCs) using established methods and plated in high glucose (H3) containing media. Microarray was used to profile secreted factors expressed by MSCs. p66 KO diabetic mice were generated and evaluated survival of MSCs in diabetic kidneys, glucose metabolism, resistance to oxidative stress and autophagy. Confocal imaging and immunofluorescence staining was used to identify MSCs, podocytes, renal tubular cells and to detect senescent protein p16(Ink4a) and proliferation marker Ki-67.

Results: Cultured p66 KO-MSCs at HG escape entry to senescence and apoptotic programs and display enhanced secretion of IGF-1, VEGF and HGF. Microarray detected unexpected crosstalk talk between p66 and Wnt regulatory genes that antagonize senescence. Kidney sections from p66 KO diabetic mice show increased numbers of MSCs in glomeruli and tubules, with barely detectable histologic markers of aging and near normal urine albumin excretion. Kidney nuclei staining (+) for p16(Ink4a) was upregulated, whereas p16(Ink4a) was downregulated.

Conclusions: These findings suggest a genetic link between p66 longevity gene, stem cell aging and senescence phenotype(s) in diabetic kidneys.

Funding: Private Foundation Support

SA-PO317

The Full Time Course and Localization of mTOR Activation in Compensatory Renal Hypertrophy
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Background: Previous studies documented an essential role for mTOR activation in mediating compensatory renal hypertrophy induced by unilateral nephrectomy (UNX) but the time course and localization of the mTOR activation are unclear.

Methods: 8-week-old male FVB/NJ mice were subjected to right UNX or sham surgery, followed by sacrifice at different time points to collect left kidney and determine the time course and localization of mTOR activation by immunoblotting and immunofluorescence staining for phospho-S6K1 and phospho-p56, along with nephron segment-specific markers.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: In this inbred mouse strain, UNX induced 8.27 ± 0.93% renal hypertrophy within 1 week. The hypertrophy continued to rise up to 12.74 ± 3.32%, 39.78 ± 7.06%, 45.56 ± 7.72%, 45.92 ± 2.80%, 49.13 ± 2.09%, and 50.26 ± 9.87% by 48 hours, 1 week, 2 weeks, 1 month, 3 months, and 4-7 months, respectively. Thus, the hypertrophy is complete within 3-4 months, with ~50% hypertrophy on average. Immunoblotting indicated that UNX increased the expression of CCN3 within 3 min, indicative MTOR activation, but had no effect on Akt, TSC2, AMPK, or ERK1 and ERK2 phosphorylation in the remaining kidney at any time points examined. The mTOR activity peaked at 24 h, remained at the plateau level even after 48 h, declined but still activated by 1 month, and returned to the basal level by 3 months in UNX. Immunofluorescence staining visualized the most prominent mTOR activation in the cytoplasm of LTL-positive tubules in response to UNX, although the basal mTOR activity in the kidney of sham-operated control mice was largely confined in THP-, calbindin-, and DBA-positive tubules, with very little in LTL-positive tubules. Therefore, mTOR activation represents a very modest reduction of VEGF-A secretion indicating that mTOR and p42/44 MAPK may act via parallel pathways in VEGF-A regulation. Finally, we demonstrate that the hypertrophy continued to rise up to 23.66 ± 3.32%, 69.53 ± 10.54%, 84.81 ± 13.73%, and 91.75 ± 15.92% by 48 hours, 1 week, 2 weeks, and 3 months, respectively, post UNX.

Funding: NIDDK Support

SA-PO317

EGF Dependent Regulation of VEGF-A Secretion by Proximal Tubule Cells
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Background: Vascular endothelial growth factor A (VEGF-A) plays a critical role in periarticular capillary development by promoting vasculogenesis and angiogenesis. It is now recognized that there is increased expression of VEGF-A by proximal tubular epithelial cells in ischemia reperfusion injury and in chronic tubulointerstitial injury. Although hypoxia is known to induce expression of VEGF-A at the protein level in this cell type, it remains unclear how hypoxia affects the regulation of VEGF-A at the transcriptional level and in vivo, the mechanisms regulating VEGF-A secretion by proximal tubule epithelial cells in normoxia has not been established.

Methods: We utilized HK2 cells, an immortalized human proximal tubule cell line, to characterize the epithelial growth factor (EGF)-dependent regulation of VEGF-A secretion by proximal tubular epithelial cells.

Results: The intracellular expression of VEGF-A, EGF receptor and upregulation of mTOR and p42/44 MAPK pathways. P42/44 MAPK dependent even in normoxia. EGF stimulates HIF1-a and VEGF-A via activation of the EGF receptor, and stimulation of HIF1-a. EGF stimulates proliferation of HK2 cells via the secretion of HGF. EGF-induced VEGF-A expression is mediated by a canonical pathway that is partially dependent on MAPK.

Conclusions: The present study indicates that there is increased expression of VEGF-A by proximal tubular epithelial cells in ischemia reperfusion injury and in chronic tubulointerstitial injury. It is now recognized that there is increased expression of VEGF-A by proximal tubular epithelial cells in ischemia reperfusion injury and in chronic tubulointerstitial injury. Although hypoxia is known to induce expression of VEGF-A at the protein level in this cell type, it remains unclear how hypoxia affects the regulation of VEGF-A at the transcriptional level and in vivo, the mechanisms regulating VEGF-A secretion by proximal tubule epithelial cells in normoxia has not been established.

Funding: Veterans Administration Support

SA-PO318

Selective Regulation of a Novel Truncated CCN3 Protein by TGFβ1 in Human Tubule Epithelial Cells
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Background: CCN3 is a member of the matricellular CCN family of proteins along with the structurally similar CCN2/CTGF, a powerful fibrotic agent, but recent work supports hypothesis that CCN2 and CCN3 are in opposition to each other regulating fibrosis. In renal cells, CCN3 is induced by TGFβ. The truncated form of CCN3 in HT-1080 cells in vitro has been shown to counter regulate the expression of CCN2 and CCN3 in the vertebral nucleus pulposus and in mesangial cells. We have previously characterised TGFβ1 induction of CCN2 in proximal tubule epithelial cells (PTEC) here we investigate the expression of CCN3 in human PTEC and its potential regulation by TGFβ1.

Methods: Primary human PTEC were cultured on collagen IV in supplemented medium. At 80% confluence cells were treated with TGFβ1 (1-25-2.5 ng/ml) for 24 & 48h, medium was collected and cells lysed. Equal amounts of lysate were subjected to PAGE and Western blotting then probed with antibodies (Ab) to the C-terminal Ab (anti-CCN3 hinge) and the N-terminal Ab (anti-CCN3). Immunoblotting indicated that TGFβ1-stimulated excess of full length CCN3, but not the truncated form apparently lacking the CT domain. The characteristics of this smaller protein are not consistent with any known splice variants and may represent an alternative splice variant of CCN3. The lack of the CT domain would change the 3 dimensional conformation of the protein, inhibit its binding to various interactions and potentially remove the ability of the molecule to inhibit cell proliferation.

Funding: Veterans Administration Support

SA-PO319

Deletion of TGF-β Receptor in Renal Proximal Tubule Cells Impairs HGF Signaling
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Background: The growth factors TGF-beta and HGF have antagonistic and synergistic interactions that govern renal development and response to injury. We previously showed that TGF-beta worsens the epithelial response to acute renal injury, so we postulated that impairing TGF-beta signaling may inhibit responsiveness to HGF, a growth factor that mediates beneficial effects following epithelial injury. Methods: To address how TGF-beta signaling alters epithelial responsiveness to HGF, we generated proximal tubule (PT) cDNA with the TGF-beta type 2 receptor, necessary for cell signaling, either intact (TbRII) or deleted in vitro with adenov-Cre (TbRII). Responses to HGF was assessed by receptor (cMet) phosphorylation, and the biological relevance of altered HGF signaling was determined by branching morphogenesis studies in 3D gels and migration assays.

Results: TbRII PT cells had increased tubular branching and impaired migration compared to cells with the receptor intact. Unexpectedly, PT cells lacking TbRII had impaired response to HGF in both branching morphogenesis and migration assays compared to TbRII cells. Consistent with this, TbRII PT cells had impaired cMet phosphorylation associated with reduced membrane expression of cMet and transcriptional downregulation of the HGF receptor. Notch signaling, a known inducer of cMet transcription, was increased in cells with TbRII intact, and Notch inhibition by gamma-secretase equalized the responses to HGF by PT cells with and without the receptor.

Conclusions: PT cells lacking TbRII have impaired responsiveness to HGF signaling, and this result is due to reduced Notch-mediated cMet transcription. Thus, efforts to block TGF-beta signaling may inadvertently inhibit signaling pathways of other growth factors such as HGF.

Funding: Veterans Administration Support

SA-PO329

Enhancement of HGF-Induced Tubulogenesis by Endothelial Cell-Derived GDNF
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Background: Renal proximal tubular epithelium can regenerate itself after a variety of insults. However, the microenvironment that regulates regeneration process of renal tubules after injury remains unclear. We previously established an in vitro 3D tubulogenesis assay which at least partly mimics in vivo regeneration processes of renal tubules after injury (Am J Physiol Renal Physiol: 301: F387-95, 2011). Utilizing this system, the endothelial cell-derived factors that regulate tubulogenesis were examined.

Methods: Human renal proximal tubular epithelial cells (RPTC) were cultured in gels (type I collagen/matrigel mixture) in the presence of HGF with or without human umbilical vein endothelial cells (HUVEC) using Transwell filter system. The signaling pathway activated by co-culture with HUVEC in tubular structures were examined using phospho-receptor tyrosine kinase (RTK) array.

Results: HGF, a potent renotrophic factor, induced aquaporin-1-positive tubular structures with microvilli, suggesting that these structures are morphologically equivalent to tubulogenic structures in vivo. When co-cultured with HUVEC, HGF-induced tubular formation was significantly enhanced. Tubulogenic effect of HGF was also enhanced in the presence of HUVEC-conditioned media (HUVEC-CM), but not in the presence of VEGF, basic FGF or PDGF. Co-culture with HUVEC did not induce tubular structures in the absence of HGF. RTK array revealed that phosphorylation of RET (GDNF receptor) was markedly enhanced in tubular structures cultured with HUVEC-CM compared to those without HUVEC-CM. HUVEC produces GDNF and RPTC expresses both RET and GFR alpha1 (co-receptor). HGF-induced tubulogenic formation was significantly enhanced by addition of GDNF.

Conclusions: RET is the receptor for GDNF acting in a paracrine manner. GDNF-RET signaling may play a role in the crosstalk between renal tubular cells and surrounding endothelial cells during tubular regeneration after injury.

Funding: Veterans Administration Support

SA-PO321

Massive Formation of Ang(1-7) from AngII(1-8) Is Largely ACE2 Independent
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Background: Ang(1-8) degradation mechanisms are complex including clevage by aminopeptidases that form AngIII and carboxypeptidases like ACE2 and PDGF. Co-culture with HUVEC did not induce tubular structures in the absence of HGF. RTK array revealed that phosphorylation of RET (GDNF receptor) was markedly enhanced in tubular structures cultured with HUVEC-CM compared to those without HUVEC-CM. HUVEC produces GDNF and RPTC expresses both RET and GFR alpha1 (co-receptor). HGF-induced tubulogenic formation was significantly enhanced by addition of GDNF.

Conclusions: RET is the receptor for GDNF acting in a paracrine manner. GDNF-RET signaling may play a role in the crosstalk between renal tubular cells and surrounding endothelial cells during tubular regeneration after injury.

Funding: Veterans Administration Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Methods: After acute AngII(1-8) infusion to WT mice plasma concentrations of AngII(1-8), Ang(1-7) and Ang(1-5) were measured by LC-MS/MS. Additional measurements of Ang(1-7) by RIA and ELISA were performed for confirmatory purposes. Plasma ACE2 and PRPC activity in WT mice was measured using a fluorogenic substrate.

Results: Following AngII(1-8) infusion to WT mice plasma Ang(1-7) levels measured by MS were extremely high. Similarly high levels were also found when this peptide was measured by RIA and ELISA (Table).

<table>
<thead>
<tr>
<th></th>
<th>AngII(1-8)</th>
<th>Ang(1-7)</th>
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</thead>
<tbody>
<tr>
<td>MS</td>
<td>244 ± 21 pg/ml</td>
<td>766 ± 199 pg/ml</td>
</tr>
<tr>
<td>RIA</td>
<td>n.a.</td>
<td>1527 ± 240 pg/ml</td>
</tr>
<tr>
<td>ELISA</td>
<td>1012 ± 223 pg/ml</td>
<td>1137 ± 394 pg/ml</td>
</tr>
</tbody>
</table>

In an ACE2 KO line there was no significant difference in Ang(1-7) levels as compared to WT mice and the levels of ACE2 activity in plasma of WT mice were low. Moreover, activity of PRPC, another Ang(1-7) forming enzyme is very low at the plasma normal pH. We therefore hypothesize that Ang(1-7) formation after AngII(1-8) infusion must be largely ACE2 and PRPC independent. To give further support for this hypothesis, we infused a different set of mice with AngII(1-8) in the presence of recombinant murine ACE2 or ACE2 + MLN, a specific inhibitor. Under all these conditions the levels of Ang(1-7) were massively increased and therefore unaccountable only by the conversion of AngII(1-8) to Ang(1-7) by ACE2 cleavage.

Conclusions: Formation of Ang(1-7) during AngII(1-8) infusion is massive and largely ACE2 independent. The increase in Ang(1-7) after AngII(1-8) infusion suggests the presence of unknown Ang(1-7) forming enzymes that are very active in plasma.

Funding: NIDDK Support

SA-PO322

HIF1α and HIF2-Induced Erythropoietin Production Along the Nephron

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Background: Kidney peritubular interstitial cells produce erythropoietin (Epo) in response to hypoxia and/or anemia. By using in situ hybridization method, we have shown that Epo is also produced by the cortical nephrin segments (mainly in PCT, DCT and CCD) in control and/or hypoxic conditions (Nagai, et al, 2014). The role of renin-angiotensin-aldosterone system has been suggested to exacerbate anemia in chronic kidney disease, suggesting aldosterone-regulated erythropoietin production.

Methods: To characterize the molecular machineries for Epo production in renal tubules, we examined the mRNA expressions of HIF1α, HIF2α, PHD2, mineralocorticoid receptor (MR) and EGF-receptor (EGFR) along the nephron in basal condition. Each nephrin segment from SD rats was microdissected in the presence of ribonucleoside vanadyl complexes. After the extraction of RNA, mRNA expression was measured using RT-PCR and real time PCR.

Results: Epo mRNA expression was confirmed in whole nephron segments by RT-PCR in basal condition. The expressions of HIF1α, HIF 2α and PHD2 mRNAs were detected in whole nephrin segments both in RT-PCR and real time PCR. The largest expression of HIF2α mRNA was observed in PCT. HIF2α mRNA expression was larger than HIF1α in whole nephron segments both in RT-PCR and real time PCR. The largest expression in basal condition. The expressions of HIF1α, HIF 2α and PHD2 mRNAs were detected in whole nephrin segments both in RT-PCR and real time PCR.

Conclusions: The results suggest the presence of HIF2α induced-Epo reduction in renal tubules. The presence of MR in whole nephrin segments suggest that aldosterone may have physiological effects for Epo production not only in distal but also in proximal tubules.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO323

Cytokine Response of Primary Human Mesangial Cells In LS Strain Dependent

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Background: LPS stimulation of Toll-like receptor 4 (TLR4) induces the release of proinflammatory cytokines which activate potent immune responses. LPS is an important structural component of the outer membrane of Gram-negative bacteria and consists of three parts: lipid A, a core oligosaccharide, and an O side chain. It has been studied extensively in models of inflammation with E.coli 011:B4 most often referenced in the literature. The antigenicity of LPS varies from strain to strain depending on the composition of its O side chain. A comparative study was designed to identify the optimal strain to be used for LPS-stimulated release of proinflammatory mediators from primary human mesangial cells (HMC).

Methods: HMC were stimulated with 7 strains of LPS and 24 hour supernatants were analyzed for production of inflammatory mediators ([IL-1β, IL-6, IL-8, TNF-α and MCP-1]). Cell viability of HMC was assessed with MTS kits Proliferase and Annexin V/PI assays for 4-plex II and MCP-1. TLR4 antagonists EXX0076824 a small molecule and FHAN_2014062 an antibody were tested to evaluate inhibition of LPS activity in HMC using 3 LPS strains with most pronounced inflammatory effects.

Results: LPS induced strain-dependent increases in IL-6, IL-8, and MCP-1 in HMC, while there was no effect on IL-1β and TNF-α. When compared to controls, IL-6 production was significantly (p<0.05) increased. E.coli 0111:B4 (25X), LPS-EB (10X), E.coli K12 (44X), E.coli 055:BS (8X), S.Minnesota (99X), S.pyogenes (18X) and P.gingivitis (6X). All strains induced IL-8 and MCP-1 except for E.coli 055:BS (IL-8) and E.coli K12 (MCP-1). Both TLR4 antagonists blocked LPS induced production of IL-6, IL-8, and MCP-1 in a dose dependent manner. IC50 values for both inhibitors (EXX0076824: 30-60mM; FHAN_2014062: 800-2700ng/ml) were consistent across LPS strains and analyte detected.

Conclusions: In this study we demonstrate that LPS-stimulated release of inflammatory mediators in HMC is strain dependent, and can be blocked using TLR4 antagonists. These data highlight the importance of identifying the most effective LPS strain in a cell type of interest, prior to initiating pharmacology studies.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals Inc.

SA-PO324

Effect of Angiotensin II Type 1 Receptor Blocker on 12-Lipoxygenase Activity and Slit Diaphragm Protein Nephrin and P-Cadherin Expression in Type 2 Diabetic Rat Glomeruli

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Background: 12-lipoxygenase (12-LO) and angiotensin II/AngII interaction plays an important role in the development of diabetic nephropathy (DN), in which proteinuria was thought to be associated with decreased expression of glomerular slit diaphragm protein nephrin and P-cadherin. However, it is unclear whether Ang II type 1 receptor blocker (ARB) regulates 12-LO activity and slit diaphragm protein expression in type 2 diabetic rat glomeruli and hence was investigated in this study.

Methods: Podocytes and glomeruli isolated from rats were used in this study. The 12-LO products 12(S)-HETE and Ang II were infused to rats by osmotic mini-pump. Rats fed high fat diet received low dose streptozotocin to make type 2 diabetes. Glomeruli were isolated with sieving method and classified into small glomeruli (SG, on the 75mm sieve) and large glomeruli (LG, on the 125mm sieve). ELISA, RT-PCR and Western blot for related targets were performed respectively.

Results: Ang II increased 12(S)-HETE levels in podocytes and glomeruli. Direct infusion of rats with 12(S)-HETE and Ang II significantly decreased LG nephrin, but increased SG nephrin expression compared to control. The glomerular P-cadherin expression was reduced after Ang II and 12(S)-HETE treatment and there was no difference between LG and SG. ARB did not affect blood glucose levels but completely attenuated increases in 12(S)-HETE content, AT1 expression and proteinuria induced by diabetes. Nephrin protein expression was significantly reduced in diabetic LG but increased in diabetic SG compared to control. P-cadherin expression was decreased in both diabetic LG and SG. These abnormalities were partially but significantly prevented by ARB treatment.

Conclusions: ARB could ameliorate the progression of DN via upregulation of glomerular nephrin and P-cadherin expression through inhibition of 12-LO activation in type 2 DN.

Funding: Government Support - Non-U.S.

SA-PO325

APOL1 Risk Variants and HIV Stimulate Induction of PDGF-β Receptor in Podocytes

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Background: Clinical reports demonstrated that two coding sequence variants (G1 and G2) in the APOL1 gene are responsible for the higher percentage of kidney disease in African Americans. This disparity between patients with APOL1 variants versus wild type APOL1 increases by 10 fold for the development of HIVAN in patients of HIV infection who are not on antiretroviral therapy. Podocytes do not express platelet-derived growth factor (PDGF) receptors constitutively but, nonetheless, in experimental animal models, podocyte

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700A
unregulated expression of PDGFs manifested as progressive glomerulonephritis. We hypothesized that APOL1 risk variants and HIV carry potential for the induction of the activation of the PDGF pathway in podocytes.

**Methods:** To determine the effect of APOL1 and APOL1 variants expression, stably expressing Vector, APOL1, APOL1G1, or APOL1G2 human podocyte (HP) cell lines were developed. Expression of HIV (NL4-3 or empty vector) (control) virus was transduced into APOL1G0/HPs, APOL1G1/HPs and APOL1G2/HPs. After 48 h, RNAs were extracted. cDNAs were amplified with specific primers for PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFRβ. Hairpin transcript significantly induced expression of PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFRβ in podocytes.G0/HPs, G1/HPs, and G2/HPs with or without HIV transduction did not display any change in the expression of PDGF-B, PDGF-C, or PDGF-D, when compared with vector; whereas, G2/HPs in HIV milieu displayed enhanced expression of PDGF-A. Interestingly, both G1/HPs and G2/HPs displayed 10 fold increase in PDGFRβ expression when compared to vector or G0/HPs.

**Conclusions:** These findings indicate that PDGFs and their receptor PDGFRβ can be induced by HIV and APOL1 risk variants. The present study could lead to new therapeutic targets for HIVAN.

**Funding:** NIDDK Support

**SA-PO326**

**Assessment of Urinary Liver Type Fatty Acid Binding Protein in Patients of Type 2 Diabetes Mellitus with Early Chronic Kidney Disease**

**Om Prakash Kalra, 1 Mohit Garg, 1 Ashok Kumar Tripathi, 1 Sanil Agrawal, 1 Medicine, UCMS & GTB Hospital, Delhi, India; 2 Biochemistry, UCMS & GTB Hospital, Delhi, India.

**Background:** Diabetes mellitus is the most common cause of chronic kidney disease (CKD) worldwide. Various markers are being indentified which can detect nephropathy at an earlier stage. Both glomerular and tubular injury play an important role in etiopathogenesis of diabetic nephropathy (DN) and tubular damage precedes glomerular damage. Tubular markers are considered as tubular injury markers. Liver type fatty acid binding protein (L-FABP), a 14 kDa cytosolic protein expressed in a wide variety of tissues including peritubular myofibroblasts, is increased in kidney injury. In the present study, we assessed the role of urinary L-FABP as a tubular injury marker.

**Methods:** This was a case control, cross sectional study. Eighty four subjects in the age group 30–60 years of either sex were taken and were divided into three groups: Group I: Healthy controls (n=28) Group II: Type 2 diabetes patients with normoalbuminuria (n=28) Group III: Type 2 diabetes patients with microalbuminuria (n=28). Detailed history, physical examination, investigations were done and creatinine to albumin ratio (ACR) was done. Urinary L-FABP was measured by ELISA (CMIC, Tokyo).

**Results:** The urinary ACR levels were comparable in group I and II. Subjects in Group III had significantly elevated ACR values. Levels of urinary L-FABP were higher in subjects of group II and III when compared with group I. Values of L-FABP were also higher in group III compared to group II. There was a significant positive correlation found between urinary ACR and urinary L-FABP levels. A significant negative correlation was found between urinary L-FABP and eGFR.

**Conclusions:** Urinary L-FABP are markedly increased in patients of diabetic nephropathy as compared to healthy controls. Levels were also increased in diabetes patients with normoalbuminuria suggesting early tubular injury in these patients. This suggests that urinary L-FABP may be a promising early marker for detection of diabetic nephropathy.

**Funding:** NIDDK Support

**SA-PO327**

**Neuropilin1 Regulates Pericyte Behavior in Postnatal Kidney**

**Monika Neuropilin1 (Nrp1) is a transmembrane co-receptor implicated in the regulation of endothelial cell migration during angiogenesis. In the adult kidney, Nrp1 is however not only expressed in pericytes but also by pericytes including peritubular pericytes and mesangial cells.

**Methods:** To determine the effect of Nrp1 and Nrp1 variants expression, stably expressing Vector, APOL1, APOL1G1, or APOL1G2 human podocyte (HP) cell lines were developed. Expression of HIV (NL4-3 or empty vector) (control) virus was transduced into APOL1G0/HPs, APOL1G1/HPs and APOL1G2/HPs. After 48 h, RNAs were extracted. cDNAs were amplified with specific primers for PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFRβ. Hairpin transcript significantly induced expression of PDGF-A, PDGF-B, PDGF-C, PDGF-D, and PDGFRβ in podocytes.G0/HPs, G1/HPs, and G2/HPs with or without HIV transduction did not display any change in the expression of PDGF-B, PDGF-C, or PDGF-D, when compared with vector; whereas, G2/HPs in HIV milieu displayed enhanced expression of PDGF-A. Interestingly, both G1/HPs and G2/HPs displayed 10 fold increase in PDGFRβ expression when compared to vector or G0/HPs.

**Conclusions:** These findings indicate that PDGFs and their receptor PDGFRβ can be induced by HIV and APOL1 risk variants. The present study could lead to new therapeutic targets for HIVAN.

**Funding:** NIDDK Support

**SA-PO328**

**Development of a Spontaneous, Reproducible and Treatable Kidney Fibrosis Model**

**Jessica Marie Overstreet, Ming-Zhi Zhang, Raymond C. Harris, Medicine, Vanderbilt Univ, Nashville, TN.

**Background:** Kidney fibrosis in chronic kidney diseases causes gradual loss of kidney functionality. Currently, only a few kidney fibrosis models are available. New kidney fibrotic models are needed. Since our previous studies indicated that activation of epidermal growth factor receptor (EGFR) contributes to the development of renal fibrosis, we have developed a model with selective overexpression of an EGFR ligand, human heparin-binding EGF (hHB-EGF) in renal proximal tubule, were generated. Male C57BL/6 homozygous HBB-EGF mice received vehicle (water) or erlotinib (80 mg/kg/ day) by daily gastric gavage & females to control.

**Results:** Kidney cortical hHB-EGF mRNA and protein levels were dramatically higher in homozygous hHB-EGF mice than in heterozygous mice. Profound renal interstitial fibrosis was found in both B6D2 and C57BL/6 homozygous hHB-EGF mice, but not in heterozygous mice, as indicated by histology and increased levels of the pro-fibrotic and fibrotic components (CTGF, a-SMA, collagen I and IV). Homozygous hHB-EGF mouse kidneys also exhibited increased oxidative stress and infiltration of both macrophages and T lymphocytes. Interstitial fibrosis appeared as early as 4 weeks old. Homozygous hHB-EGF mice exhibited increased kidney fibroblast activation (increased phosphorylation of EGFR) and activation of downstream signaling, p-ERK and p-AKT. In addition, there was markedly increased p-Smad 2/3. p-EGFR, p-ERK, and p-Smad 2/3 were all primarily localized to proximal epithelial cells, indicating that hHB-EGF-mediated EGFR activation in proximal epithelial cells is the primary event in the development of interstitial fibrosis. Treatment with erlotinib, an inhibitor of EGFR tyrosine kinase activity, inhibited EGFR signaling pathways and attenuated the development of renal interstitial fibrosis.

**Conclusions:** These studies suggest that ligand-mediated EGFR activation in renal proximal tubular epithelial cells leads to spontaneous, reproducible, and treatable renal interstitial fibrosis. Therefore, homozygous hHB-EGF mice may be a useful renal fibrosis model to test the effectiveness of anti-fibrotic agents.

**Funding:** NIDDK Support

**SA-PO329**

**LPA-LPA, Signaling Regulates Fibroblast Proliferation and Myofibroblast Differentiation Dependent on Epithelial Cell-Fibroblast Interaction**

**Norihiko Sakai, Yasutaka Kamikawa, Akihiro Sagara, Yasuyuki Shinozo, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Miho Shimizu, Kengo Furuchi, Takashi Wada. Div of Nephrology, Kanazawa Univ, Kanazawa, Japan.

**Background:** Renal fibrosis is a common pathway of progressive renal diseases, resulting in renal failure regardless of its cause. The accumulation of fibroblasts and myofibroblasts is a hallmark of renal fibrosis. The activation of downstream signaling, p-ERK and p-AKT. In addition, there was markedly increased p-Smad 2/3. p-EGFR, p-ERK, and p-Smad 2/3 were all primarily localized to proximal epithelial cells, indicating that hHB-EGF-mediated EGFR activation in proximal epithelial cells is the primary event in the development of interstitial fibrosis. Treatment with erlotinib, an inhibitor of EGFR tyrosine kinase activity, inhibited EGFR signaling pathways and attenuated the development of renal interstitial fibrosis.

**Methods:** In this study, we focused on the effects of LPA-LPA, signaling on the interaction between renal tubular epithelial cells (RTEC) and renal fibroblasts (RFB). The stimulation of RTBC with LPA-induced CTGF expression in both RTEC and RFB in a time- and dose-dependent manner. The induction of CTGF in both cells was suppressed by the treatment with LPA, antagonist (AM095). In addition to that, LPA-induced CTGF expression in both cells was diminished by the treatment with Rho inhibitor (C3 toxin) and Rho kinase inhibitor (Y27632). In both cells, LPA enhanced the nuclear translocation of myocardin-related transcription factor (MRTF)-A/B and the transcriptional activity of MRTF-serum response factor (SRF), whereas Y27632 treatment inhibited those. The inhibition of MRTF-A/B-SRF pathway by the treatment with siRNA or a chemical inhibitor suppressed the expression of CTGF in both RTBC and RFBC. Finally, the treatment of LPA-LPA enhanced the proliferation of RFBC and the expression of alpha smooth muscle actin in RFBC.

**Conclusions:** In conclusion, LPA-LPA, signaling regulates epithelial cell-fibroblast interaction to induce fibroblast proliferation and differentiation into myofibroblasts through CTGF production dependent on Rho/Rho kinase/MRTF-SRF pathway.

**Funding:** Government Support - Non-U.S.

**SA-PO330**

**TWEAK/Fn41 Signaling Promotes Kidney Disease by Driving Myofibroblast Activation, Inflammation and Vascular Instability**

**Ivan G. Gomez, 1 Allie M. Roach, 1 Gamze Karaca, 1 Linda Burkly, 1 Jeremy Stuart Duffield. 1 Medicine, Univ of Washington, Seattle, WA.

**Background:** We identified Fibroblast growth factor-inducible 14 (Fn41) as a receptor on pericytes, which is strongly upregulated as they differentiate into myofibroblasts in vivo in kidney disease. TNF-related weak inducer of apoptosis (TWEAK), a TNF-family
cytokine produced predominantly by myeloid leukocytes has been reported to activate NFκB and TAZ. We have previously reported that NFκB signaling was activated in myofibroblasts in vivo and hypothesized that TWEAK/Fn14 signaling might be an important driver of pathological myofibroblast in kidney disease.

Results: Fn14 deficiency ameliorates myofibroblast appearance, fibrosis and microvascular pathology in vivo. TWEAK activates primary human cultures of kidney fibroblasts and epithelial cells, which suggests that TWEAK activation could be involved in the progression of kidney fibrosis. TWEAK activation was observed in kidney fibroblasts and epithelial cells in vivo and in vitro.

Conclusions: These findings suggest that targeting the TNF superfamily TWEAK/Fn14 pathway is an approach to modulate myofibroblast activation and a novel way to block both inflammatory and fibrotic aspects of chronic kidney disease.

Funding: Pharmaceutical Company Support - Biogen

SA-PO331
Deregulation of Hippo-TAZ Pathway During Renal Injury Promotes Fibrotic Phenotype Rohan Samarawick, Lucas Falke, Roel Goldschmeding, Paul J. Higgins. 1Center for Cell Biology and Cancer Research, Albany Medical Center, Albany, NY; 2Dept of Pathology, Univ Medical Center Utrecht, Utrecht, Netherlands.

Background: Hippo pathway is the principal regulator of organ size. Transcriptional co-activator with PDZ-binding motif (TAZ), a nuclear transducer of Hippo pathway, is activated during renal injury, tensional forces and soluble factors. TAZ has been implicated in the progression of lung fibrosis and cancer. However, role of Hippo-TAZ pathway in chronic kidney disease (CKD) is unknown.

Methods: We utilized three mouse models of renal injury [ureteral ligation (UOL), aristoclastic acid nephropathy (AAN), streptozotocin (STZ)-driven diabetic nephropathy] and TAZ genetic manipulation in HK-2 tubular epithelial cells and NRK-49F renal fibroblasts to investigate role of TAZ in renal fibrosis.

Results: TAZ is activated [as evident by increased nuclear accumulation (4-fold) and expression (2.5-fold) at both in the tubular and interstitial cells and decreased TAZ-dependent phosphorylation] in the UO kidney compared to contralateral controls. TAZ expression is also upregulated in AAN and STZ-induced renal injury models. TAZ activation correlated with increased pSmAD3 in the fibrotic kidney. TGF-beta1 and Angiostatin II stimulation, moreover, promoted TAZ and pSmAD3 nuclear entry in HK-2 cells suggesting that these cytokines likely disable core Hippo signaling. TAZ stable gene silencing in HK-2 cells, indeed, suppressed TGF-beta1 and Angiostatin II induced CTGF, PAI-1 and fibronectin expression. Stable TAZ overexpression in HK-2 cells promoted epithelial dedifferentiation and proliferative arrest.

Conclusions: Activated during renal injury, TAZ is a novel profibrotic effector of TGF-beta1 and Angiostatin II induced phenotypic responses. TAZ nuclear accumulation in response to TGF-beta1 and Angiostatin II is suggestive of cross-talk among Hippo pathway and these cytokines.

Funding: Other NIH Support - GM057242

SA-PO332
Design and Characterisation of Novel BMP Agonists and Antagonists Daniel Craig, Satnam Surace, Finian Martin, Catherine Godson. UCD; UCD; UCD.

Background: We have previously reported a role for the Bone Morphogenic Protein [BMP] antagonist Gremlin in a driver of diabetic nephropathy and fibrosis in both kidney and lung. Bone Morphogenetic Proteins are integral regulators of bone and organ development. BMPs are secreted proteins and signal by associating with membrane bound receptors. The activity of BMP agonists is modulated by a family of secreted protein antagonists, including Noggin, Chordin and Gremlin that limit BMP receptor association by binding to the ligand and thereby inhibiting receptor binding.

Methods: We have analysed BMP-receptor and BMP-antagonist interactions using a newly designed automated pipeline, Protein Complex Tool (PCT). Co-crystal structures of the BMP-BMP receptor and the BMP-antagonist complexes were submitted to PCT and in silico alanine substitution scans were performed to calculate the free energy contribution of each BMP-2, or BMP-7, residue to the stability of the complexes with receptors, BMPRIA (BMP-2 only) and AciriRla, and antagonists, Crossveinless-2 (BMP-2 only) and Noggin (BMP-7 only).

Results: The free energy calculations identified the key contributions of BMP residues to both binding events and suggested mutations that might generate super-agonist and dominant negative molecules. Further in silico analysis was performed by mutating each residue to each of the other 19 amino acids. From this we identified potential super-agonist and dominant negative mutants for both BMP-2: L51V and N102T (super-agonists) and S88G and L92D (dominant negatives), and BMP-7: E60T, D191H, I124A and K127E (super-agonists) and F117E and V122D (dominant negatives). The super-agonists will bind and activate the receptor but will be resistant to binding by antagonist, in contrast, the dominant negatives, bind antagonist but not receptor.

Conclusions: Data will be presented from our investigations of these molecular tools, which may be involved in upregulating genes associated with the unfolded protein response and potential therapeutic leads for treating fibrotic disease and renal DN.

Funding: Pharmaceutical Company Support - ROCHE

SA-PO333
Engaged Growth Factors to Treat Acute Kidney Injury Shalwdeh Fahhabi, Karin Kuchenbecker, Tim Stowe, Matt Onsum. Silver Creek Pharmaceuticals, San Francisco, CA.

Background: Acute kidney injury remains a major unmet medical need and economic burden. There are no therapies that act directly on damaged kidney cells to promote survival. At Silver Creek Pharmaceuticals, we are engineering a new class of therapeutics called Smart Growth Factors that act selectively on damaged kidney cells to safely deliver pro-survival signals and restore kidney function.

Methods: We harness the ability of growth factors to act on survival and mitogenic signaling of growth factors and engineer more desirable drug-like properties, including extended half-life and cell type-specific targeting. Our first SGF, designed to reduce cardiomyocyte death following acute myocardial infarction, has shown positive pre-clinical efficacy and is being prepared for an Investigational New Drug Application. We are now designing an SGF to treat acute kidney injury, where apoptosis of proximal tubule cells is a leading mechanism of pathology. We developed an in vitro model of tubule cell apoptosis using hypoxia to screen wild type growth factors for the ability to restore cell viability and promote proliferation. We then used computational models to design SGFs that could maximize pro-survival signaling and targeting in damaged kidney tubule cells.

Results: SGF variants were built, expressed and purified in-house, and screened for their ability to act on pro-survival and proliferative signals selectively in damaged cells using the in vitro hypoxia model. SGFs with favorable rescue ability, selectivity and pharmacokinetics will be tested in a rodent AKI model using bilateral ischemia.

Conclusions: Smart growth factors have the potential to transform the treatment of acute kidney injury, but safely delivering potent pro-survival and mitogenic signals specifically to damaged cells, hopefully leading to better outcomes for this patient population.

SA-PO334
Loss of the Podocyte Glucocorticoid Receptor Exacerbates Proteinuria Julie Goodwin, Xia Fei Tian, Shuta Iwahashi, Pediatrics, Yale Univ School of Medicine, New Haven, CT; Internal Medicine, Yale Univ School of Medicine, New Haven, CT.

Background: Nephrotic syndrome is one of the most common renal diseases in children and podocyte foot process effacement is the histologic hallmark. Glucocorticoids (GC) are the mainstay of treatment. Podocytes express the glucocorticoid receptor (GR) and new evidence suggests that podocyte-specific GC effects may be central to controlling proteinuria.

Methods: Mice with knockout of GR in podocytes were generated by crossing GR null mice with podrec Cre mice. Proteinuria was induced using both a systemic stimulus (LPS) and a renal-specific insult (nephrotic serum (NTS)). Urine protein/creatinine ratios, serum albumin and GIM morphology were assessed in both controls and knockout animals. In vitro, wound healing assays and analysis of stress fiber formation after stimulation with LPS in the presence or absence of dexamethasone (DEX) were performed in primary podocytes isolated from animals of both genotypes.

Results: Podocyte GR knockout mice did not have a phenotype at baseline. Their weight, serum creatinine, serum albumin, urine protein/creatinine ratios and foot process diameter were similar to controls. When challenged with low-dose LPS (12.5 mg/kg, IP), knockout mice developed significantly more proteinuria (2.11 ± 0.77 vs. 0.60 ± 0.21; p<0.05, n=5/group) than did controls. Knockout mice also showed greater foot process effacement by EM after LPS (855 ± 157 nm vs. 466 ± 8 nm, p<0.05, n=5/group) compared to controls. When treated with NTS, similar results were noted. In vitro, GR knockout podocytes showed fewer and more disorganized stress fiber formation and impaired wound healing after LPS treatment compared to control podocytes. Administration of DEX could rescue the in vitro phenotype in control, but not GR knockout, podocytes.

Conclusions: These results demonstrate that (1) loss of podocyte GR exacerbates proteinuria in two different models in vivo, (2) podocytes lacking GR are more intolerant to injury, and (3) DEX administration ameliorates cellular injury in control, but not GR- deficient podocytes. We conclude that the podocyte GR plays a key role in maintaining the integrity of the slit diaphragm after injury.

Funding: NIDDK Support

SA-PO335
Deletion of Inositol-Requiring Enzyme-1a in Podocytes Disrupts Glomerular Capillary Integrity and Autophagy Daniel Robert Kaufman,1 Joan Papillon,2 Takao Iwawaki,3 Andrey V. Cybulsky.

1Physiology, McGill Univ, Montreal, QC, Canada; 2Medicine, McGill Univ, Montreal, QC, Canada; 3Medicine, Gamma Univ, Maebashi, Japan.

Background: Inositol-requiring enzyme-1a (IRE1a) is an endoplasmic reticulum (ER)-transmembrane endoribonuclease-kinase, which plays an essential function in normal development, and is activated during ER stress. IRE1a is involved in upregulating genes associated with the unfolded protein response and...
ER-associated degradation, as well as in the activation of c-Jun N-terminal kinase (JNK)-1, and induction of apoptosis and autophagy. In this study, we address the functional role of miR-192 in podocytes.

Methods: Podocyte-specific miR-192 knockdown (KO) mice were generated by breeding mice with loxP sites surrounding exons 20-21 with podocin (NPHS2)-Cre mice. LoxP-mediated excision in glomeruli was confirmed by PCR.

Results: In male mice, deletion of miR-192 in podocytes resulted in albuminuria beginning at 5 months of age, and worsening with time. Electron microscopy revealed focal podocyte foot process effacement in 9 month old male KO mice, as well as microvillous transformation of podocyte membranes and cytosolic vacuolation. By light microscopy, glomerular cross-sectional area (an indicator of hypertrophy) was greater in KO mice, compared with control, and capillary lumens occupied a higher fractional area of KO glomeruli, suggesting formation of anurysms. By immunofluorescence microscopy, WT-positive cells per glomerulus were comparable in KO and control males. Immunoblotting showed reduced LC3B-II expression and JNK-1 phosphorylation in KO glomeruli, in keeping with reduced autophagy. There was also a reduction in nephrin maturation in KO glomeruli, suggesting impaired ER function. Finally, expression of IRE1α or IRE1α K599A (dominant inhibitor) in cultured COS-1 kidney cells did not affect ERAD, as monitored by the efficient detection of the CD3A ERAD reporter.

Conclusions: Podocyte-specific deletion of IRE1α leads to albuminuria and morphological evidence of podocyte injury. Thus, IRE1α is essential to the maintenance of podocyte integrity as mice age. The mechanism may, at least in part, relate to disruption of autophagy in podocytes.

Funding: Government Support - Non-U.S.

SA-PO336

Consistent Downregulation of Autophagy Gene Atg12 Through MicroRNA-192 in Diabetic Nephropathy

Supriya Deshpande, Mitsuo Kato, Mei Wang, Rama Natarajan.

Background: Autophagy (Atg) plays a key role in the pathogenesis of kidney diseases, however its role in Diabetic Nephropathy (DN), and particularly in mesangial cells (MC) is not clear. TGF-β1, a key player in the pathogenesis of DN, regulates expression of various microRNAs (miRs) including miR-192. Also, several miRs regulate expression of various Atg genes. We hypothesized that miR-192 plays an important role in Atg regulation in DN.

Methods: Atg gene expression was analyzed in type-2 diabetic (db/db) and in STZ-injected type-1 diabetic mice. To analyze the role of miR-192 in Atg regulation, STZ-injected type-1 diabetic mice were treated with control locked-nucleic acid (LNA) oligonucleotides (oligo) or LNA oligos targeting miR-192 (anti-miR-192-LNA), and Atg gene expression was analyzed in kidneys. Atg gene expression was also analyzed in kidneys of WT and STZ-injected miR-192 knockout (KO) mice. The effect of TGF-β1 on Atg gene expression and GFP-RFP-LC3 puncta formation was analyzed using mouse MC (MMC).

Results: Expression of several Atg genes was decreased in kidneys of type-1 and type-2 diabetic mice compared to controls. Treatment with LNA-anti-miR-192 reversed the effect of diabetes on some of the Atg genes. Further, Atg gene expression was not affected in kidneys of diabetic miR-192-KO mice compared to controls. In vitro studies using MMC treated with TGF-β1 also showed a decrease in Atg gene expression compared to control. Transfection of MMC with miR-192 mimic oligos decreased expression of certain Atg genes. In addition, transfection of MMC with a GFP-RFP-LC3 plasmid decreased the average number of RFP-LC3 puncta/cell following TGF-β1 treatment, and this effect was reversed in MMC from miR-192-KO mice. Of all Atg genes analyzed, Atg12 expression was consistently decreased in these mouse models, and its decrease was reversed by anti-miR-192 LNA oligos as well as in miR-192-KO mice.

Conclusions: These results demonstrate that consistent downregulation of Atg12 through miR-192 contributes to an overall decrease in autophagy and subsequent increase in cellular hypertrophy in response to TGF-β1 in MC and in glomeruli of diabetic mice leading to DN.

SA-PO337

mTOR Dependent Regulation of the Podocyte Metabolic Profile

Tillmann Bork, Wei Liang, Tobias B. Huber.

Background: Podocytes play a critical role in the formation and maintenance of the kidney filtration barrier. Previously we have highlighted the role of mTOR signaling as regulator of podocyte adaption, differentiation and size-control. However, the eventual link between podocyte size control and the regulation of podocyte metabolism by mTOR remains elusive.

Methods: Mice models of mTOR hyperactivation (Tsc1 PcKO) and mTOR loss of function (Raptor PcKO) were crossed to a Tomato/eGFP reporter line to efficiently isolate podocytes for primary cell culture studies. Mitochondrial respiration and ATP synthesis were assessed using Seahorse bioanalyzer with specific inhibitors of glycolysis and ATP synthase.

Results: Lipids are the main source for ATP synthesis due to oxidative phosphorylation in podocytes. Anerobic glycolysis is the dominating pathway to use glucose. Active mTOR signaling pathway massively enhances basal metabolic activity and the capacity for oxidative phosphorylation in podocytes.

Conclusions: Podocyte metabolism relies on β-oxidation of lipids and anerobic glycolysis. mTOR signaling regulates metabolic activity without affecting the preferences for the used metabolic pathways. Targeting the predominant metabolic pathways of podocytes might help to ameliorate diabetic nephropathy or podocyte ageing.

Funding: Government Support - Non-U.S.

SA-PO338

Derlin-2 Knockout Mice Unravel an Essential Role for Protein Dislocation in Podocytes

Guohui Ren, Kwi Hye Koh, Jing Li, Changli Wei, Mehmet M. Altintas, Jochen Reiser.

Background: Protein quality control represents a balance between chaperone-assisted removal and folding of misfolded proteins from the endoplasmic reticulum (ER). Disturbed balance results in ER stress in podocytes that is associated with cellular injury. Derlin-2, a component that mediates cellular dislocation machinery, has been identified as an important element in skeletal and matrix producing cells.

Methods: Western blot and immunofluorescence staining were used for detection of protein expression. Derlin-2 knockdown or overexpression in podocytes was achieved with transfection of lipirivus containing shRNA or CDN. Podocyte-specific Derlin-2 knockout mice were generated by crossing Derlin-2-flox mice with podocin-Cre mice. Autophagy was detected with the conversion of LC3-I to LC3-II. Activation of caspase-12 was measured by cleavage of procaspase-12.

Results: Derlin-2 was expressed in both mouse and human podocytes. Derlin-2 deficiency in podocytes could be compensated for by inositol-requiring enzyme 1 (IRE1) induced autophagy at baseline conditions. However, in situations with induced ER stress owed to adriamycin (ADR) or other compounds, the compensatory response of autophagy was overwhelmed. Meanwhile, caspase-12 mediated apoptosis pathway was activated, and severe cellular injury ensued, leading to heavy proteinuria in podocyte-specific Derlin-2 knockout mice, as compared with wild type C57BL/6j control mice. In contrast, Derlin-2 overexpression in vitro attenuated podocyte injury. Derlin-2 expression was induced during in situ glomerulosclerosis (FSGS) and diabetic nephropathy (DN) as well as in ADR nephropathy in BALB/cj mice, streptozotocin (STZ)-induced diabetic mice and BBTR oh/oh DN mice.

Conclusions: Podocytes like osteocytes and chondrocytes emerge from mesenchyme and belong to a group of cells that employ Derlin-2 to guarantee protein quality and minimize ER stress for cellular homeostasis. Overexpression of Derlin-2 may be a mechanism to rescue damaged podocytes. Induction of Derlin-2 expression in vivo may have applications for prevention and therapy of glomerular diseases.

SA-PO339

Protein O-GlcNAcylation Is Essential for Normal Podocyte Structure and Function

Shinya Ono, Masako Yasuda, Shiniji Kume, Osamu Sekine, Jun Nakazawa, Hisuzumi Araki, Masami Kanasaki, Shin-ichi Araki, Daisuke Koya, Masakazu Haneda, Takashi Uzo, Hiroshi Maegawa.

Background: Podocytes like osteocytes and chondrocytes emerge from mesenchyme and belong to a group of cells that employ Derlin-2 to guarantee protein quality and minimize ER stress for cellular homeostasis. Overexpression of Derlin-2 may be a mechanism to rescue damaged podocytes. Induction of Derlin-2 expression in vivo may have applications for prevention and therapy of glomerular diseases.

Results: O-GlcNAcylation was immunohistochemically observed in the nuclei of podocytes in wild-type mice, but was completely absent in Podo-OGTKO mice. Podo-OGTKO mice showed normal birth rate and growth up to 32 weeks of age. Proteinuria was first apparent at 8 weeks of age and increased with age up to 32 weeks. Scanning transmission electron microscopy showed disruption of podocyte foot processes in Podo-OGTKO mice after 8 weeks of age. Immunofluorescence showed podocin to have a punctate distribution in Podo-OGTKO podocytes and to be at a reduced level compared with wild-type mice. Furthermore, the numbers of podocytes in 16-week-old Podo-OGTKO mice were significantly decreased compared with wild-type mice. Finally, severe glomerular sclerosis with tubulointerstitial damage was observed in Podo-OGTKO mice at 32 weeks of age.

Conclusions: O-GlcNAcylation of intracellular proteins by OGT is necessary to maintain podocyte numbers and normal foot process structure. Our results provide new insight into podocyte biology.

SA-PO340

Identification of Novel Gene Products That Regulate Podocyte Function

Davide Pietro Cina, Chengjin Li, Jason Moffatt, Susan E. Quaggin.

Background: Podocytes are a major component that nucleates cellular dislocation machinery, has been identified as an important element in skeletal and matrix producing cells. To identify novel gene products that regulate podocyte function, we designed an mTOR dependent regulation of the podocyte metabolic profile.
SA-PO341

Targeted Deletion of Drp1 in Podocytes Mitigates Mitochondrial Remodeling and Progression of Diabetic Nephropathy

Methods: A pool of knockdown podocytes was generated using this library and plated on both 24-well plates followed by separation of the adherent and floating fractions and deconvolution by illumina sequencing. We developed a stringent method for statistical analysis and 'hit' determination and performed a small-scale validation of this method by interrogating top candidate genes individually. We also performed a larger scale validation using a secondary, focused pooled Cas9 mediated knockdown screen.

Results: We identified 121 genes that increased adhesion to fibronectin and 145 genes that increased adhesion to sFLLT1/Fc. We also identified 66 genes that decreased adhesion to fibronectin and 106 genes that decreased adhesion to sFLLT1/Fc. DPH1, DPH2, DPH3 and DPH4 were among the top ten hits for increased adhesion to both fibronectin and sFLLT1/Fc. Stable podocyte knockdown lines for these genes displayed increased adhesion to both substrates. We also generated Cas9 mediated podocyte knockout lines for DPH1, DPH2 and DPH3, which displayed increased adhesion and a spreading defect.

Conclusions: We have developed a novel method for identifying genes that regulate podocyte function. Future work will investigate how DPH1, DPH2 and DPH3 regulate podocyte adhesion, and select novel candidate genes that decrease podocyte adhesion. This unbiased approach will yield a list of genes that broaden our understanding of podocyte physiology and the disease states that perturb this system resulting in kidney disease.

Funding: Government Support - Non-U.S.

SA-PO343

Cytosolic Phospholipase A2 Alpha Regulates G1 Progression Through Modulating Forhead Box Protein 01 Activity

Methods: We have developed a novel method for identifying genes that regulate podocyte function. Future work will investigate how DPH1, DPH2 and DPH3 regulate podocyte adhesion, and select novel candidate genes that decrease podocyte adhesion. This unbiased approach will yield a list of genes that broaden our understanding of podocyte physiology and the disease states that perturb this system resulting in kidney disease.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Podocyte Oxidative Stress Coupled with Ubiquitin C-Terminal Hydroxylase Deletion Exacerbates Renal Damage

Kidney Disease Branch, NIDDK, NIH, Bethesda, MD.

Background: Ubiquitin C-terminal hydroxylase L1 (UCHL1) may promote antioxidation by hydrolyzing ubiquitin-thioester bonds on glutathione (GSH) thereby protecting GSH from degradation. Podocyte UCHL1 is upregulated in diseased glomeruli where it may maintain redox balance. UCHL1 deleted mice overexpress podocyte-specific NOX5 should exhibit exacerbated glomerular damage due to unregulated oxidative stress.

Methods: COST cells were infected with AdGFP or AdNOX5 and UCHL1 levels determined by immunoblotting, mRNA levels determined by qPCR. UCHL1+/+ and NOX5−/− mice were crossed to generate NOX5−/−/UCHL1−/− mice. Albuminuria (ACR) was measured by ELISA. Renal mass was normalized to tibia length. Glomerular filtration rate (GFR) was assessed by FITC-Inulin. Immunofluorescence with anti-PNA and anti-renin was performed on renal sections. Blood pressure was determined by tail cuff plethysmography.

Results: UCHL1 protein increased 1.9-fold in COST cells infected with AdNOX5 vs. AdGFP-infected controls. Similarly, glomeruli from 12-week-old NOX5−/− mice showed limited UCHL1 mRNA induction (1.5-fold). ACR increased in NOX5−/−/UCHL1+/+ mice at 12 weeks (40 μg/mg) but not in nonTG, UCHL1−/− and NOX5−/−/UCHL1−/− mice (24, 28 and 25 μg/mg). Renal mass was reduced by 10% in both UCHL1+/+ and NOX5−/−/UCHL1+/+ mice as compared to nonTG mice. Interestingly, GFR was elevated in NOX5−/−, UCHL1+/+ and NOX5−/−/UCHL1+/+ mice (283, 362 and 352 μl/min) vs. nonTG (196 μl/min). In UCHL1−/− mice regardless of NOX5 expression, hypercellularity was evident in the juxtaglomerular region. However, no differences were found in renin or PCNA expression, suggesting that the increased GFR is independent of the renin-angiotensin system. Blood pressure in NOX5−/−/UCHL1−/− mice (121 mmHg) was the same as NOX5−/−/UCHL1+/+ mice, but was different from NOX5−/− mice (127 mmHg) at 12 weeks.

Conclusions: UCHL1-null mice have altered renal function and mass. When intercrossed with NOX5−/− mice, UCHL1 deletion combined with unchecked oxidative stress promotes filtration barrier damage.

Funding: Private Foundation Support

Inulin Receptor Isoform A Is Implicated in Podocyte Injury in Diabetic Kidney Disease

Kidney Disease Branch, NIDDK, NIH, Bethesda, MD.

Background: Genetic variants apolipoprotein L1 (APOL1), present in individuals of recent African descent, are strongly associated with glomerular disease, but the molecular mechanisms through which APOL1 nephropathies may be driven by podocyte inflammation and the TLR and IL-1 pathways have not been established. We hypothesized that APOL1 nephropathies may be driven by podocyte inflammation and the TLR and IL-1 pathways.

Methods: Differentiated human podocytes were cultured in the presence of TNFa (100 ng/ml) and Caspase 3 activator was determined in human podocytes. Cyclodexrin (CD) was used to deplete cholesterol.

Results: FSGS sera treated podocytes demonstrated increased TNFα expression. Increased TNFα expression correlate with decreased ABCA1 expression in glomerular basement membrane (GBM) of FSGS patients and treatment of podocytes with TNFa + CD for 12 weeks (40ug/mg) but not in nonTG, UCHL1−/− and NOX5−/−/UCHL1−/− mice. Albuminuria (ACR) was measured by ELISA. Renal mass was normalized to tibia length. Glomerular filtration rate (GFR) was assessed by FITC-Inulin. Immunofluorescence with anti-PNA and anti-renin was performed on renal sections. Blood pressure was determined by tail cuff plethysmography.

Results: UCHL1 protein increased 1.9-fold in COST cells infected with AdNOX5 vs. AdGFP-infected controls. Similarly, glomeruli from 12-week-old NOX5−/− mice showed limited UCHL1 mRNA induction (1.5-fold). ACR increased in NOX5−/−/UCHL1+/+ mice at 12 weeks (40 μg/mg) but not in nonTG, UCHL1−/− and NOX5−/−/UCHL1−/− mice (24, 28 and 25 μg/mg). Renal mass was reduced by 10% in both UCHL1+/+ and NOX5−/−/UCHL1+/+ mice as compared to nonTG mice. Interestingly, GFR was elevated in NOX5−/−, UCHL1+/+ and NOX5−/−/UCHL1+/+ mice (283, 362 and 352 μl/min) vs. nonTG (196 μl/min). In UCHL1−/− mice regardless of NOX5 expression, hypercellularity was evident in the juxtaglomerular region. However, no differences were found in renin or PCNA expression, suggesting that the increased GFR is independent of the renin-angiotensin system. Blood pressure in NOX5−/−/UCHL1−/− mice (121 mmHg) was the same as NOX5−/−/UCHL1+/+ mice, but was different from NOX5−/− mice (127 mmHg) at 12 weeks.

Conclusions: UCHL1-null mice have altered renal function and mass. When intercrossed with NOX5−/− mice, UCHL1 deletion combined with unchecked oxidative stress promotes filtration barrier damage.

Funding: Private Foundation Support

Cyclodexrin Improves Renal Function in Experimental Alport Syndrome

Kidney Disease Branch, NIDDK, NIH, Bethesda, MD.

Background: Alport syndrome (AS) is an inherited disease caused by gene mutations involved in collagen type IV biosynthesis. No treatments are currently available for AS. 2-hydroxypropyl-β-cyclodextrin (CD) is a cholesterol depleting agent that is now in clinical trials for treating Niemann-Pick disease type C. We have recently reported that CD protects in experimental DKD by reducing cholesterol dependent podocyte damage. We hypothesized that CDs improves renal function in an experimental model of AS.

Methods: Collagen Co4a3 knockout (KO) mice were used as a model for AS. Four-week-old Co4a3 (KO) and wild type (WT) female mice were injected subcutaneously with CD (4000 mg/kg) or vehicle (0.9% Saline solution). 3 times per week for 3 weeks. Four weeks post CD treatment or vehicle treatment, renal function was tested by measuring serum creatinine and blood urea nitrogen (BUN) which were measured by mass spectroscopy and ELISA respectively. Additionally,_fence perfused kidneys from Co4a3 KO and WT mice. Kidneys were harvested for histological analysis (H&E, PAS) and for Oil Red O (Staining).

Results: H&E staining showed no toxicity at the site of CD injections. No body weight changes were observed during treatment. CD administration reduced glomerular

Funding: NIDDK Support, Pharmaceutical Company Support - Hoffman La Roche

Santos, Gloria Michelle Ducasa, Sandra M. Merscher, Christopher E. Pedigo, Judith T. Molina David, Mayrin Correa-Medina, Catherine A. Pedigo, Paula Zelaya, Allia Mitrofanova, Sandra M. Merscher, Alessia Fornoni, Div of Nephrology & Hypertension, Univ of Miami, FL, Dep of Surgery, Univ of Miami, FL.

Results: Podocytes overexpressing SMPDL3b (OE) showed significant increase of IRB/IRA mRNA expression ratio compared to control podocytes (CT) (1.0±0.00 vs. 0.74±0.05, p<0.05). Co-IP demonstrated that both IRA and IRB interact with Cav1. SMPDL3b overexpression augmented IRA/Cav1 interaction and suppressed IRB/Cav1 interaction. OE podocytes showed bigger cell surface area compared to CT (2778±0.00 vs. 2467 and 2117±0.54, p<0.05). Insulin stimulation had no effect on the caspase-3 activity in CT podocytes while it induced apoptosis in OE cells (1.19±0.08 and 2.14±0.32, p<0.05).

Conclusions: Our data suggest SMPDL3b overexpression in human podocytes impairs IRB signaling leading to increased apoptosis and augments IRA signaling resulting in cell death and apoptosis.

Funding: NIDDK Support, Other NIH Support - The study is supported by NIH DK039036, NIH/NIDDK 5UL24D070169

TGF Mediated NFAT Activation Causes Podocyte Cholesterol Accumulation in FSGS

Christopher E. Pedigo, Peggy and Harold Katz Family Drug Discovery Center, Univ of Miami, Miami, FL, Dep of Surgery, Univ of Miami, FL.

Methods: Cyclodexrin improves renal functional in experimental Alport Syndrome. Cyclosporine A (CsA) which directly influences podocyte Nuclear Factor of Activated T-Cells (NFAT) activation. However, a potential link between TNFα-NFAT-APOL1 nephropathies has not been established. We hypothesized that TNFα causes NFAT mediated lipopid dependent podocyte apoptosis in FSGS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
ORO staining and prevented the development of mesangial expansion in *WT* mice. A trend in reduced serum creatinine. CD treatment did not affect ACR, renal function or morphological changes in WT mice.

Conclusions: Based on these results, we conclude that CD improves renal function in a mouse model for AS and could be a new therapeutic strategy for the treatment of AS patients.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Hoffman La Roche

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**SA-PO350**

The Glomerular Matrisome in Alport Syndrome Is Altered prior to the Onset of Albuminuria

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**Background:** Alport Syndrome is caused by genetic defects in COL4A3, COL4A4 or COL4A5, but despite this knowledge there are currently no targeted therapies. We aimed to build our basic understanding about the glomerular extracellular matrix (ECM) in Alport syndrome and performed global analysis of composition and ultrastructural imaging in the Col4a3/-/- mouse.

**Methods:** Cellular and extracellular matrix (ECM) fractions from wild type and Col4a3/-/- mice at 6 and 16 weeks of age were analysed by mass spectrometry (MS) and imaged using serial block face-scanning electron microscopy (SBF-SEM).

**Results:** MS analysis revealed moderate changes in the composition of glomerular ECM at 6 weeks, even prior to the onset of barrier dysfunction. These included complete absence of type IV collagen α3, α4, α5 and upregulation of type VI collagen in α2, α6 and type V1 collagen. At 16 weeks more dramatic changes were detected including elevated type IV collagen α1, α2, fibronectin, type 1 collagen, laminin α2 and fibrinogen chains. Global and pathway analysis of cellular fractions indicated changes in actin regulating proteins at 6 weeks and mitochondrial dysfunction at 16 weeks. SBFSEM demonstrated thickened and irregular glomerular basement membranes with evidence of podocyte protrusions into this ECM.

**Conclusions:** Our data demonstrate that Alport syndromes progress with distinct early changes in ECM followed by more profound ECM accumulation, disruption and mitochondrial dysfunction. Enhanced understanding about the pathways that control podocyte matrix adhesion may ultimately inform therapeutic strategies to correct or repair glomerular barrier function in Alport syndrome.

**Funding:** Private Foundation Support

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**SA-PO351**

Creation and Analysis of Mouse Models of Human Nephrotic Syndrome Caused by the Laminin b2 (LAMB2) S80R Mutation

*Steven Daniel Funk, Jeffrey H. Miner. Renal Div, Washungton Univ School of Medicine, St. Louis, MO.*

**Background:** Most cases of congenital nephrotic syndrome in the first year of life are caused by mutations in 4 genes expressed in podocytes: NPHS1, NPHS2, LAMB2, LAMB2 encodes laminin b2, a glomerular basement membrane component critical for glomerular filtration. We previously created transgenic mice using the laminin promoter to study missense mutations discovered in patients with congenital nephrotic syndrome, including R246Q and C321R, which inhibit laminin-521 secretion and/or LAMB2 polymerization domain that was discovered in a delayed nephrotic syndrome patient; this delay suggests that chronic dysfunction in glomerular filtration may be the pathogenic mechanism.

**Methods:** In our first approach the S80R mutation was engineered into the rat laminin b2 cDNA and placed under the control of the nephrin promoter; this construct was used to create transgenic mice expressing S80R in podocytes on the LAMB2-/- background. In a second approach, we utilized CRISPR/Cas9 and homologous recombination to "knock-in" the S80R point mutation into the endogenous LAMB2 gene.

**Results:** Several transgenic mouse lines were characterized as very high, high, and moderate expression in podocytes in the LAMB2-/- background. In a second approach, we utilized CRISPR/Cas9 and homologous recombination to "knock-in" the S80R point mutation into the endogenous Lamb2 gene.

**Conclusions:** The LAMB2-S80R mutation seems to be mild vs. other LAMB2 mutations. S80R is in the laminin N-terminal (LN) domain important for laminin polymer formation. High transgenic expression may compensate for S80R-induced polymorphism defects, which will be avoided with CRISPR/Cas9-induced, S80R knock-in mutants.

**Funding:** NIDDK Support

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**SA-PO352**

Differential Roles of Cell Surface Proteoglycans in Podocyte-Glomerular Basement Membrane Adhesion

*Angela C. DiPoto-Brahmhatt, Deborah J. McCarthy, Kevin J. McCarthy. Pathology and Translational Pathobiology, LSU Health Sciences Center-Shreveport, Shreveport, LA.*

**Background:** Cell surface proteoglycans (PG), via their heparan sulfate (HS) chains, work in a cooperative fashion alongside integrins to mediate podocyte (PG)-glomerular basement membrane (GBM) interactions. Results of our previous studies have shown that the expression of HS at the podocyte cell surface leads to the establishment of foot process effacement. Since podocyte HS have been shown to be capable of mediating such interactions, the purpose of this study was to determine the effects of selective deletion of the cell surface PG, syndecan-1 (Sdc1) or syndecan-4 (Sdc4) on podocyte function in vivo.

**Methods:** Frozen tissue sections of kidneys from *Col4a3* knockout (KO) mice were immunostained with antibodies against the core proteins of Sdc1 and Sdc4, HS (antibody HS4C3), syndaptoedin (SYN), nephrin, and α-actinin-4. To determine the potential for loss of anionic charge associated with HS, 500nm sections of unfixed kidneys were treated with polyethyleneimine (PEI) followed by fixation and processing for transmission electron microscopy.

**Results:** TEM studies showed that the GBMs of both Sdc1 and 4 KO mice had GBM irregularities, the POD in Sdc4KO mice showing moderate foot process effacement. Immunostaining for HS did not show differences in staining intensity for HS between Sdc1 and Sdc4KO mice. However, PEI labeling showed that the GBMs in Sdc4 KO mice had larger aggregates of PEI than those found in the GBM of Sdc1 KO mice. Immunostaining showed that a compensatory increase in Sdc4 expression in Sdc4KO glomeruli or Sdc1 expression in Sdc4KO glomeruli did not occur. The glomeruli of Sdc1 KO mice showed disruption of nephrin organization compared to Sdc4 and WT mice. Immunostaining for α-actinin-4 in both Sdc1 KO and Sdc4KO glomeruli was also disrupted compared to control.

**Conclusions:** The data show that disruption of either Sdc1 or Sdc4 interactions with the GBM affects the manner by which POD interact with the GBM. Although loss of Sdc4 was associated with the development of foot process effacement, the loss of either Sdc1 or Sdc4 have effects on POD cytoskeletal organization.

**Funding:** NIDDK Support

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**SA-PO353**

ERMT Protein Activation by CLIC4 in Glomerular Endothelial Cells

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**Background:** We reported (J. Cell Sci. 2014, 127:1564) that the podocyte-predominant CLIC5A stimulates PI[4,5]P2 production and consequent ERM ( ezrin, radixin, moesin) protein activation (pERMs) and a decrease in the endothelial glycocalyx as a contributor to development of albuminuria (albumin in the urine) and eventually DN. TNFα which is important in the development of microvascular diseases in diabetes caused a disruption of the glomerular endothelial cells (GEnC) and a key regulator of vascular permeability. Increasing evidence points to disruption of such interactions, the purpose of this study was to determine the effects of selective deletion of the cell surface PG, syndecan-1 (Sdc1) or syndecan-4 (Sdc4) on podocyte function in vivo.

**Methods:** Frozen tissue sections of kidneys from *Col4a3* knockout (KO) mice were immunostained with antibodies against the core proteins of Sdc1 and Sdc4, HS (antibody HS4C3), syndaptoedin (SYN), nephrin, and α-actinin-4. To determine the potential for loss of anionic charge associated with HS, 500nm sections of unfixed kidneys were treated with polyethyleneimine (PEI) followed by fixation and processing for transmission electron microscopy.

**Results:** TEM studies showed that the GBMs of both Sdc1 and 4 KO mice had GBM irregularities, the POD in Sdc4KO mice showing moderate foot process effacement. Immunostaining for HS did not show differences in staining intensity for HS between Sdc1 and Sdc4KO mice. However, PEI labeling showed that the GBMs in Sdc4 KO mice had larger aggregates of PEI than those found in the GBM of Sdc1 KO mice. Immunostaining showed that a compensatory increase in Sdc4 expression in Sdc4KO glomeruli or Sdc1 expression in Sdc4KO glomeruli did not occur. The glomeruli of Sdc1 KO mice showed disruption of nephrin organization compared to Sdc4 and WT mice. Immunostaining for α-actinin-4 in both Sdc1 KO and Sdc4KO glomeruli was also disrupted compared to control.

**Conclusions:** The data show that disruption of either Sdc1 or Sdc4 interactions with the GBM affects the manner by which POD interact with the GBM. Although loss of Sdc4 was associated with the development of foot process effacement, the loss of either Sdc1 or Sdc4 have effects on POD cytoskeletal organization.

**Funding:** NIDDK Support

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**SA-PO354**

Vascular Glycoalyx Syndeac (SDC) 4 Loss Coincides with Albuminuria in Diabetic Nephropathy (DN)

*Raina D. Ramnath, Amy Russell, Rebecca R. Foster, Gavin Iain Welsh, Andy Salmon, Simon C. Mylne, Steven Daniel Funk, Renal Unit, Univ of Bristol, Bristol, United Kingdom.*

**Background:** The endothelial glycocalyx is a critical determinant of vascular health and a key regulator of vascular permeability. Increasing evidence points to disruption of the endothelial glycocalyx as a contributor to development of albuminuria (albumin in the urine) and eventually DN. TNFα which is important in the development of microvascular disease in diabetes causes a disruption of the glomerular endothelial cells (GEnC)

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Online; Underline represents presenting author. 706A
glycosalys through shedding of SDC4 and heparan sulphate (HS). We seek to investigate the role of vascular endothelial glycosalys in DN and determine the mechanisms involved in its disruption in DN.

**Methods:** DN was induced in DBA2 mice by giving daily intraperitoneal injection of streptozotocin (STZ) at 50mg/kg for 5 days. The mice became hyperglycemic at 2 weeks and significantly albuminuria in glomeruli in DN, suggesting shedding of vascular SDC4. An increase in SDC4 shedding was recorded in a mock mechanism resulting in an increase in SDC4 mRNA synthesis in isolated glomeruli and Gfrc. The glycosalys SDC4 synthesis coincides with albuminuria, strongly suggesting that vascular glycosalys SDC4 damage is likely to contribute to albuminuria in DN. There was a significant elevation in gelatinase matrix metalloproteinase-9 (MMP9) in glomeruli in DN, suggesting that MMP9 could mediate SDC4 shedding. My in vitro data in human Gfrc showed that gelatinase MMP9 was upregulated and resulted in the shedding of SDC4 and HS. This resulted in an increase in BSA permeability across the monolayer.

**Conclusions:** MMP9-mediated shedding of SDC4 is likely to contribute to vascular endothelial glycosalys damage and albuminuria observed in DN. Potential therapies targeted at glycosalys protection will be of benefit not only in DN but also in ameliorating systemic vascular disease in diabetes.

**Funding:** Private Foundation Support

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**SA-PO355**

**Blood Cell Velocities in Glomerular Capillaries Measured by 2-Photon In Vivo Microscopy:** Revealing Heterogeneous Blood-Flow

**Debora Pedotti,** 1, 2 Eugenio Gutierrez, 1 Luca Bordoni, 1 Sara Damiano, 1 Francesco Trecipiccione, 1 Giovanni Batista Capanna, 1, 2, 3 Sebastian Frische. 1, 2 Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark; 3 Dept of Cardio-Thoracic and Respiratory Science, Second Univ of Naples, Napoli, Italy; 1 Center for Functionally Integrative Neuroscience, Aarhus Univ, Aarhus, Denmark; 2 Biogem, Ariano Irpino, Italy.

**Background:** Theoretical models have shown that the blood-flow within a glomerulus may be heterogeneous and that flow heterogeneity may affect the ultrafiltration coefficient and thus GFR. The aim of this study is to provide experimental data to test these model predictions by measuring glomerular capillary flow velocities by in vivo 2-photon microscopy.

**Methods:** Male Munich-Wistar rats were intubated, anesthetized with isoflurane, and mechanically ventilated. Blood pressure and heart-rate were monitored. The left kidney was externalized and the rat placed in the 2-photon microscope. Blood plasma was labeled by i.v. injection of 0.2 mg oxytetracycline/kg. Longitudinal lines in the lumen of capillaries in superficial glomeruli were scanned at a frequency of >700 Hz. The axial movement of single blood cells was measured. 308 different capillaries were analyzed in 17 glomeruli from 5 different rats.

**Results:** Blood cell velocity was 2.99 mm/s ± 0.54. A Gaussian distribution and a Gamma-distribution were fitted to data from 13 glomeruli in which >12 capillaries were studied. C-tests (p = 0.05) showed 5 of 13 datasets not to follow a Gaussian distribution and 1 of 13 not to follow a Gamma-distribution. The data from all 308 capillaries normalized to the mean of the respective glomerulus did not follow a Gaussian distribution (p < 0.05). The Gamma-distribution allows an asymmetrical distribution around the mean and provided the best description.

**Conclusions:** This study provides experimental evidence of heterogeneity and an asymmetrical distribution of blood cell velocity in glomerular capillaries. This new experimental evidence calls for refinement of current models of glomerular blood flow heterogeneity and invokes the possibility to investigate the potential regulatory control of the ultrafiltration coefficient by regulation of capillary flow heterogeneity, e.g. by the activity of mesangial cells.

**Funding:** Government Support - Non-U.S.

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**SA-PO356**

**Assessment of Exosomes Derived from Mesangial Cells Stimulated with High Glucose**

Antonio S. Novoa, 1 Fernanda Teixeira Borges, 1 Marcus Dias, 1, 2 Mirian A. Boim. 1, 2 Medicine, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; 1 CIPE - Centro Internacional de Pesquisa, A.C. Camargo Cancer Center, Sao Paulo, SP, Brazil.

**Background:** Exosomes and microvesicles (MV) are extracellular vesicles (EV) that are released by cells and contain substances such as proteins and nucleic acids such as microRNAs (miRNA). This study aimed to ascertain the role of exosomes and MV secreted by human mesangial cells (MC), a cell type involved in glomerular diseases, including IgA nephropathy (IgAN). Platelet-derived growth factor (PDGF) is a potent stimulator of MC, activating multiple signaling pathways associated with proliferation of MC. Our global kincrome profiling revealed that activity of multiple kinases in MC increased after PDGF stimulation, including tyrosine kinase Axl. As there is limited information on the association of PDGF signaling and activation of Axl in human MC, we studied details of Axl involvement in human MC stimulated by PDGF.

**Methods:** MC were obtained from a commercial source or isolated from biopsy samples of patients with IgAN or other glomerular diseases. Quiescent primary human MC were stimulated by PDGF AB in the presence or absence of different inhibitors. MC lysates were analyzed by global tyrosine-kinome profiling using PamStation®12 platform and Western blotting. MC proliferation was measured by BrdU incorporation. The expression and distribution of Axl in MC were assessed by immunofluorescence.

**Results:** Tyrosine-kinome profiling indicated that PDGF AB increased Tyro3, Abl, and Ltk kinase activities. Further data analyses predicted Axl as one of the key upstream kinases activated in PDGF-AB-stimulated MC. We found that Axl was activated in all tested primary human MC. PDGF AB stimulated proliferation of MCs; this effect was inhibited by Axl-specific inhibitor R428. Signaling studies revealed that PDGF AB increased phosphorylation of multiple signaling proteins, including Axl, PDGFR-β, Akt1, and ERK1/2. R428 significantly inhibited phosphorylation of Axl and Axl1, and, to a lesser extent, also of ERK1/2 and PDGFR-β. MEK1/2 inhibitor U0126 and PI3K inhibitor LY294002 did not affect phosphorylation of Axl.

**Conclusions:** Axl is involved in PDGF-induced proliferation of cultured MC through multiple signaling pathways. Targeting Axl may provide a new therapeutic strategy for IgAN.

**Funding:** Government Support - Non-U.S.

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**SA-PO358**

**Different Effects and Mechanisms of Prostaglandin E2 Receptor Subtypes EP1, EP4 in TGF-β1-Induced Mesangial Cell Injury**

Chen Xiao Lan, 1, 2 Yuan Li, 1 2 Affiliated Hospital of Nantong Univ; 2 Affiliated Hospital of Nantong Univ.

**Background:** To study effects of prostaglandin E2 receptor subtypes 1 and 4 (EP1 and EP4) in mesangial cell injury by transforming growth factor -β1 (TGF-β1) and relevant signaling pathways.


**Results:** 1. After TGF-β1 stimulation, expression of FN and CTGF increased; the expression of FN and CTGF in Group EP2KO increased; the expression of FN and CTGF in EP4KO decreased; 2. after TGF-β1 stimulation, the Smad3 phosphorylation level in EP2KO increased; while the Smad3 phosphorylation level markedly decreased in EP4KO; 3. the PGE2 level of WT mesangial cell increased at 12h after TGF-β1 treatment; 5. the AML-1 phosphorylation in EP2KO was less than that of the control; PKA activity obviously declined; the PGE2 content in EP4KO after stimulation with TGF-β1, the PGE2 content obviously declined; PKC activity increased; 6. ERK inhibitor blocks the function caused by agonist EP4; while PKA inhibitor blocks the inhibition function of agonist EP2.

**Conclusions:** EP2 and EP4 have different regulating effects on injury and renal fibrosis of mesangial cells: EP2 receptor mediated PGE2 induced up-regulation of the level of cAMP and PKA activity, so as to inhibit transduction effects of TGF-β1/IgA3 pathway and reduced the occurrence of injury and fibrosis of mesangial cell; while EP4 may mediate the promoting effect of mesangial cell injury induced by TGF-β1 by activating phosphorylation ERK pathway, resulting in regulating effects different from that of EP2.

**Funding:** Government Support - Non-U.S.
Characterization of Circulating APOL1 Complexes and Their Kidney Distribution in African Americans

**Background:** The apolipoprotein L1 gene (APOL1) G1 and G2 renal-risk variants associate with non-diabetic nephropathy and cardiovascular disease in African Americans (AAs). Although substantial APOL1 protein is present in the circulation, with enrichment in podocytes compared to other renal cells, little is known about circulating APOL1 protein.

**Methods:** Total serum APOL1 levels were examined by Western blot in a cohort of healthy AAs who had a 1-year relative degree with kidney disease. APOL1 protein complexes were isolated from fast protein liquid chromatography (FPLC) peak fractions and characterized by proteomic analyses. Results were subsequently verified by co-immunoprecipitation and Western blot.

**Results:** No significant differences were detected in serum APOL1 protein concentration based on APOL1 genotypes. However, serum APOL1 protein is bound to other protein complexes. Non-denaturing gel electrophoresis and FPLC demonstrated that serum APOL1 protein existed in two non-overlapping peaks (12.2nm and 20.0nm in diameter, respectively). The smaller complex was labeled complex A and the larger complex B. Density gradient ultracentrifugation and agarose gel electrophoresis confirmed that neither APOL1 protein complex was associated with HDL or LDL cholesterol. The exposure of APOL1 complex A surface epitopes appeared to be altered by G1/G2 renal-risk variants based on avicabeadic specificity to a monoclonal antibody from a non-G1/G2 associated immunogen (p=0.01). APOL1, haptoglobin-related protein (HPR), and complement C3 were present in APOL1 complex A. APOL1, HPR, IgM, and fibronectin were present in APOL1 complex B. In APOL1 complex A, HPR-α was more abundant in those with G1 and G2 renal-risk variants, relative to G0 (GENMOD p=0.04, total N=12). Serum HPR-α was only present in APOL1 complexes. Small amounts of HPR protein were detected in renal tubule cells but not glomeruli, whereas HPR mRNA was absent in the kidney.

**Conclusions:** Results provide unique insights on the composition of circulating APOL1 complexes. The role of circulating APOL1 in kidney and cardiovascular disease in AAs requires further investigation.

**Funding:** NIDDK Support

Deep Mapping of the Native Mouse Podocyte Proteome

**Background:** The entirety of proteins expressed within a podocyte is still not known.

**Methods:** We performed mass spectrometry based absolute and relative quantification of the proteome of FACS-sorted native mouse podocytes.

**Results:** We resolved the podocyte proteome at a near-comprehensive resolution (more than 8000 identified proteins). Absolute copy numbers of proteins correlated with copy numbers obtained from deep-sequencing transcriptomic analysis. The dataset indicates agreement between transcriptome and proteome regarding expression of proteins which are mutated in hereditary forms of proteinuria and FSGS in humans. 541 proteins were enriched within podocytes at very high ratios and significance. This study suggests that the podocyte is not only target to inflammatory stimuli such as TNFalpha and IFN gamma, but also unanticipated other stimuli. In addition, this study delineates podocyte enriched tyrosine kinases, a few of these are drugable. Protein domains significantly enriched in podocyte proteins comprise not only PDZ and Fn3 domains, but also i-set domain, an adhesion domain. The majority of podocyte specific proteins also stain positive for filaments in human samples, with a weak correlation between staining intensity and absolute protein abundance measured by MS/MS.

**Conclusions:** This initial, near comprehensive draft of the podocyte proteome reveals untapped molecules and mechanisms. This dataset will be of benefit to understand podocyte physiology, pathobiology and develop potential therapeutic strategies.

Maternal Obesity Is a Significant Risk Factor for the Development of Diabetic Nephropathy

**Background:** Our previous studies have shown that maternal obesity is associated with increased proteinuria in the offspring. We hypothesised that a second-hit such as diabetes may further exacerbate diabetic nephropathy in offspring exposed to maternal obesity.

**Methods:** Female C57Bl6 mice were fed either normal or high-fat diet (HFD) for 6 weeks prior to pregnancy, during pregnancy and weaning and their offspring were weaned to chow diet or HFD. At Week 8, the male offspring were randomized to streptozotocin (STZ) 55mg/kg/day for five consecutive days. 100 mg/kg once or placebo. Weight and glucose levels were measured fortnightly. 24 h urine collection was performed at Week 20 and 30. The kidneys were harvested at Week 32. The renal structure was observed. Serum levels of proinflammatory, prooxidative and oxidative stress markers were measured by real time PCR and confirmed with protein quantification with Western blot and/or immunohistochemistry.

**Results:** Offspring of obese mothers had increased fat deposition. Diabetic offspring had reduced weight gain, hyperglycaemia, glycosuria and microalbuminuria. Urinary albumin levels in offspring were highest in offspring of obese mothers exposed to 5 days of STZ. The kidneys of the offspring exposed to maternal obesity and induced with diabetes had increased structural damage, renal fibrosis and increased inflammatory changes and markers of oxidative stress when compared to the kidneys of diabetic offspring of normal weight mothers. There was significant intrarenal lipid deposition in obese offspring, exacerbated by maternal obesity and diabetes.

**Conclusions:** Offspring exposure to maternal obesity accelerates the severity of damage to the kidney caused by diabetes. Fetal programming of renal inflammation and oxidative stress may be a key component to the accelerated risk. Offspring diet has a powerful effect on renal outcome.

**Funding:** Government Support - Non-U.S.

Leucine-Rich Glycoprotein 1 : A Candidate Biomarker for Early Renal Function Decline in Type 2 Diabetes

**Background:** Patients with type 2 diabetes were recruited into training (n=56) and independent, non-overlapping test (n=37) groups (median baseline eGFR = 80.3 ± 29.5 ml/min/1.73m²). LRG1 was measured in spot urine collections by ELISA, and performance was assessed as area under the receiver operating characteristic curve (AUC) with adjustment for clinical covariates of DKD.

**Methods:** Patients with type 2 diabetes were recruited into training (n=56) and independent, non-overlapping test (n=37) groups (median baseline eGFR = 80.3 ± 29.5 ml/min/1.73m²). LRG1 was measured in spot urine collections by ELISA, and performance was assessed as area under the receiver operating characteristic curve (AUC) with adjustment for clinical covariates of DKD.

**Results:** Urine LRG1 was associated inversely with eGFR (r = −0.546, P=0.001) and positively with ACR (r = 0.283, P = 0.034). The AUC of LRG1 for identifying participants with baseline eGFR 90 – 60 was 0.815 ± 0.103, in contrast, the AUC of the albumin/creatinine ratio was 0.465 ± 0.093 (P < 0.01 versus LRG1). Adjustment for age, sex, race, duration of diabetes, and HbA1c, did not alter the AUC for LRG1, and these results were replicated in the test group. In participants with eGFR > 60/ml/min/1.73m² at baseline, LRG1 predicted a 5-year outcome of eGFR < 60 or ESRD better than ACR (0.782 ± 0.085, P = 0.01 versus ACR, 0.520 ± 0.119).

**Conclusions:** Taken together, these results suggest LRG1 may identify patients with early renal function decline more accurately than ACR. Evaluation of LRG1 in prospective cohorts of type 2 diabetes may lead to a better biomarker for identifying and monitoring DKD.

**Funding:** Other NIH Support - NIH RO1 DK 096549

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

**Underline represents presenting author.**
SA-PO364

A Longitudinal Study on Kidney Function, Pathology, and Multiple Urinary Biomarkers in ZSF1 Rat Model of Type II Diabetic Nephropathy  
Kidney Research, Abivie, North Chicago, IL.

Background: Obese ZSF1 rats display many clinical features of human type II diabetic nephropathy (DN). To further understand this model and to identify relevant biomarkers of disease progression, we followed the development of DN by measuring glomerular filtration rate (mgFR), histopathology, and a variety of urine and tissue biomarkers over 24 weeks after uninephrectomy (Unx). Correlations between mgFR and individual urinary biomarkers were assessed.

Methods: Male rats (9-week old) underwent either a sham or Unx (right kidney) surgery and were fed a high carbohydrate diet. GFR was measured by transdermal clearance of FITC-sinistrin. Urine samples were collected every 2-4 weeks for biomarker analysis, and renal tissue was examined for collagen deposition as well as for the levels of key inflammatory and fibrogenic genes.

Results: Kidney hypertrophy was observed (2-3 fold increase in mgFR) in obese rats 2-week after surgery lasting until week 4. The mgFR subsequently declined over time in these rats and was 2-fold lower than control rats by end of study. Compared to lean rats, obese rats also demonstrated time-dependent increases in urinary excretion of protein, KIM-1, L-FABP, NGAL, Cystatin C, Clustatin, Beta2-microglobulin, alpha1-acid glycoprotein, VEGF, MCP-1, TIMP-1, Collagen IV, TGF-b1, and TGF-b2. A significant correlation was found between mgFR and a number of urinary biomarkers (L-FABP, KIM-1, TIMP-1, Clustatin, Cystatin C, and TGF-b2). Kidney fibrosis was significantly elevated by week 12 post surgery and continued to expand in the following weeks. Unx increased the weight and glomerulosclerosis of the remaining kidney and accelerated the decline of mgFR in obese rats during late weeks of observation.

Conclusions: ZSF1 rats showed a progressive increase of fibrosis and loss of mgFR over the 24-week study. A number of urinary biomarkers demonstrated a strong inverse correlation with the time-dependent changes in mgFR. Additionally, Unx significantly increased glomerulosclerosis and loss of GFR in obese rats.

SA-PO365

Haptoglobin 2-2 Genotype Is Associated with Decreased Levels of Vitamin D Receptor (VDR), Klotho and Accelerated Renal Apoptosis in Mice and Humans with Diabetic Nephropathy  
Farid N. Makhouil,1 Farber Evgeny,2 Nadia Thawho,3 Andy Levy,4 Inbal Dahan.5  
Diabetic Nephropathy Lab, Baruch-Paduch Porvus M. Center, Lower Galilee, Israel; 5Nephrology, Faculty of Medicine In Galilee Bar Ilan Univ, Israel; 6Vascular Medicine, Technion, Haifa.

Background: Haptoglobin (Hp) is an antioxidant protein by its ability to bind free hemoglobin (Hb) and prevents heme-iron mediated oxidation. Diabetic mice & humans with different Hp genotype (1-1, 2-2) have a different susceptibility to develop Diabetic Nephropathy (DN) due to impaired Hb clearance and increased iron deposits in the lysosomes of the kidney proximal tubules (PCT). This leading to increased renal oxidative stress and cell damage. Our study proposed a molecular mechanism explaining the influence of Hp genotype, klotho expression on 1-α hydroxylase and active vitamin D/VDR in DN patients.

Methods: Slides from kidney biopsies of DN patients and mice with different Hp genotype (1-1, 2-2) were subjected to Immunohistochemistry staining of iron modified with DAB method, klotho, active caspase 3, vitamin D receptor (VDR) and 1-α hydroxylase, using specific antibodies. Blood samples to Haptoglobin test and ELISA DAB method, klotho, active caspase 3, vitamin D receptor (VDR) and 1-α hydroxylase, were used to measure Vitamin D levels.

Results: There were significant increased iron deposits in the renal PCT of Hp-2/2 mice and patients there was a significant increase expression of active caspase-3 staining that was accompanied with decreased renal expression of VDR, 1α hydroxylase and klotho levels.

Conclusions: Hp 2-2 genotype associated with increased iron deposits and high levels of PCT apoptosis Decreased levels of the anti oxidant klotho and VDR in the renal PCT. We propose a molecular mechanism explaining the influence of Hp genotype and klotho expression on renal PCT apoptosis in DN patients. These results provide new insights into the role of Klotho and VDR expression on the pathogenesis of DN in patients with Hp-2-2 genotype.

SA-PO366

Resistance Exercise Training Prevents Kidney Hypertrophy and Increases the Biogenesis Mitochondrial in Diabetic Rats  
Luciana Jorge,1 Kleiton Augusto Santos Silva,2 Rafael Luiz,2 Rodolfo Rosseto Rampaso,1 Janaina Paulini Aguair,2 Nestor Schor.1  
Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil; 2Molecular Biology, Univ of Utah, Salt Lake City, UT.

Background: Diabetic nephropathy(DN) is a progressive complication arising from diabetes. kidney cell response to injury includes cell division, cell hypertrophy and apoptosis. Increasing evidence indicates that the disruption of mitochondrial bioenergetics and structural change in the kidney may be important in the development and progression of DN. Therefore, is fundamental the understand of a non pharmacological intervention as exercise training to prevent those complications. We investigated the effect of resistance training(RT) on the DN pathogenesis.

Methods: Male Wistar rats were divided into control(C), control trained(CT),diabetic(D) and diabetic trained (DT). DM was induced by STZ. Trained groups were submitted to a resistance exercise training on Ladder climb (8wk). Urinary volume and proteinuria were evaluated.Tissue weight/tibial length ratio was used as kidney hypertrophic index. Expression of P-Akt,P-Mtor,P-AMPK and Mfn2 protein was evaluated by western blotting.

Results: RT improved renal parameters in DT group show a decreased urinary volume(160±160;120±120;13±13;14±14;proteinuria(45±32;32;17;7 mg/24h) (p<0.05).Diabetes resulted in increased hypertrophic index (50%) and RT prevented it. Renal expression of PAMPK and Mfn2 was reduced in D group and RT normalize this expression(p<0.05). Moreover, the renal expression of PAKT and PmTOR were increased in the DM and the RT influence on it(p<0.05). Histological analysis showed glomerular hypertrophy in D and RT prevent this complication.

Conclusions: RT attenuated progression of diabetic nephropathy; Those improvements could be a result of increased AMPK/Mfn2 pathway, an important pathway to biogenesis mitochondrial; and inhibition of AKT/mTOR pathway, responsible for hypertrophic response, demonstrating that those complications were prevented by exercise training. Our findings demonstrated that RT is an important approach to avoid, both molecular and functional complications in diabetic kidney.Funds from FAPESP,CNPq and CAPES.

SA-PO367

Aerobic Exercise Training Improves Proteinuria and Renal Inflammatory Factors in Rats with Diabetic Nephropathy  
Rodolfo Rosseto Rampasso, Rafael Luiz, Kleiton Augusto Santos Silva, Luciana Jorge, Edison Andrade Pessoa, Mario Luis Ribeiro Cesaretti, Nestor Schor. Nephrology, UNIFESP, SP, Brazil.

Background: The objective of this study was to evaluate the effects of aerobic exercise training in controlling the progression of diabetic nephropathy, inflammatory factors, and its possible renoprotective effects.

Methods: Adult male Wistar rats/4 groups, n=8/group: Sedentary controls (C-SED), Diabetics+Sedentary (DM-SED), Diabetes+Exercise (DM-EXE) and control exercise (C-EXE). Diabetes was induced with STZ,50 mg/kg. The exercise training were conducted on a treadmill 60min/day, 5 days/week/8 weeks. Weekly certain, maximal exercise test(set at 65-70% of MEtest). Glycemia after post 24 education(24 glycemiapt), MEtest, creatinine clearance(BW)(CCRWB), arterial pressure(AP), proteinuria(protein), renal inflammatory factors IL-6, IL-10 and TNF-a were measured. Data as mean ± SD.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C-SED</th>
<th>DM-SED</th>
<th>DM-EXE</th>
<th>C-EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycemiapt (mg/dl)</td>
<td>103±2.03</td>
<td>551±7.03* #</td>
<td>491±5.30* &amp;</td>
<td>83±2.57</td>
</tr>
<tr>
<td>uProtein (mg/24h)</td>
<td>17±0.88</td>
<td>46±2.05* #</td>
<td>18±0.72</td>
<td>16±1.99</td>
</tr>
<tr>
<td>Cr/Creatinine (mg/dl)</td>
<td>5.65±0.66</td>
<td>5.92±0.43</td>
<td>4.9±0.37</td>
<td>4.2±0.29</td>
</tr>
<tr>
<td>AP (umol/l)</td>
<td>122±1.89</td>
<td>133.88±1.79* #</td>
<td>122±1.35</td>
<td>121±1.12</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>455±6.0</td>
<td>236±4.41* #</td>
<td>324±3.94* &amp;</td>
<td>387±8.71</td>
</tr>
<tr>
<td>MfTest (m/min)</td>
<td>32.3±0.49</td>
<td>19.5±0.57* #</td>
<td>35.1±0.97</td>
<td>37.5±0.57</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>541±98</td>
<td>993±40* #</td>
<td>768±74* &amp;</td>
<td>391±22</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>545±86</td>
<td>876±34* &amp;</td>
<td>654±31* &amp;</td>
<td>453±28</td>
</tr>
<tr>
<td>TNF-a (pg/ml)</td>
<td>3.0±0.4</td>
<td>5.1±0.76* #</td>
<td>4.08±0.22* &amp;</td>
<td>2.32±0.51</td>
</tr>
</tbody>
</table>

Conclusions: Reductions in blood glucose and AP ~11% comparing DM-EXE vs DM-SED. The DM-EXE controlled weight loss ~40% compared to DM-SED, but did not prevent change in CCRWB with this protocol. However, the effect was surprisingly observed EXE reduction in both excretion through uPro ~60% and ~25% in MD-inflammatory factors comparing SED vs DM-EXE. Preliminary data suggests that aerobic exercise can reduce proteinuria and inflammatory factors in diabetic animals and hence reduce the potential effects caused by diabetic nephropathy and could reduce the progression of renal failure.
Inhibition of miR-25 Processing Mediated by MeCP2 Phosphorylated by HIPK2 Can Uregulate NOX4 in Early Diabetic Nephropathy

**Background:** Altered microRNA (miR) levels play key roles in the pathogenesis of diabetic nephropathy (DN), but it is unclear if miR processing is involved. Phosphorylated methyl-CpG binding protein 2 (p-MeCP2), known to act as a transcriptional repressor, was recently reported to suppress the processing of several miRs. Homeo-domain interacting protein kinase2 (HIPK2) can bind to and phosphorylate MeCP2. However, it is not known if MeCP2 and HIPK2 are involved in processing and expression of candidate miRs in DN.

**Methods:** p-MeCP2 and HIPK2 staining in kidney sections from 4-week streptozotocin (STZ) injected diabetic and control mice, was studied by immunohistochemistry. Protein, miRNA and miR levels were examined by Western blotting (WB) or RT-qPCRs in TGf-b1- or high glucose (HG)-treated mouse mesangial cells (MMCs).

**Results:** p-MeCP2 and HIPK2 immunostaining, and their protein levels were significantly higher in renal glomeruli (but not cortex) of STZ mice than control. Moreover, Seven in Absentia Homolog 1 (SIAH1), which mediates proteasomal degradation of HIPK2, was decreased in STZ mice compared with control. Among several regulated miRs, miR-25 and -93 levels were significantly decreased in STZ mice relative to control. The precursors of miR-25 and -93 were also significantly decreased in STZ mice, while conversely, NADPH oxidase4 (NOX4), a target of miR-25 that is associated with renal fibrosis and DN, was significantly increased in STZ mice. Protein levels of p-MeCP2 and HIPK2 were also increased in vitro in TGf-b1-or HG-treated MMCs compared to control. Moreover, miRNA levels of the genes mentioned above in vivo were similarly regulated in MMCs in vitro, although only miR-25 and its precursor were significantly decreased in the treated MMCs.

**Conclusions:** These data suggested that podocyte injury is associated with defective autophagy level under high glucose condition. Ursolic acid could reduce podocyte injury with 3-MA treatment at 8 weeks and with DA1229 at 12 weeks in diabetic mice. However, activity of serum DPPIV was not different from each other. Activity of serum DPPIV combined treatment with DA1229 or LC158809 significantly decreased accumulation of ECM protein, TLR4 and oxidative stress markers were not different from each other. Activity of serum DPPIV was significantly reduced with DA1229. 24h albuminuria significantly decreased with LC158809 treatment at 8 weeks and with DA1229 at 12 weeks in diabetic mice. However, no additive effect on albuminuria was observed with combined treatment. Administration of DA1229 or LC158809 significantly decreased accumulation of ECM protein, TLR4 and NOX4 expressions in glomeruli. Nephropathy was observed in the group with untreated albuminuria. Urinary excretion of nephrin was increased in diabetic mice and was decreased in combined treatment with DA1229 and LC158809. In vitro, DPPIV was expressed on the surface of podocytes. The expression of podocyte associated protein and endogenous accumulation of LC3. autophasogosomes were observed using electron microscopy.

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**710A**
podocyte membrane and its expression was activated by angiotensin-II. Nephrin expression in cultured podocyte was attenuated by high glucose and angiotensin-II. This attenuation was recovered with DA1229 treatment, but not with other DPPIV inhibitors.

**Conclusions:** Our data suggest that renoprotective effects of DA1229 in experimental diabetic mice might be associated with protective effect of podocyte injury. DA1229 might be a potential therapeutic agent to slow the progression of diabetic nephropathy.

**SA-PO373**

**PBI-4425, A Novel Anti-Inflammatory/Fibrotic Compound, Improves Kidney Function and Structure in the Diabetic db/db Mouse Model**


**Background:** Kidney disease associated with diabetes mellitus is a major health problem worldwide. Glomerular injury plays a pivotal role in the development of diabetic nephropathy. PBI-4425 possesses a pleiotropic mechanism of action with anti-inflammatory, antioxidant and anti-fibrotic properties. The aim of this study was to investigate the protective effect of PBI-4425 on kidney function and structure in uninephrectomized (NX) diabetic (db/db) mice.

**Methods:** Total nephrectomy of the right kidney was performed on day 0 and animals were treated with vehicle or PBI-4425 (100 mg/kg, oral once a day) from day 1 through 105. Kidney function (GFR), kidney mesangial lesions, modulation of gene expression, and serum cytokines were investigated.

**Results:** GFR assessed by inulin clearance was significantly reduced in NX-db/db mice compared to NX-C57BL/6j negative control mice, and PBI-4425 treatment significantly improved GFR. As shown by PAS staining, NX-db/db mice had larger glomeruli with increased mesangial lesions scores which were significantly reduced by PBI-4425 treatment. Gene expression of inflammation, fibrosis, oxidative stress, and extracellular matrix remodeling markers were assessed. Kidney MCP-1, IL-6, Collagen I, NOS, MMP2, and Timp1 mRNA expression were markedly increased in NX-db/db mice, and PBI-4425 treatment induced a significant decrease of these markers. Glomerular response to injury was accompanied by activation of kidney development-related genes, such as glomerular epithelial protein 1 (GLEPP1); expression of GLEPP1 was significantly increased in NX-db/db mice, and restored to the negative control level following treatment with PBI-4425. Moreover, PBI-4425 significantly reduced serum pro-inflammatory cytokines IL-6, IL-1β, IL-12(p70), as well as THP-1-type pro-inflammatory cytokine IL-9.

**Conclusions:** These results suggest that PBI-4425 offers the potential as a novel therapy for diabetic nephropathy by improving kidney function and structure, and reducing pro-inflammatory and pro-fibrotic markers.

**SA-PO374**

**The Effect of Nox Inhibitor APX-15 on Diabetic Kidney Disease**

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**Background:** Excess reactive oxygen species generated by NADPH oxidases (Nox) have been implicated in the inflammatory and fibrotic processes of chronic kidney disease. Recent studies have suggested the importance of renal Nox in the progression of diabetic nephropathy. Therefore, we investigated the effect of a novel NOX-inhibitor APX-15 on diabetic nephropathy in an experimental model of type 2 diabetic mice.

**Methods:** 8 to 10 week old db/m and db/db mice were treated with APX-15 for 12 weeks. APX-15 was administered by oral gavage at a dose of 60mg/kg/day. To compare the effects of APX-15 with a selective Nox inhibitor, db/db mice were treated with GKT136901 according to same protocol.

**Results:** APX-15 significantly improved insulin resistance in diabetic mice similar to GKT136901. Oxidative stress measured by plasma 8-isoprostane level was decreased in APX-15 group compared to diabetic control. All lipid profiles, both in plasma and tissues (kidney, fat, liver) improved with Nox inhibition. Nox mRNA expressions in adipose tissue (Nox1, Nox2) and in kidney tissue (Nox4) were downregulated and Nox protein expressions were decreased with APX-15. 24 hour urinary albumin excretion was reduced and creatinine clearance was preserved with APX-15. In diabetic kidney, structural changes were notably attenuated with APX-15. Importantly, mesangial expansion was significantly improved with APX-15, but not with GSK 136901. Kidney PAI-1 and TGF-β expressions were decreased and nephrin expression increased in both APX-15 and GKT136901 groups compared to diabetic control. Additionally, F4/80 infiltrations in the adipose tissue and the kidney were decreased with APX-15.

**Conclusions:** Our findings suggest that APX-15 may have a better renoprotective effect compared to selective inhibitor GKT136901 in experimental animal model of diabetic nephropathy. Broad Nox inhibition with APX-15 might be a promising therapy for diabetic nephropathy.
Methods: Male db/db mice at 8 weeks of age were fed resveratrol (20 mg/kg/day) via gavage for 12 weeks. Serum and renal tissue were obtained to analyze for changes in metabolic parameters, molecular levels and renal structure.

Results: Resveratrol treatment showed favorable effects on albuminuria, glomerular matrix expansion and inflammatory cell infiltration. Increased expressions of AdipoR1 and AdipoR2 were observed with increased phosphorylated AMPK and PPAR-α level. It also ameliorated free fatty acid and triacylglycerol accumulation in the kidney which was related to increases in the phosphorylation of AMPK and the activation of SIRT1-PGC-1α signaling and of the key downstream effectors, the PPARs. Resveratrol increased the expression of the anti-inflammatory/anti-fibrotic activator and converted the circadian rhythm of blood pressure from a non-dipper to dipper pattern. It improved glucose metabolism. Luseogliflozin also significantly decreased blood pressure (−1.6 and −132.0 mmHg, P=0.04 and P<0.01, respectively) and urine protein (−0.7 and −148.0 mg/dL), or (iv) luseogliflozin + diuretics for 5 weeks (n = 6 for each group). Blood pressure and glucose metabolism were evaluated by a telemetry system and oral glucose tolerance test, respectively.

Results: Vehicle-treated SHRcp developed non-dipper type hypertension (dark-light period mean arterial pressure (MAP) 148.0±7.0 and 148.0±7.0 mmHg, respectively, P<0.01), which were associated with a significant increase in urininary excretion of sodium. Addition of diuretics did not influence luseogliflozin-induced improvement of glucose metabolism and circadian rhythm of blood pressure in SHRcp.

Conclusions: These data suggest that a SGLT2 inhibitor elicits its beneficial effects on glucose metabolism and hypertension in subjects with metabolic syndrome undergoing treatment with ACE inhibitors.

Funding: Other NIH Support - the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (KAKENHI), Pharmaceutical Company Support - Taisho-Toyama Pharm.

SA-PO380

SGLT2 Inhibition Slows the Progression of Diabetic Nephropathy in the db/db Mouse
Li Tang, Yuanyuan Wu, Yufeng Huang. Fibrosis Research Laboratory, Div of Nephropathy, Univ of Utah, Salt Lake City, UT.

Background: It has been shown that SGLT2 inhibitor not only enhanced renal glucose excretion and lowered blood glucose (BG) but also reduced albuminuria in patients with Type 2 diabetes (T2DM). However, the renoprotective effect of SGLT2 inhibition in diabetes has not fully established.

Methods: This study sought to determine whether dapagliflozin, a selective SGLT2 inhibitor, could slow the progression of glomerulosclerosis in the uninephrectomized db/db mouse, a model of T2DM.

Results: Untreated uninephrectomized db/db mice developed progressive albuminuria and glomerulosclerosis between wks 18 and 22, associated with increased renal expression of TGFβ1, PAI-1, type IV collagen and fibronectin. Treatment with dapagliflozin (1mg/kg/d) via gel diet from wks 18 to 22 did not affect body weight but reduced BG from 573.3±21.7 to 373.1±45.52 mg/dL, P<0.05) and HbA1c levels. Of note, treatment with dapagliflozin reduced the increase in albuminuria and markers of glomerulosclerosis seen in db/db mice between wks 18 to 22. Renal expressions of NF-kBp67, MCP-1, Nox4, Nox2, and p47phox and urinary TBARS levels, the markers of renal inflammation and oxidative stress, were increased during disease progression in db/db mice. Treatment with dapagliflozin reduced these markers. In addition, db/db mice had markedly increased daily water intake, urinary output, urinary sodium and potassium excretion but decreased urinary osmolality. Dapagliflozin had no effects on these measurements. Interestingly, dapagliflozin

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ameliorated diabetes-induced glomerular hyperfiltration determined by elevated creatinine clearance rates (2.44±0.55 ml/min in treated db/db vs. 1.72±0.63 ml/min in db/db) and caused a significant reduction in renal RAS activity determined by urinary aldosterone levels (45.5±4.93 vs. 60.9±4.01, p<0.05).

Conclusions: These results suggest that SGLT2 inhibitor not only reduces albuminuria but also leads to regression in the glomerulosclerosis resulting from T2DM by improving hyperglycemia and renal inflammation and oxidative stress. Decreasing glomerular hyperfiltration and negatively regulating renal RAS activity by SGLT2 inhibitor may be also renoprotective.

Funding: Pharmaceutical Company Support - AstraZeneca R&D

SA-PO384

Background: SGLT2 inhibitors have recently been approved in type 2 diabetes and long-term clinical trials are ongoing to further establish efficacy and safety. Humans with familial renal glycosuria due to mutations in SGLT2 do not show signs of general renal tubule dysfunction or other pathological changes, and they seem to have normal life expectancies. Here we compared the phenotype of non-diabetic aged male mice (at 24 months) that lack SGLT2 (Sgl2−/−) with their wild-type littermates (WT).

Methods: In awake mice, blood pressure (BP) and heart rate (HR) was measured by an ultrasonic tail-cuff system and GFR by FITC-inulin plasma eliminations kinetics.

Results: Out of initially 11 Sgl2−/− and 14 WT, 2 mice per genotype died for unknown reasons before reaching an age of 24 months; thus 9 Sgl2−/− and 12 WT mice were analyzed. Consistent with results previously reported in young adult mice (3-5 months): aged Sgl2−/− and WT showed similar blood pressure (133±6.0 vs. 132±10.9 mm Hg), glucose blood (105±6 vs. 116±10 mg/dl), and GFR (329±36 vs. 370±20 ml/min); Sgl2−/− had higher urinary glucose excretion (381±71 vs. 5±1 µmol/ml creatinine) associated with higher intake of food (3.8±0.1 vs. 3.2±0.1 g/day) and fluid (9.8±0.2 vs. 5.1±0.1 ml/day) and smaller adipocytes in subcutaneous and epididymal fat tissue (4790±446 vs 6348±130 and 809±390 vs 11811±778 µm² in each P<0.01); urine pH was similar (6.0±1 vs. 6.5±0.2) and no bacterial growth detected in bladder urine. Different from previous findings in young adult mice: aged Sgl2−/− had modestly higher kidney weight (15.4±0.9 vs 12.6±0.4 g/body weight), BP (105±2 vs 93±1 mm Hg) and HR (660±7 vs 625±9 1/min) than WT and lower hematocrit (38±1±0 vs 41.3±0.4%) each P<0.01.

Conclusions: Aged Sgl2−/− mice show many of the expected phenotypes previously observed in young adult mice, and have preserved GFR and no evidence for ascending blood vessels. An increased kidney weight has been previously reported in 7.5 months old Sgl2−/− mice. Further analyses aim to better understand the latter findings and the observed modest changes in BP and hematocrit.

Funding: NIDDK Support

SA-PO385
Renal Secretion of the SGLT2 Inhibitor Empagliflozin and Rightward Shift in Its Glucosuric Response Curve in Mice Lacking OAT3 Yiling Fu,1 Akira Onishi,1 Panai Song,2 Falk Bernhard Batz,3 Eric W. Mayoux,Volker Vallon.1 1Div of Nephrology, UC San Diego & VA San Diego Healthcare System, La Jolla, CA; 2Boehringer Ingelheim, Biberach, Germany.

Background: SGLT2 inhibitors, like empagliflozin (EMPA), may reach their target in the brush border of the early proximal tubule through nephrone filtration and tubular secretion. The organic anion transporter OAT3 in the basolateral membrane of the proximal tubule contributes to secretion.

Methods: Renal H+-inulin clearance studies were performed in wild-type (WT) mice to characterize the renal handling of EMPA. EMPA was given in diet for 3 weeks (~30mg/kg body wt x day) i.p. bolus (10 mg/kg 1 hr before study)). EMPA was determined by LC/MS/MS. Mean fractional protein binding of empagliflozin in mouse plasma is constant over a wide range (up to ~50µM) at 88.1±1.0±0.5%. B) Metabolic cage studies were performed in mice lacking OAT3 and WT littermates (EMPA 0.3-30 mg/kg) or vehicle was applied i.p. bolus (10 mg/kg 1 hr before study)). EMPA was determined by LC/MS/MS. Mean fractional protein binding of empagliflozin in mouse plasma is constant over a wide range (up to ~50µM) at 88.1±1.0±0.5%. B) Metabolic cage studies were performed in mice lacking OAT3 and WT littermates (EMPA 0.3-30 mg/kg) or vehicle was applied i.p. bolus (10 mg/kg 1 hr before study)). EMPA was determined by LC/MS/MS. Mean fractional protein binding of empagliflozin in mouse plasma is constant over a wide range (up to ~50µM) at 88.1±1.0±0.5%. B) Metabolic cage studies were performed in mice lacking OAT3 and WT littermates (EMPA 0.3-30 mg/kg) or vehicle was applied i.p. bolus (10 mg/kg 1 hr before study)). EMPA was determined by LC/MS/MS. Mean fractional protein binding of empagliflozin in mouse plasma is constant over a wide range (up to ~50µM) at 88.1±1.0±0.5%. B) Metabolic cage studies were performed in mice lacking OAT3 and WT littermates (EMPA 0.3-30 mg/kg) or vehicle was applied i.p. bolus (10 mg/kg 1 hr before study)). EMPA was determined by LC/MS/MS.

Results: Comparing freely filtered and excreted amounts of EMPA revealed a fractional renal excretion of ~350-500% for free plasma concentrations in the range of 1-2 nM (with chromatographic delay in diet, which is close to the IC50 for mouse SGLT2) to 20-22 nM (with additional bolus application), indicating that 2/3 or more of the renal excretion of EMPA derived from renal secretion. B) OAT3−/− showed a small but significant rightward shift in the glucosuric response curve to EMPA (ED50 ~6.5 vs. 3 mg/kg in WT; with significantly lower glucosuria at 1.3, and 10 mg/kg (P<0.05), whereas vehicle (0.3 mg/kg and 30 mg/kg induced similar minimal and maximal glucosuria, respectively) (n=19-20/dose).

Conclusions: The SGLT2 inhibitor empagliflozin is secreted by the kidney; this may involve OAT3 in the early proximal tubule whose activity is a determinant of the acute glucosuric effect of EMPA.

Funding: NIDDK Support, Pharmaceutical Company Support - Boehringer Ingelheim

SA-PO386
SGLT Inhibition Significantly Increases Oxygen Consumption of the Medullary Thick Ascending: A Modeling Study Anna T. Layton, Volker Vallon, Aurelie Edwards.1 1Mathematics, Duke Univ; Durham, NC; 2Medicine and Pharmacology, Univ of California San Diego, La Jolla, CA; 3Centre National de la Recherche Scientifique, Paris, France.

Background: The objective of this study was to investigate how changes in sodium reabsorption in the proximal tubule affect oxygen (O2) consumption and the metabolic efficiency of the nephron.

Methods: To do so, we developed a detailed mathematical model of solute transport in a nephron of the rat kidney. Glucose is reabsorbed via sodium-glucose cotransporters (SGLTs) in the proximal tubule, which expresses the isoform SGLT2 in S1-S2 and the isoform SGLT1 in S3. We used the model to investigate the effect of inhibiting SGLT2, a novel treatment for reducing proximal tubule glucose uptake in diabetes, on renal Na+ transport and renal oxygen consumption (QO2).

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Results: Inhibiting SGLT2 shifts Na\(^+\)-transport to downstream nephron segments, possibly increasing their Q\(_{\text{m}}\). In particular concerns are the S3 segment and medullary thick ascending limb (mTAL), which are at risk for hypoxic injury. Dual SGLT1-SGLT2 inhibition protects the S3 segment, but could further reduce mTAL oxidation. Model simulations suggest that SGLT2 inhibition substantially increases S3 Q\(_{\text{m}}\). Together with elevated renal perfusion (mTALi) increase mTAL Q\(_{\text{m}}\). Additionally, we used the model to determine the optimal combination of SGLT1 and SGLT2 inhibition, in terms of suppressing tubular glucose uptake and maintaining sufficiently low S3 and mTAL Q\(_{\text{m}}\).

Conclusions: SGLT inhibition significantly increases oxygen consumption of the mTAL. This research was supported in part by NIH grant DK-89066.

Funding: NIDDK Support

SA-PO387

SGLT2 Expression Is Increased in Human Diabetic Nephropathy: SGLT2 Inhibition Decreases Renal Lipid Metabolism, Inflammation, and the Development of Nephropathy in Diabetic Mice

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Evgenia Dobrinshkikh,1
Almen Gnutz,1
Michal Herman-Eidelstein,1
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Jeffrey B. Kopp,1
A. Rosenberg,1
Moshie Levi,1
J. Univer of Colorado Denver; NIDDK; Rabin Medical Center; Univ of Warzburg.

Background: The renal sodium gradient dependent glucose transport protein SGLT2 expression is increased in renal biopsies from human subjects with diabetic nephropathy.

Methods: To determine the potential mechanisms of beneficial effects of SGLT2 inhibition in progression of diabetic renal disease we treated db/db mice with a selective SGLT2 inhibitor.

Results: We found that SGLT2 inhibition caused marked decreases in systolic blood pressure, kidney weight:body weight ratio, urinary albumin (745±3.8 mg/kg in db/db vs. 207±5 mg/kg in treated db/db, p<0.001) and urinary thromboxin A2-reacting substances (TBARS). SGLT2 inhibition also a) prevented renal lipid accumulation via inhibition of LPL, SCAD-1 and DGAT1, key enzymes that mediate fatty acid and triglyceride synthesis, b) decreased inflammation via inhibition of CD68 macrophage accumulation, and expression of p65, TLR4, MCP-1 and 1OPN, and c) increased CD73 and decreased adenosine A receptors. Among the factors associated with mesangial expansion, accumulation of extracellular matrix proteins fibronectin and type IV collagen, as well as loss of podocyte markers WT1 and synaptopodin, as determined by quantitative immunofluorescence microscopy.

Conclusions: In summary, our study showed that SGLT2 inhibition modulates renal lipid metabolism and inflammation and prevents the development of nephropathy in db/db mice.

Funding: Pharmaceutical Company Support - J&K

SA-PO388

Loss of Angiotensin-Converting Enzyme 2 Alters Glomerular Structure in Non Obese Diabetic Mice

Heleia Roca-1
Maria Jose Soler,1
Vanderbilt Univ.

Background: ACE2 has been shown to play an important role in diabetic nephropathy (DN). We studied renal morphology and kidney function in non-obese diabetic (NOD) female mice (with spontaneous autoimmune diabetes) carrying a deletion on ace2 gene (NOD.-/-.). We studied in WT and ACE2KO mice (C57BL6/J and FVB/N genetic backgrounds) that were rendered diabetic using STZ (2x150 mg/kg).

Methods: Treated female NOD.ACE2-/- mice (with spontaneous autoimmune diabetes) carrying a deletion of ace2 gene (NOD.-/-.). We studied renal morphology and kidney function in non-obese diabetic (NOD) female mice. Treated female NOD.ACE2-/- mice (with spontaneous autoimmune diabetes) carrying a deletion on ace2 gene (NOD.-/-.).

Results: Glomerular hypertrophy, mesangial matrix expansion and podocyte loss were found in female NOD.ACE2-/- mice. In diabetic NOD.ACE2-/- and NOD.ACE2+/- mice, there was a modest but significant reduction in podocyte number in diabetic NOD.ACE2-/- mice. These results suggested that ACE2 deletion worsens kidney injury in diabetic NOD mice.

Funding: Government Support - Non-U.S.

SA-PO389

Ace2 Deficiency Accenutated AngII-Induced Hypertension and Albuminuria in Diabetic Mice

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Background: Angiotensin-II (AngII) promote renal vasoconstriction, albuminuria, fibrosis, apoptosis and inflammation. ACE2 deficiency exacerbates hypertension in AngII-infused male mice. However, the effect of ACE2 deletion on diabetic and AngII-infused female mice has not been previously studied.

Methods: We evaluated the effect of AngII infusion in age matched C57BL/6 wild-type (WT) and ACE2KO streptozotocin (STZ)-induced female mice and their respective non-diabetic controls. At week 8 of follow-up, mice were anesthetized and micromops for AngII infusion and AngII were surgically implanted. Sham-operated (SHAM) mice were used as control groups. Study groups: WT-Control (CONT) + SHAM, WT-CONT + ANGII, WT-Diabetic (DB) + SHAM, WT-DB + ANGII, ACE2KO-CONT + SHAM, ACE2KO-CONT + ANGII, ACE2KO-DB + SHAM, ACE2KO-DB + ANGII. Blood glucose, body weight, kidney weight:body weight (KW/BW), heart weight:body weight (HW/BW), systolic blood pressure (SBP) and urinary albumin excretion (UAE) were studied.

Results: Hyperglycemia and reduced BW were observed in all groups given STZ. ACE2 deletion and AngII infusion suppressed a modest decrease in body weight in control and diabetic mice. Both, SHAM and AngII-infused ACE2KO diabetic mice showed higher HW/BW as compared to WT. AngII infusion significantly augmented HW/BW and SBP in control and diabetic ACE2KO mice as compared to non-infused mice. Diabetes and AngII infusion were accompanied by increased UAE in all groups. This increase was more pronounced in ACE2KO mice. Within AngII-infused groups, ACE2KO-CONT + ANGII and ACE2KO-DB + ANGII showed significantly higher HW/KW, SBP and UAE than WT-CONT + ANGII and WT-DB + ANGII.

Conclusions: Loss of ACE2 accentuated renal hypertrophy and AngII-induced hypertension, albuminuria and cardiac hypertrophy in diabetic female mice.

Results: In ACE2 deficient db/db mice, there was a modest but significant reduction in podocyte count (3.0±0.9 vs. 2.4±0.7, p<0.001) and an increase in glomerular cellularity which was identified by PAS-positive material in the glomerulus and factored by the glomerular tuft area. Area calculations were performed using ImageJ software. To assess podocyte number in glomerular tuft, WT-1 staining was performed.

Conclusions: Glomerular hypertrophy, mesangial matrix expansion and podocyte loss were found in female NOD.ACE2-/- mice. In diabetic NOD.ACE2-/- and NOD.ACE2+/- mice, there was a modest but significant reduction in podocyte number as compared to NOD.ACE2+/-

Funding: Pharmaceutical Company Support - J&K

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714A
Conclusions: Genetic ACE2 ablation worsens glomerular hypercellularity in diabetic mice whereas GFP and ACR are not significantly altered and other markers of glomerular pathology are minimally affected.

Funding: NIDDK Support, Private Foundation Support

SA-PO391
Blood Pressure-Independent Amelioration of Glomerulosclerosis in Diabetic Rats Treated with Dual AT1,Receptor-Neprilysin Inhibition versus AT1-Receptor Blockade Alone

Lodzi C.W. Roksnog,1 Richard Van Veldh,1 Marian Claesen - van Groningen,2 René De Vries,1 Ingrid M. Garrelsd,1 Usha M. Bhaggoe,1 Jeanette M. Van Gool,1 Edith C.H. Friesema,1 Frank P.J. Leijten,1 Ewout J. Hoorn,3 Alexander H. Danser,1 Wendy W. Batenburg.1 Div. Pharmacology and Vascular Medicine; Dept Internal Medicine, Erasmus MC, Rotterdam, Netherlands; 2Dept Nephrology, Dept Internal Medicine, Erasmus MC, Rotterdam, Netherlands; 3Dept Pathology, Erasmus MC, Rotterdam, Netherlands.

Background: Dual AT1 receptor-neprilysin inhibition (ARNI) has recently been shown to exert beneficial effects on blood pressure (BP), NT-proBNP, and estimated GFR in heart failure patients, compared with AT1 receptor blockade (ARB) alone. Neprilysin is upregulated in epineural arterioles of diabetic rats. We hypothesized that ARNI improves cardiac and kidney parameters in diabetic TGR(mREN2)27 rats, a model displaying angiotensin II-mediated hypertension.

Methods: Rats were made diabetic with streptozotocin, for 5 or 12 weeks. In the final 3 weeks rats were treated with vehicle, the ARB irbesartan (15mg/kg/day) or irbesartan (15mg/kg/day) + the neprilysin inhibitor thiorphan (0.1mg/kg/day; ARNI). BP was measured by telemetry in the 5-week group only.

Results: Baseline mean arterial BP (MAP) was 157±5mmHg. ARNI and ARNI lowered MAP identically over the 3-week period, reaching a maximum reduction of –50mmHg around day 7. Heart weight/body weight ratio in 12-week diabetic rats was 17% lower after ARNI treatment vs. ARB treatment (P<0.05). Proteinuria and albuminuria were observed in 8% of diabetic mice towards. ARNI reduced proteinuria more strongly than ARB (78% vs. -48%, P<0.05), and a similar trend was seen for albuminuria. Kidneys of ARNI-treated rats showed less focal segmental glomerulosclerosis than those of ARB-treated rats. At the end of the study, no differences between ARNI- and ARB-treated rats were found regarding diuresis, natriuresis, plasma endothelin-1, vascular reactivity (acetylcholine and endothelin-1 responses), or kidney sodium transporters.

Conclusions: ARNI reduces proteinuria, focal segmental glomerulosclerosis, and cardiac hypertrophy in diabetic TGR(mREN2)27 rats more strongly than ARB, and this occurs in a blood-pressure-independent manner.

SA-PO392
Collateral Effects of Atrasentan on Renin-Angiotensin System Lidia Aquipano, Marta Riera, Marta Rebull, Julio Pascual, Maria Jose Soler.
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Background: Endothelin-1 is a vasoconstrictor peptide that has been shown to be increased in diabetic kidney disease. In kidney cortex from obese diabetic mice ACE2 activity is increased whereas ACE activity is decreased. Objective: study the effect of atrasentan, an antagonist of type II endothelin receptor, on renin-angiotensin system (RAS) in obese diabetic mice (db/db) and its respective controls (db). Methods: Diabetic groups: vehicle (VehDB), 10mg/kg/day atrasentan (10DB), 25mg/kg/day atrasentan (25DB), 50mg/kg/day atrasentan (50DB). Non-diabetic groups: vehicle (VehCONT), 10mg/kg/day atrasentan (10CONT). Animals were included in the study at 12-weeks of life and treated for 16weeks. Systolic (SBP) and diastolic (DBP) blood pressure and ACE and ACE2 enzymatic activities in serum and kidney were analyzed.

Results: See table. Atrasentan therapy significantly decreased SBP and DBP in diabetic mice. Circulating and renal ACE2 activities were significantly increased in VehDB mice as compared to VehCONT. Atrasentan treatment at 25 and 50mg/kg/day reduced circulating and renal ACE2 activities. Circulating and renal ACE2 activities were decreased in VehDB as compared to VehCONT, with no modulation by atrasentan treatment.

Conclusions: Atrasentan prevented the increase of circulating and renal ACE2 in diabetes, indicating a collateral effect by RAS modulation. These results suggest that the beneficial effect of atrasentan in diabetic nephropathy may be related with endothelin blockade and its effect in the non-classic RAS pathway.

SA-PO393
P16\textsuperscript{ink4a} Expression Is Increased via 12-Lipoxigenase in High-Glucose-Stimulated Glomerular Mesangial Cells and Type 2 Diabetic Glomeruli Yuanjuan Zhang, Fu-zhe Ma, Tao Sun, Wan-ning Wang, Hang Yuan, Zong-gao Xu.
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Background: Arachidonic acid-metabolizing enzyme 12-lipoxigenase (12-LO) is involved in glomerular hypertrophy of diabetic nephropathy (DN), in which cyclin-dependent kinase inhibitors (CDKs) play important roles. However, it is unclear whether 12-LO regulates the expression of the CKI p16\textsuperscript{ink4a} in DN.

Methods: Primary glomerular mesangial cells (MCs) and glomeruli isolated from rats were used in this study. The rats were fed a high-fat diet and given low-dose streptozotocin to induce type 2 diabetes. The 12-LO product 12(S)-hydroxy-6,9,11-eicosatrienoic acid [12(S)-HETE] was infused through an osmotic minipump. Enzyme-linked immunosorbent assay, Western blot, and morphometric analyses were performed.

Results: High glucose (HG) increased p16\textsuperscript{ink4a} protein expression in MCs, but this increase was prevented by the 12-LO inhibitor cinammyl-3,4-dihydroxy-o-cynanoacetamine (CDA). The levels of p-p38MAPK and p16\textsuperscript{ink4a} in MCs were significantly elevated after 12(S)-HETE treatment, whereas the p38MAPK inhibitor SB203580 prevented these increments. Compared with levels in control MCs, marked increases in p38MAPK activation and p16\textsuperscript{ink4a} expression were observed in MCs plated on collagen IV, while CDA treatment prevented these changes. Subcutaneous injection of CDA did not affect glucose levels but completely attenuated the diabetes-related increases in 12(S)-HETE content, p16\textsuperscript{ink4a} expression, p-p38MAPK levels, glomerular volume, and kidney/body weight ratio. Compared with levels in controls, p16\textsuperscript{ink4a} and p-p38MAPK in the glomeruli derived from 12(S)-HETE-treated rats were significantly increased.

Conclusions: 12-LO-p38MAPK mediates the upregulation of p16\textsuperscript{ink4a} in HG-stimulated MCs and type 2 diabetic glomeruli, and new therapies aimed at 12-LO inhibition might be beneficial in ameliorating diabetes-induced glomerular hypertrophy.

SA-PO394
The Effect and Mechanism of Probufol on Diabetic Nephropathy Tubulointerstitial Injury via Down-Regulating P66Shc Shi-kun Yang,1 Xiaoxuan Xu,1 Chun Hu,1 Li Xiao,1 Fuyou Liu,1 Lin Sun.1 Dept of Nephrology, Kidney Inst of Central South Univ, Changsha, Hunan Province, China; 2Dept of Nephrology, Kidney Inst of Central South Univ, Changsha, Hunan Province, China.

Background: P66Shc induce mitochondrial ROS overproduction and lead to renal oxidative stress. Probufol has the renal protective effect on the progression of DN. However, the mechanism remains poorly understood.

Methods: ICR mice were divided into control (n=10), DN (n=10), probufol (10mg/kg/d) group (n=10), DMSO group (n=10). The DN model was induced by injection of STZ (40mg/kg body weight). Probufol was intraperitoneally injected to the mice every other day for 12 weeks after the model was built. Renal lesions and the expression of SIRT1, P300, AcH3, P66Shc, FN were detected by HE staining, TUNEL, DHE, immunohistochemistry and western-blot respectively. In addition, HK-2 cells were incubated with different concentrations of D-glucose (5, 30mM) with or without probufol, 1mM AICAR or 20mM Dormorphin or 1mM EX-527. The expression of P66Shc, SIRT1, P300, AcH3, AMPK, p-AMPK in HK-2 cells were detected by realtime-PCR,Western-blot and immunofluorescence assays. In addition, chromatin immunoprecipitation (ChIP) assay was used to determine the effect of probufol on acetylation of histone of P66Shc gene. Results: Compared to control, the reduced ECM protein and renal tubular damage were observed in DN mice after treated by probufol. It also decreased the expressions of P300, P66Shc, FN in the kidney of DN mice. In addition, Probufol can reduce the levels of renal ROS levels and apoptosis, while boost the expressions of p-AMPK and SIRT1. Furthermore, pretreatment with the selective AMPK inhibitor Dormorphin or SIRT1 inhibitor EX-527 could block the inhibitory efficiencies of probufol. The ChIP analysis showed that probufol treatment could decrease the acetylation of histone h3 in p66shc gene promoter regions (-535 bp to -276 bp) in HK-2 cells induced by high glucose.

Conclusions: Probufol could epigenetically suppress the expression of P66Shc through p-AMPK-SIRT1-AcH3 pathway, then ameliorate the apoptosis and oxidative injury in HK-2 cells induced by high glucose.

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SA-PO395
Macrophages in Type 2 Diabetic Nephropathy Celine Klessens, Malu Zandbergen, Ron Wolterbeek, Jan A. Bruijn, Ton J. Rabelink, Ingeborg M. Bajema, Daphne Thomas-ijpelaar. Leiden Univ Medical Center.

Background: Inflammation seems to play a role in type 2 diabetic nephropathy (DN). Therefore, novel therapies focus on inhibition of inflammation to inhibit renal failure in DN. Intestinal macrophages are present in progressive interstitial lesions, however, the role of glomerular macrophages in the development of diabetic glomerular damage remains incompletely understood. In this study we investigated the accumulation of macrophages in glomeruli and interstitium of humans with various stages of DN.

Methods: Kidney samples obtained at autopsy of type 2 diabetes patients (N=88) with histologically proven DN were stained with CD68 and CD163, as global and M2 macrophage markers. As controls, renal autopsy samples of 5 non-diabetic and 18 diabetic
patients without DN were used. Macrophages in 50 glomeruli per sample were counted. Intestinal and interstitial macrophages were counted semi-quantitatively. Glomerular and interstitial macrophages were correlated to histological and clinical parameters.

Results: Glomerular CD68+ and CD163+ cells were present in all stages of DN according to the histopathological class and did not differ between classes, but the accumulation was varied widely. The mean influx of glomerular CD68+ cells over the classes was 4.2 (range 0-19) and the mean influx of glomerular CD163+ cells was 2.1 (range 0-14.74). The mean ratio of CD163/CD68+ cells amounted 0.5. Glomerular macrophages were also present in the control groups. Renal function was associated with the number of CD163+ cells. CD163+ cells were significantly associated with histological lesions. Intestinal macrophages significantly correlated with clinical parameters like GFR stage and albuminuria.

Conclusions: We showed that macrophages (including anti inflammatory CD163 + macrophages) are present in all stages of DN both in the glomerulus and interstitium. Correlation between clinical data and interstitial macrophages indicates that interstitial inflammation probably influences the progression of DN. In addition, presence of glomerular macrophages in early diabetic nephropathy suggests that they influence the glomerular diabetic damage as well. Therefore, therapies targeting macrophages might be a useful novel therapy in DN.

SA-PO396
Activation of CXCL16/CXCR6 Pathway by Inflammation Accelerates the Progression of Diabetic Nephropathy Zhe Hu, Kun Ling Ma, Yang Zhang, Wn Yu, Bi-Cheng Liu.

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Background: Diabetic nephropathy(DN)was considered as a chronic inflammatory disease. Inflammation plays critical roles in the progression of DN. This study investigated the role of CXC chemokine ligand 16 (CXCL16)/CXCL6 pathway in DN under inflammatory stress and explored its potential mechanisms mediated by purinergic receptor P2X ligand-gated ion channel 7 (P2X7RT).

Methods: Diabetes were randomly divided into two groups: db/db, and db/db+casein for eight weeks. Casein was subcutaneously injected to induce chronic inflammation. The morphological change of renal pathology and ultra-microstructure were checked by pathological staining and electron microscopy. Lipid accumulation in kidneys was observed by Filtrin staining and quantitative assay of intracellular free cholesterol. The expression of CXCL16/CXCL6/CXCR6 pathway, inflammatory cytokine, and fibrin index related molecules were detected by immunohistochemistry, immunofluorescence staining, and Western Blas.

Results: The 24-hour urinary protein, tubulointerstitial injury, inflammatory cell infiltration, and the expression of monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor α (TNFα), CD68, A-smooth muscle actin (a-SMA), and fibronecin (FN) in kidneys of db/db+casein mice were significantly increased compared with the db/db mice. Furthermore, there was significant lipid accumulation, increased protein expression of CXCL16 and CXCR6 and decreased disintegrin and metalloproteinase-10 (ADAM10) expression in kidneys of db/db+casein mice compared with db/db mice, with increased P2X7R expression. Further analysis demonstrated that there was a positive correlation between P2X7R and CXCL6/CXCR6 expression.

Conclusions: Inflammation accelerates tubulointerstitial injury in DN partly through the activation of CXCL16/CXCR6 pathway, which may facilitate inflammation induction and lipid accumulation in cells. The P2X7R pathway may be involved in the activation of CXCL16/CXCR6 pathway.

SA-PO397
Albumin Glycation Induces Structural Changes That Reduce Proximal Tubule FcRn Binding and Reclamation Mark C. Wagner, J.ered Myśliński, Shiv Pratap Singh Yadav, George Rhodes, Raben M. Sandoval, Sudhanshu Kumar, Sarah E. Wean, Fnu Ashish, Bruce A. Moltisort 1,2 Nephrology, Dept of Medicine, Indiana Univ School of Medicine, Indianapolis, IN; 1 Cellular & Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN; 1 CSIR-Inst of Microbial Technology, Chandigarh, India.

Background: Diabetic nephropathy remains the leading cause of chronic kidney disease (CKD) and ESRD. It results in increased albumin glycation and this is believed to be involved in proximal tubule cell injury and the pathophysiology of interstitial fibrosis and CKD progression.

Methods: To understand the mechanisms we have addressed specific in vitro albumin modifications and their impact on albumin-FcRn binding since proximal tubule FcRn is necessary for transcytosis and reclamation of filtered albumin.

Results: These studies showed markedly reduced binding to FcRn when albumin was glycated proportional to the level of glycation. To address the mechanism for reduced PT pH dependent FcRn binding, which alters lysosomal catabolism resulting in reduced PT pH dependent FcRn binding, which alters lysosomal catabolism leading to transcytosis and reclamation resulting in a shorter serum half life and may mediate the enhanced interstitial inflammation and fibrosis in diabetic nephropathy.

Funding: NIDDK Support

SA-PO398
The Effects of Glucagon-Like-Peptide-1 and Vitamin D on Inflammatory and Histological Changes of Diabetic Nephropathy in db/db Mice Yael Einbinder,1,2 Sydney Benachriti,2, Tali Zitman-Gal.1 Renal Pathology Laboratory, Dept of Nephrology and Hypertension, Meir Medical Center, Kfar Saba, Israel; 2 Sackler Faculty of Medicine, Tel Aviv Univ, Tel Aviv, Israel.

Background: Glucagon-like- peptide-1 is a gut incretin hormone that stimulates insulin secretion and may affect the inflammatory pathways involved in type 2 diabetes mellitus (T2DM). Calcitriol plays an important role in renal, endothelial, and cardiovascular protection. We evaluated the anti-inflammatory and histological effects of GLP-1 and calcitrol in a db/db mice diabetic model.

Methods: C57BL/6 (WT) and BKS.Cg-Dock7m+ /Leprdb/db (db/db) mice were randomized to: a) WT mice; b) db/db mice (diabetic control group); c) db/db mice+GLP-1 analog (100 nmol/kg); and d) db/db mice+GLP-1 analog + calcitrol (250 ng/kg). Blood glucose levels and weight were measured weekly. At the end of the 4-week treatment, kidneys were perfused and removed for protein analysis and histology.

Results: Blood glucose levels and weight were significantly higher in db/db mice compared to control WT mice. Blood glucose level was non-significantly lower in the db/ db GLP-1 group compared to untreated db/db mice (460±83.2 mg/dL vs. 526±3.33 mg/dL). GLP-1 treatment significantly up-regulated eNOS protein expression and significantly down-regulated p65 protein expression compared to the db/db control group. Vitamin D did not further improve the beneficial effect observed on protein expression. Kidney VDR protein expression increased only in the vitamin D group compared to the db/db control group. Kidney histology demonstrated beneficial effect of GLP-1 treatment on glomerular hyperfiltration in db/db mice at 26 weeks of age but had no significant effect on the severity of mesangial expansion.

Conclusions: In the experimental model of diabetic nephropathy (db/db mice), GLP-1 analog treatment improved the protein expression involved in the inflammatory response and significantly ameliorated the glomerular hypertrophy seen in the diabetic control group.

Funding: Private Foundation Support

SA-PO399
Mineral Metabolism and Interleukin-6: Predictive Risk Factors for Left Ventricular Hypertrophy in Patients with Diabetic Nephropathy Teresa M. Jeronimo,1 André Fragoso,1 Filipa Brito Mendes,1 Ana Paula Silva,1,2 Ana Pocinho Pimentel,1 Nelson Tavares,2 Pedro L. Neves,1,2 Nephrology, Centro Hospitalar do Algarve, Faro, Portugal; 1 Dept of Biomedical Sciences and Medicine, Univ of Algarve, Faro, Portugal; 2 Cardiology, Centro Hospitalar do Algarve, Faro, Portugal.

Background: Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular disease in patients with diabetic nephropathy (DN) and is an independent predictor of mortality in patients with chronic kidney disease (CKD). The aim of this study was to evaluate the predictive risk factors of LVH in a population of patients with DN.

Methods: The authors analysed the relationship of LVH with gender, body mass index (BMI), systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR), albumin, cholesterol, hemoglobin A1C, calcium, phosphorus, parathyroid hormone (PTH), urine albumin-to-creatinine ratio (UACR), interleukin-6 (IL-6), hemoglobin A1c (HbA1c) and insulin resistance (HOMA-IR). Descriptive statistics, Student’s t-test and logistic regression model were used.

Results: In a cross-sectional study were included 119 type 2 diabetic patients with CKD stages 3 and 4. Patients with LVH had significant lower values of eGFR and albumin, higher levels of UACR, HOMA-IR and IL-6. Phosphorus (odd ratio (OR) = 0.602 (1.075-4.414), p = 0.038), PTH (OR = 1.009 (1.990-3.000), p = 0.004) and IL-6 (OR = 1.264 (1.836-7.619), p = 0.0001) were independently related with LVH.

Conclusions: PTH, Phosphorus and IL-6 were independent risk factors of LVH in our diabetic population with CKD stages 3 and 4.

Variable | Adjusted OR (95% CI) | p-Value
--- | --- | ---
Gender | -1.012 (0.064-2.076) | 0.255
Age | 0.032 (0.890-1.053) | 0.455
BMI | 0.810 (0.969-1.448) | 0.498
SBP | -0.008 (0.944-0.043) | 0.757
eGFR | 0.026 (0.939-1.021) | 0.279
Albumin | -0.021 (0.937-0.012) | 0.983
Hb | 0.242 (0.779-2.106) | 0.347
Phosphorus | 0.602 (1.075-4.414) | 0.038
JPTH | 1.091 (0.998-3.000) | 0.044
UACR | 0.228 (0.746-2.014) | 0.058
HOMA-IR | 0.422 (0.746-3.114) | 0.247
IL-6 | 1.264 (1.836-7.619) | 0.0001

Multivariate logistic regression model — risk factors of LVH.
SA-PO400
Far-Infrared Retrieves Pancreatic Beta Cell Function and Survival in a Streptozotocin-Nicotinamide-Induced Type 2 Diabetic Mouse Model
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Background: In diabetes, the apoptotic cell death of insulin-producing beta cells leads to insulin deficiency. Recently, we found low-temperature far-infrared (FIR) irradiation increased proliferation and survival of human umbilical vein endothelial cells via prolymicotic leukaemia zinc finger protein (PLZF)-mediated PI3K/Akt activation.

Methods: In this study, we investigate the protective effects of FIR on pancreatic beta cell function and survival in the nicotinamide (NA) and streptozotocin (STZ)-induced type II diabetic mouse model. eLS via prolymicotic leukaemia zinc finger protein (PLZF)-mediated PI3K/Akt activation.

Results: The present study showed that FIR therapy decreased non-fasting blood glucose levels and increase blood insulin levels in diabetic mice in a dose-dependent manner. Immunohistochintchemistry staining revealed that FIR therapy retrieved insulin production of pancreatic beta cells in diabetic mice. But the influence of FIR on blood glucose and insulin levels was not found in NA-STZ-treated FIR-KO-knockout mice. We also used the insulin-secreting beta cell line INS-1 to investigate the protective effects of FIR in vitro. FIR irradiation promoted cell proliferation and inhibited STZ-induced apoptosis in INS-1 cells. FIR also induced PLZF nuclear translocation and increased PI3K expression and Akt phosphorylation in INS-1 cells. PI3F siRNA transfection inhibited the influence of FIR on INS-1 cells.

Conclusions: Our data suggest that FIR therapy retrieves pancreatic beta cell function and survival in diabetic mice via a PLZF-mediated pathway.

SA-PO401
Transgenic Mice Overexpressing Human CD39 (ENTPD1) Are Protected from High-Fat Diet-Induced Obesity and Insulin Resistance
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Background: CD39 is a vascular ecto-nucleotidase that sequentially hydrolyses extracellular ATP to ADP and AMP, thus terminating P2 receptor signaling. Previously we reported that deletion of Cd39 in hepatic insulin resistance (IR). We also found that deletion of Atp1a1/Utp1a1 activated P2Y12 confers significant protection against high-fat diet (HFD)-induced obesity and IR. Hence, we hypothesized that global overexpression of human CD39 (hCD39), which decreases the availability of extracellular nucleotides should attenuate development of HFD-induced obesity and IR.

Methods: Groups of age-matched adult wild type C57/B16 (WT) and syngeneic transgenic (TG) mice globally overexpressing hCD39 (HCD39), which decreases the availability of extracellular nucleotides should attenuate development of HFD-induced obesity and IR. We hypothesized that global overexpression of human CD39 (hCD39), which decreases the availability of extracellular nucleotides should attenuate development of HFD-induced obesity and IR. Hence, we hypothesized that global overexpression of human CD39 (hCD39), which decreases the availability of extracellular nucleotides should attenuate development of HFD-induced obesity and IR.

Results: In response to HFD feeding, both genotypes showed significant increases in BW over the experimental period as compared to their counterpart pairs fed regular diet. However, the gain in BW in HCD39 mice was significantly less in TG vs. WT mice (mean 21.5 ± 0.3 vs. 15.3 ± 0.3 g, n = 7, p = 0.0001). There were no significant differences between the genotypes in the amount of food consumed, nor was there evidence of steatorrhea indicating malabsorption. Fasting blood glucose levels in HFD fed mice were 2-fold higher vs. WT mice (179 ± 12 vs. 88 ± 5 mg/dL, n = 7, p = 0.0001). When fed HFD, both genotypes exhibited glucose intolerance, but this was less severe in TG mice. In parallel, insulin sensitivity was significantly better in HFD-fed TG vs. WT mice.

Conclusions: Our results demonstrate that overexpression of hCD39 confers significant protection against the development of HFD-induced obesity and IR, and thus validating the proposition that dominantly deleterious roles are played by extracellular nucleotides in metabolic homeostasis.

Funding: Veterans Administration Support

SA-PO402
Mass Spectrometry Imaging Reveals a Role for Glomerular Sphingomyelin in Suppressing AMPK Activity by Stimulating ATP Production in Mesangial Cells
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Background: We have recently shown that the ATP/AMP ratio is increased in the glomeruli in a mouse model of type I diabetes by matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) and may be the basis for reduced AMP-activated protein kinase (AMPK) in diabetic glomeruli. Here, we applied MALDI-MSI to identify a key metabolic event regulating levels of global ATP/AMP.

Methods: For MALDI-MSI, 23 weeks-aged male diabetic Akita (C57BL/6J-Inj-2mouse), NOD-SCID (N), and age-matched (W) and gender-matched (H) were used. For cell culture study, murine mesangial cells (MMCs) were treated with sphingomyelin(δ18:1/16:0) (SM)-containing liposomes (SL), control liposomes (CL) and vehicle. For ATP measurements, MMCs were transfected with sphingomyelin synthase (SNSM), 2 or control siRNA before treatment with liposomes.

Results: By MALDI-MSI, we found that SM(d18:1/16:0) was preferentially distributed in the glomeruli in W and H. Importantly, we found that SM is more abundant in glomeruli of A compared with W, and associated with increased SNSM and 2 in the glomeruli of A. In SM(d18:1/16:0) stimulated AK5 expression in MMCs compared with CL (p<0.01), and was inhibited by siRNA based inhibition of SNSM. AMPKα activity and PGC1α protein expression were significantly reduced by SL (p<0.05). In addition, SL increased glucose consumption and lactate production in high glucose conditions (p<0.05) suggesting a role for increased glycrosylation.

Conclusions: We demonstrate using MALDI-MSI that the accumulation of glomerular SM in type I diabetic mice is associated with increased ATP in glomeruli and may contribute to reduced AMPK activity in diabetic cells. These findings suggest that reducing of SM may lead to novel therapeutic targets for the treatment of diabetic kidney disease.

Funding: NIDDK Support, Other NIH Support - DP3DK094352-01, Veterans Administration Support

SA-PO403
Chronic Hyperglycemia Activates Autophagy Through an Increased Lysine-63 Linked Ubiquitination: A Candidate Mechanism in the Progression of Tubular Damage in Diabetic Nephropathy
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Background: Chronic hyperglycemia, a key pathogenic factor of diabetic nephropathy (DN), can alters autophagy whose role in tubular cells under hyperglycemic conditions (HG) remains unclear. We reported that lysine63-ubiquitination (K63-Ub) plays a key role in the progression of tubular damage in DN; moreover K63-Ub promotes protein autophagic clearance. Aim of our study was to: evaluate the HG effect in modulating autophagy in tubular cells (HK2), evaluate in vivo the autophagy state in patients with diabetes without renal damage and in different DN classes, investigate the K63-Ub role in the modulation of tubular cells autophagy.

Methods: K63-Ub was inhibited in HK2 under HG (30mM) by UBE2v1 silencing. E2 enzyme involved in K63-Ub, or by NSC697923 inhibitor. The expression of the autophagic factor LC3 was monitored by western blotting and confocal microscopy, (ICHC) and immunofluorescence (IF) were performed on kidney biopsies of 3 control patients, 3 diabetic, 9 DN (classes IIb, III and IV).

Results: HK2 showed a significant increase in LC3 protein after 24h of HG. UBE2v1 silencing completely abolished LC3 induced protein expression after 24h of HG. Confocal microscopy showed the reduction of autophagic vesicles induced by HG in the presence of the K63-Ub inhibitor (NSC697923). IHC on kidney biopsies revealed an increased tubular expression of LC3 in diabetic patients vs controls, that persists in all DN classes and class IV patients showed cytoplasmatic accumulation of fused-vesicles. The same tubules with activated autophagy, expressed K63-Ub proteins both in diabetic and in DN patients (IF).

Conclusions: In conclusion, our data demonstrate that chronic hyperglycemia induces an increase in autophagy, linked to the accumulation of K63 ubiquitinated proteins. However, uncontrolled autophagic levels could lead to tubular damage through the generation of intracellular vesicles, bringing to the progression of renal damage in DN patients.

SA-PO404
Abstract Withdrawn

SA-PO405
Complexome Profiling of Mitochondrial Respiratory Chain Proteins from Podocytes of Diabetic Mice
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Background: Mitochondria play essential roles in many aspects of biology, and their dysfunction has been linked to diverse diseases, including diabetic nephropathy (DN). Central to proper mitochondrial function is oxidative phosphorylation (OXPHOS), coordinated by respiratory chain complexes encoded by both nuclear and mitochondrial genomes. Whether alterations in specific OXPHOS complex protein expression/activity contribute to mitochondrial dysfunction in DN remain largely unknown.

Methods: To assess complexome profiles, mice were isolated from podocytes of db/db mice and non-diabetic (db/dm) mice. Blue Native Gel Electrophoresis (BNE) was carried out using mass spectrometry (nano-HPLC/ESI/MS/MS) to identify known and unknown macromolecular protein complexes.

Results: We identified a total of 1216 mitochondrial proteins. Complexome profiling revealed mitochondrial complexes 1 and III were markedly reduced in podocytes compared to controls. Consistent with MS results, Complex 1 activity was significantly reduced in podocytes of db/db mice compared to controls. Importantly, we found that the protein expression levels of Ndufa2, Ndufb3 and Ndufb8, all components of complex I, were significantly reduced in podocytes of db/db mice. We further validated...
our initial results and found that the podocyte-derived mitochondria from diabetic db/db mice are decreased in mass and protein expression and reduced mRNA levels of Ndufb8. These changes are coincident with significantly decreased Complex I activity from analogously isolated and processed mitochondria derived from db/db mice.

Conclusions: Our study uncovers a previously unrecognized role of complex I in the progression of DN. We propose that deficiencies in components of complex I may disrupt complex I assembly, eventually reducing mitochondrial oxidative metabolism of podocytes in diabetic kidney disease. Further genetic studies are currently underway in our laboratory to establish the value and limitations of using Ndufb8 transgenic mice in experimental models of diabetes as a model for targeting mitochondrial dysfunction in DN.

Funding: NIDDK Support

SA-PO406

Hyperglycemia and Hyperinsulinemia Increased Cell Proliferation and Regulated DNA Damage/Repair Pathways in Type II Diabetic (db/db) Mouse

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Background: The mechanisms by which hyperglycemia and/or hyperinsulinemia activate cell proliferation to regulate the DNA damage/repair pathways and increase renal cell damage in diabetes remain unclear.

Methods: In the current study, we investigated the role of hyperglycemia and hyperinsulinemia in regulating cell survival and cell proliferation to regulate the DNA damage/repair pathways in the type II diabetic (db/db) mouse.

Results: Significant increase in proteinuria, albuminuria, creatinine in 24h urine as well as albuminuria/creatinine ratio was detected in db/db mice compared to wild type mice. Cell proliferation was measured by Ki67 staining and PCNA expression in kidney sections of the in type II diabetic (db/db) mouse. DNA damage/repair pathways were also investigated and we found that the Akt/PKB and AMPK pathways were activated in the type II diabetic (db/db) mouse. We further found that the expression of p53, Bax and cytochrome c was significantly increased in the diabetic db/db mice as compared to wild type mice. The level of PCNA was increased in the diabetic db/db mice compared to wild type mice. The level of phospho-p53 and phospho-Bax were significantly increased in the diabetic db/db mice compared to wild type mice. The level of phospho-PCNA was increased in the diabetic db/db mice compared to wild type mice.

Conclusions: In summary, our data provide a novel mechanism of increased renal cell damage through decreased binding of Nfr2 to the OGG1 promoter and consequence deficiency in DNA repair that lead to accumulate DNA damage and lead to renal complications under hyperglycemia and hyperinsulinemia condition in diabetic mice.

Funding: Veterans Administration Support

SA-PO407

Spleen Tyrosine Kinase Activation Promotes the Progression of Diabetic Nephropathy in the Early Stage

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Background: Inflammation triggered by metabolic disorder has played an important role in the pathogenesis of diabetic nephropathy (DN) in the early stage. The inflammatory cytokines binding to immunoglobulin G Fc receptors (FcγRs) in the surface of cell contribute to the progression of inflammation. It was found in our previous study that there was an increased expression of FcγRs with an immunoreceptor tyrosine-based activation motif (ITAM-FcγRs) in the kidney of diabetic CRP-Tg mouse induced by streptozotocin (STZ). It was also observed that ITAM-FcγRs were increased and spleen tyrosine kinase (SYK) were activated in rat glomerular mesangial cells (GMC) cultured with high glucose. SYK is a cytoplasmic nonreceptor tyrosine kinase and plays critical role in intracellular signal transduction of ITAM-FcγRs. It has been established that activated SYK signal cascade leads to the pro-inflammatory cytokines production in antibody-dependent kidney disease. However, the role of SYK in the progression of DN remains unclear. The present study investigates the potential of SYK activation in the early stage of DN.

Methods: Diabetes was induced by STZ in Sprague Dawley (SD) rats for assessment of kidney injury at 2, 4, 8weeks by real-time PCR, immunohistochemistry and western blot analysis. In vitro, the pathogenic effect of SYK was observed. Renal and urinary albumin excretion significantly increased in diabetic SD rats at 2, 4 and 8 weeks after STZ injection. Renal inflammation has been developed with enhanced infiltration of macrophages and T cells, and upregulation of pro-inflammatory cytokines (IL-1β, TNFα) in diabetic rats. Enhanced renal inflammation in diabetic kidneys caused the increase of SYK, phosphorylation and the over-activation of nuclear factor kB (NF-kB) signaling pathway. In vitro, high glucose significantly upregulated pro-inflammatory cytokines (IL-1β, TNFα) via SYK cascade, which further promoted high glucose-mediated renal inflammation.

Conclusions: These findings suggested that SYK may be as “signal switch” to activate NF-kB signaling pathway and promote the progression of renal injury in the early stage of DN.

Funding: Government Support - Non-U.S.

SA-PO408

Smooth Muscle Specific Heavy Chain Ferritin Knockout Mice as a Model of Obesity

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Background: Ferritin, consisting of heavy (H) and light (L) chain subunits, is a highly conserved ubiquitous protein that safely sequesters iron in a non-toxic form. During the course of our studies to evaluate the role of heavy chain ferritin (FH) in a model of vascular calcification in TGD, we generated a transgenic mouse using the cre-lox system with smooth muscle cell-specific deletion of FH (FHΔ547). Serendipitously, we discovered the FHΔ547−/− mice gained more weight compared to control “floxed” FH mice and exhibited features resembling metabolic syndrome.

Methods: To characterize FHΔ547−/− mice as a model of obesity, male FHΔ547−/− mice and FHΔ547+/− control mice were individually housed from 6-28 weeks of age to monitor weight, food intake, and body composition utilizing quantitative magnetic resonance (QMR) imaging. Protein analysis was performed on skeletal muscle and fat to determine expression levels of F sustained signaling and iron regulators. RNA analysis of inflammatory markers expressed in white fat was also performed.

Results: At 28 weeks old, FHΔ547−/− mice gained more weight (30.58g ± 2.02 vs. 27.72g ± 1.06 controls) during the observation period and consumed significantly more food starting at 20 weeks of age than the controls. QMR studies revealed that FHΔ547−/− mice had slightly more fat, lean and water mass compared to controls. Protein analyses of skeletal muscle and white fat revealed a loss of GLUT4 expression and iron trafficking proteins, respectively, in transgenic mice. Moreover, there was an increase in tissue iron concentration and gene expression of TFNα in the fat tissue of FHΔ547−/− mice compared to controls. Interestingly, review of publicly available microarray data sets (NCBI, GEO data set GDS3876) derived from human samples suggest a significant (~1.5 fold) increase in FH gene expression in obese individuals compared to lean controls.

Conclusions: Over a third of the adults in the United States are obese. Obesity predisposes individuals to other health risks, including CKD, diabetes, stroke, and cardiovascular disease. Our studies provide a novel mouse model for obesity.

Funding: NIDDK Support, Veterans Administration Support

SA-PO409

The Induction and Role of p53 in Tubular Cell Apoptosis During High Glucose Treatment and Diabetes

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Background: p53, known as a tumor suppressor, plays a crucial role in the cellular response to various stresses. P53 has been implicated in diabetic kidney disease but its role remains unclear and controversial.

Methods: Kidneys from Akita mice and STZ-treated diabetic mice were collected for in vivo studies. In vitro, renal proximal tubular cells (RPTC) with or without p53 dominant negative (p53-DN) were cultured in medium containing 5.5 mM or 30 mM glucose. Apoptosis was detected in renin tubules within a few weeks of diabetes, which was accompanied by p53-p/p53 expression. In cultured RPTC cells, high glucose induced apoptosis and p53. In these cells, there were Bax translocation to the mitochondria and cytochrome c release. Interestingly, these changes and apoptosis were attenuate in p53-DN cells. Consistently, they were also suppressed by pifithrin-α, a pharmacological inhibitor of p53.

Conclusions: These results suggest that p53 may be an upstream mediator of tubular cell apoptosis during high glucose treatment and in diabetic kidneys. P53 is induced under these conditions and may activate the mitochondrial pathway of apoptosis.

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

SA-PO410

Mechano-Growth Factor Regulates mTOR and Other Growth Factor Expression in Mouse Mesangial Cells. Enhancing Cell Proliferation and Extracellular Matrix Production: Implications for Diabetic Glomerulosclerosis

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Background: MGF-S mesangial cells (MC) overexpress Mechano-Growth Factor (MGF) protein expression, while SM22−/− mice display markedly reduced mRNA and protein expression levels of Ndufb8. These changes are coincident with significantly decreased Complex I activity from analogously isolated and processed mitochondria derived from db/db mice.

Conclusions: Our study uncovers a previously unrecognized role of complex I in the progression of DN. We propose that deficiencies in components of complex I may disrupt complex I assembly, eventually reducing mitochondrial oxidative metabolism of podocytes in diabetic kidney disease. Further genetic studies are currently underway in our laboratory to establish the value and limitations of using Ndufb8 transgenic mice in experimental models of diabetes as a model for targeting mitochondrial dysfunction in DN.

Funding: NIDDK Support

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

Underline represents presenting author.
of S6 kinase (phospho-S6 kinase) protein 8.7-fold. This increase in mTOR and active S6 kinase was dependent on cellular proliferation rate. mTORC1 had suppressed mTOR by 69%, but suppressed active S6 kinase by an insignificant amount. VEGF expression was suppressed 60% in MGF-AS vs MGF-EV. TGF beta 1 protein was increased 1.8-fold in MGF-S, and reduced 46% in MGF-AS. GLUT1 protein in MGF-S was increased 7.2-fold compared to GLUT1 expression. In contrast, H2-Dog uptake was suppressed 85% in MGF-AS vs. MGF-EV. In MGF-S, Type IV collagen (Col-Iv) was increased 4.2-fold.

Conclusions: MGF-S MC demonstrated increased mTOR with S6 kinase activation, consistent with their enhanced proliferation rate, while the increased VEGF and TGF beta 1 promote Col-Iv protein expression. Overexpression of MGF in MC to mimic events in diabetic glomeruli recreates many features of high glucose-exposed MC. MGF-AS MC demonstrate a role for MGF in basal VEGF and TGF beta 1 expression.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO411
High Fat and High Sucrose Diet Induce Steatohepatitis That Is Dependent on Fructokinase
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Background: High fructose intake from added sugars, which are high in Western diet, correlates with the epidemic rise in obesity, metabolic syndrome, nonalcoholic fatty liver disease, and chronic kidney disease. However, the interaction of fructose with high fat intake, which is also rich in Western diet, remains unclear. Here we tested the interaction between fructose and fat, and determined whether this was dependent on a primary enzyme in fructose metabolism, fructokinase.

Methods: Wild type mice and fructokinase knockout mice (C57BL6/J background, male) were assigned to one of three groups (n = 8-9) respectively, matching mean body weight among the groups. Mice had free access to tap water, and a low fat (11%, LFD), high fat (36%, HFD) or high fat (36%) and high sucrose (30%) diet (HFSD) for 15 weeks. Urine samples were collected at 13 weeks using metabolic cages. At 15 weeks, blood was withdrawn, and tissues including kidney and liver were taken after 6 h fasting.

Results: Both wild type mice fed HFD and fructokinase knockout mice fed HFD developed high hepatic steatosis without hepatic inflammation compared to mice fed LFD. In contrast, wild type mice fed HFSD developed more severe hepatic steatosis and low grade inflammation and fibrosis in pathological analysis, but not in fructokinase knockout mice. Increased CD68, TNF-alpha, MCP-1, alpha-smooth muscle actin, and collagen I and TIMP1 expression were found in wild type mice fed HFSD. These changes were prevented in the fructokinase knockout mice. Meanwhile, there was no significant change of urinary protein and urinary NGAL, and no apparent renal pathological change among groups.

Conclusions: This study demonstrated an additive effect of high fat and high sucrose diet on the development of hepatic fat accumulation. Furthermore, the combination of sucrose with high fat diet may induce steatohepatitis. These results indicate the important role of fructose in the development of fatty liver and nonalcoholic steatohepatitis.

Funding: NIDDK Support

SA-PO412
The Succinate Receptor 1 Contributes to Obesity-Induced Type II Diabetes and Chronic Kidney Disease
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Background: Cell stress-induced release of mitochondrial succinylate and activation of its SUCNR1 receptor in the macula densa is essential for type 1 diabetes mellitus (T1DM)-related renin release and hypertension. Obesity-induced T2DM and Chronic Kidney Disease (CKD) are aggravated by hypertension and go with cell stress in adipose/kidney tissue and macrophages, which express SUCNR1. Here we tested the role of SUCNR1 in obesity-induced T2DM and CKD.

Methods: Wild-type (wt) and SUCNR1-/- mice were fed a low fat diet (LFD; 10%) or high (H) FD (60%). At different weeks, mice were weighed, and subjected to metabolic cages (electrolyte measurements), glucose tolerance tests (GTT). Mice were sacrificed and blood and tissues collected.

Results: Blood succinate was increased in diabetic patients versus healthy controls. Isolated adipose tissue of wt and SUCNR1-/- mice revealed increased succinate release with hypoxia or high glucose. 16 weeks LFD/HFD showed similar body weight and kidney weight gain for both HFD groups, but liver and heart weight gain was reduced in HFD SUCNR1-/- versus wt mice. Starving glucose levels were similarly increased in both HFD groups, but SUCNR1-/- mice had a better GTT response. Inflammatory signals and macropage infiltration was higher in adipose tissue of wt than SUCNR1-/- mice. Bone marrow derived cells of SUCNR1-/- mice migrated less efficiently towards chemotactic signals from diabetic/hypoxic 3T3 cells. Blood sodium and urine volumes were similarly decreased and eGFR increased in both HFD groups versus LFD controls. However, only HFD SUCNR1-/- mice showed albuminuria, elevated collagen IV expression, and some increase in inflammatory gene expression in the kidney.

Conclusions: SUCNR1-mediated chemotaxis of macrophages to affected adipose tissue, locally increased SUCNR1-mediated hypertension, contributes to obesity-induced T2DM and CKD development. If similar in humans, SUCNR1 may form a novel therapeutic target for T2DM and CKD.

Funding: Government Support - Non-U.S.

SA-PO413
Fluoxetine Disrupts E-Cadherin-Mediated Cell Adhesion and Calcium Homeostasis in Pancreatic β Cells
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Background: Major depressive disorder (MDD) is a common psychiatric illness and it affects as many as 840 million people.MDD and Type 2 diabetes (T2D) are disorders with various risk factors identified in prevalence study reports. Antidepressant treatment could be another critical factor affecting the bidirectional associations between MDD and T2D. Long-term use of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of antidepressants, is associated with an increased risk of developing T2D. E-cadherin mediated cell-cell adhesion has been linked to diseases such as cancer and diabetes. Loss of cell-cell adhesion in beta cells decreases insulin secretion.

Methods: Here we examine the effects of the SSRI fluoxetine (Prozac®) on beta cell function employing MIN6 cells, a mouse beta cell line, to elucidate the underlying molecular mechanisms.

Results: We showed that fluoxetine treatment significantly reduced glucose stimulated insulin secretion (GSIS). We found that fluoxetine has no effect on the total expression of E-cadherin, but decreased the surface of E-cadherin. Moreover, fluoxetine triggered E-cadherin reorganizing in cell border, mainly localized in Golgi, not in endoplasmic reticulum (ER). Our immunohistochemistry showed that reduction cell surface E-cadherin is due to increased endocytosis. Moreover, ER calcium release and the activation of store-operated calcium entry (SOCE) were suppressed by fluoxetine.

Conclusions: Taken together, the results suggested that the impairment of E-cadherin and calcium homeostasis may be underlying mechanisms by which fluoxetine caused the reduction of GSIS in pancreatic beta cells.

Funding: Government Support - Non-U.S.

SA-PO414
Involvement of Ischemic Condition in the Pathophysiology of Renal Damages in Obesity-Induced Kidney Injury
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Background: We have reported hypertrophic proximal tubules in obese mice which implies an inefficient oxygen supply in this area (Obesity Int, 2012). We examined whether hypoxic condition in proximal tubules is involved the pathogenesis of obesity-induced renal injury. We also test the hypothesis that this injury can be ameliorated by molecular intervention of prolyl hydroxylase domains (PHDs), sensors for tissue oxygen levels that is a crucial molecule for tissue response to hypoxia.

Methods: Tissue hypoxic conditions were assessed by pimonidazole immunostaining. Peritubular capillaries (PTCs) were evaluated by counting CD34 stained vessels. Tamoxifen (Tam)-inducible proximal tubules-specific PHD2 deficient mice were created by crossing PHD2floxtm/mice and Tam-inducible N-myc downstream-regulated gene-I-Cre mice on C57BL6/J background. These inducible conditional knock out (KO) mice mised their wild-type littersmates (WT) were fed a high fat diet (HFD) or a low fat diet (LFD) for 12 weeks. The expressions of PHD2 and VEGF were measured by real-time PCR and immunohistochemistry.

Results: The WT mice on HFD manifested renal histological changes, including cellular enlargement of proximal tubules and a rarefaction of PTCs, which were consistent with more hypoxic area in proximal tubules than in WT mice on LFD. Urinary albumin and NGAL excretion were higher in HFD-fed mice, indicating ischemic tissue damage in proximal tubular area. However, expression of either PHD2 or VEGF was unchanged in HFD-fed WT mice, suggesting the lack of hypoxic tissue response in HFD-fed WT-Injecting Tam to HFD-fed KO mice downregulated PHD2 in proximal tubules, increased VEGF expression, increased the number of PTCs, decreased hypoxic area, and attenuated proximal tubular damages and albuminuria.

Conclusions: Hypoxic condition due to enlarged cell with vascular rarefaction is evident in the proximal tubular area of obese mice whereas tissue reaction to hypoxic damages failed to properly compensate. The early reduction of PHD2 specifically in the proximal area may constitute a novel strategy against the progression process from an early stage of obesity-induced kidney injury.

SA-PO415
Herbal Mixture of Radix Puerae and Fructus Crataegi Prevents Renal Injury in Type 2 Diabetes via Inhibition of AKT/P38
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Background: It has been reported recently that radix puerae (RP) is one of the best herbal medicines for metabolic diseases, as it has pronounced anti-oxidative effects and helps improving insulin resistance and lowering blood sugar and lipid levels. Fructus crataegi

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(FC) also possesses strong antioxidant activity in vitro. The present study was designed to investigate whether RF and FC together (RF/FC) can prevent renal injury through a diabetic rat model generated by a high-fat diet and a low-dose streptozotocin (STZ).

**Methods:** A Type 2 diabetic model was generated by feeding rats with high-fat diet followed by injecting a low dose of STZ. Rats were randomly divided into five groups: normal diet, high-fat diet plus RF/FC prevention, diabetes mellitus plus RF/FC prevention. RF/FC was given to rats daily by intragastric gavage for 3 weeks. The rats were monitored for body weight, blood glucose, oral glucose tolerance, blood insulin and lipids, serum creatinine and urea nitrogen, urine protein. Renal pathological changes were examined with hematoxylin and eosin staining, periodic acid schiff staining, and Masson trichrome staining. The mRNA and protein levels of α-smooth muscle actin (α-SMA) and collagen IV in the kidney were detected by RT-PCR, Western blot and immunohistochemical staining. The levels of PI3K and AKT were determined by Western blot.

**Results:** Rats treated with RF/FC showed reduced 24 h urinary protein excretion and decreased blood glucose level compared with corresponding vehicle treated rats, but RF/FC prevention did not affect blood lipids. Glomerular mesangial matrix expansion, renal capsule constriction, and renal tubular epithelial cell edema were less severe following RF/FC prevention. Moreover, RF/FC prevention markedly reduced protein levels of PI3K, AKT, α-SMA and collagen IV in the kidney of diabetic rats.

**Conclusions:** Combined prevention with RF/FC may inhibit the PI3K/AKT pathway in the kidney, thereby preventing renal injury in diabetic rats.

**Funding:** Private Foundation Support

SA-PO416

High Protein Diet Markedly Accelerates Diabetic Nephropathy Whilst Nephrectomy Inhibits Its Development Effects In Obese Diabetic Mice

**Background:** Progression of diabetic nephropathy (DN) is accompanied by an increase in urinary albumin excretion rate (AER) and severity of lesions. obese diabetic BTBR ob/ob mice exhibit hyperinsulinemia and hyperglycemia with marked albuminuria and glomerular morphological alterations. Disease progression was increased in the presence of high protein content diet. Using high protein content diet appears to be a straightforward approach to investigate the effects of high protein diet on obesity and type 2 diabetes.

**Methods:** Obese BTBR ob/ob mice at 8 weeks of age were fed a normal diet or high protein diet (18 weeks) with or without unilateral nephrectomy (performed at 7 weeks of age). Glomerular filtration rate (GFR) was measured by 125I-iothalamate clearance, blood pressure was measured by tail cuff, blood glucose level was measured by tail prick. The urinary albumin excretion rate (AER) was measured by an enzyme-linked immunosorbent assay (ELISA) kit. The mRNA and protein levels of α-smooth muscle actin (α-SMA) and collagen IV in the kidney were examined with real-time quantitative PCR and Western blot.

**Results:** High protein diet increased AER 332-fold in BTBR ob/ob at 18 weeks age compared with lean controls. Nephrectomy significantly decreased the number of podocyte slits per mm GBM. Although the high protein diet increased GBM thickness and decreased the number of podocyte slits per mm GBM, the urinary albumin excretion rate (AER) remained unchanged. Moreover, nephrectomy increased the number of podocyte slits per mm GBM, indicating a partial preservation of podocyte ultrastrutures.

**Conclusions:** High protein diet markedly accelerates diabetic nephropathy, whereas nephrectomy inhibits its development.

**Funding:** Private Foundation Support

SA-PO417

Insulin Stimulates Renal Proximal Tubule Sodium Transport in Overt Type 2 Diabetic Nephropathy

**Background:** Type 2 diabetic nephropathy is a major cause of end-stage renal disease. Although insulin is secreted in response to hyperglycemia, the role of insulin in the pathogenesis of diabetic nephropathy remains unclear. We determined the role of insulin in regulating renal sodium transport and glomerular filtration rate (GFR) in a model of type 2 diabetic nephropathy.

**Methods:** Male wild-type and db/db mice were fed either a normal or high-fat diet for 8 weeks. After 8 weeks of diet intervention, the mice were injected with streptozotocin (STZ) to induce diabetes. Blood glucose levels were monitored weekly. Kidney function was assessed by determining serum creatinine and urine albumin concentrations. Kidney morphology was evaluated by light microscopy.

**Results:** In db/db mice, insulin administration significantly increased GFR and renal sodium reabsorption. In contrast, in wild-type mice, insulin had no effect on GFR or renal sodium reabsorption.

**Conclusions:** These results suggest that insulin plays a role in the pathogenesis of diabetic nephropathy by regulating renal sodium transport.

**Funding:** Private Foundation Support

SA-PO418

Modulation of Akt/AS160 Phosphorylation Mediates Insulin Resistance in a Rat Model of Metabolic Syndrome

**Background:** Insulin resistance is the underlying pathophysiological hallmark of metabolic syndrome (MS) which is most often associated with obesity. While adipokines and inflammatory cytokines have been implicated in the insulin resistance of MS, the exact underlying mechanisms and signaling processes have not been defined. The current study assessed the molecular mechanisms of insulin signaling in the skeletal muscle in ZSF1 rats which have leptin receptor mutation and phenotypically manifest MS.

**Methods:** Obese ZSF1 rats were maintained from the 8th week and sacrificed at 24 or 32 weeks and fed on high calorie high fat diet (Purina 5008) while control rats (lean ZSF1) were fed normal chow. Blood weights and water intake were monitored weekly and blood and urine samples were obtained at 8 weeks and at the time of sacrifice for determination of serum glucose, insulin and lipids by standard laboratory procedures. The mRNA and protein levels of insulin signaling related proteins, insulin receptor substrate-1 (IRS-1), Akt, AS160, and Glut4 were examined by Western blot.

**Results:** The obese ZSF1 rats showed full blown MS with obesity, hyperlipidemia, hypertension and hyperglycemia while the lean ZSF1 and SD rats were normoglycemic. The expression of GLUT4 was decreased in both skeletal muscle and fat tissue of obese rats. Studies done previously in our lab demonstrated that compared to non-diabetic rats, plasma adiponectin levels were lower in obese ZSF1 rats and adiponectin expression was decreased in fat tissue but not in skeletal muscle. The expression of adiponectin receptor 1 and insulin receptor substrate 1 (IRS1) were similar in all rats. Furthermore, the expression of phosphorylated Akt and AS160 were reduced by 74% and 38% in diabetic obese ZSF1 rats compared to non-diabetic controls.

**Conclusions:** Our results demonstrate that while GLUT4 expression in insulin sensitive tissues is decreased in obesity mediated diabetes, several intermediary steps in insulin signaling are unaltered. However the most consistent finding was reduced phospho Akt/ AS160, which could be a major determinant of insulin resistance in obesity.

**Funding:** Private Foundation Support
Blockade of CDK9 and Smad3/4 Signaling Reduces Renal Fibrosis in Mice with Unilateral Ureteral Obstruction


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Background: TGFβ1/Smad signaling plays a central role in the pathogenesis of renal fibrosis. Smad3 and Smad4 are pro-fibrotic, while Smad2 is anti-fibrotic. However, these Smads form heterogeneous complexes the functions of which are poorly understood.

This study investigated Smad complexes in renal fibrosis in mouse unilateral ureteric obstruction (UUO).

Methods: UUO was established in wild type mice, mice heterozygous or homozygous for Smad3 and/or Smad4 (reduction of 50 mmol/L) but most importantly in an increase in survival (55% non-treated versus 80% with late treatment) at day 128. Results: Early treatment with PBI-4050 resulted in significant improvement (up to three months) relative to control in GFR. There were significantly reduced proteinuria, histological lesion scores of kidney were also significantly (p<0.05) decreased in PBI-4050-treated rats (2.7 ± 1.5) compared to control (3.9 ± 1.4), as determined by HPE, PAS and Masson's trichrome staining. Early treatment with PBI-4050 induced a significant reduction of urine protein level. Furthermore, early treatment with PBI-4050 reduced the overexpression of fibrogenic (TGFβ1, collagen I and α-SMA), pro-fibrotic cytokines (IL-23p19 and IL-6), remodeling (MMP2, SPARC and fibronectin), and oxidative stress (iNOS) markers. Late treatment with PBI-4050 resulted in mild improvement of GFR and serum creatine level (decrease of 50 mmol/L) but most importantly in an increase in survival (55% non-treated versus 80% with late treatment) at day 128.

Conclusions: These results suggest that PBI-4050 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and may potentially improve residual kidney function in patients with end-stage renal failure.

SA-PO424

Fibroblast Growth Factor 23 Is Synthesised Locally by Renal Proximal Tubular Cells and May Be Pro-Fibrotic

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Background: Physiologically, FGF23 synthesis occurs predominantly in bone and regulates mineral handling in the kidney. In Chronic Kidney Disease, circulating levels have been found elevated and are thought to be strongly predictive of disease progression. However, the mechanisms by which FGF23 acts are not fully understood. Recent studies suggest that FGF23 may act to exacerbate chronic kidney disease and fibrosis.

Methods: We aimed to determine whether FGF23 production is increased in vivo in chronic kidney disease in a model of chronic kidney disease.

Results: In a 5/6 nephrectomised rat model of chronic kidney disease, serum FGF23 levels were increased compared to non-kidney disease controls. FGF23 was expressed by renal proximal tubular cells in vivo, as assessed by immunohistochemistry and in situ hybridisation.

Conclusions: These findings suggest that FGF23 synthesis is increased in vivo in chronic kidney disease, and that FGF23 may contribute to the progression of chronic kidney disease by an autocrine mechanism.

SA-PO423

Targeting Cardiorenal Connectors Reduces Renal and Cardiac Fibrosis in Experimental Chronic Renocardiac Failure

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Background: Cardiorenal connectors (CRC) play a major role in progression of organ dysfunction in chronic kidney disease (CKD). Our studies suggest that PBI-4050 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and may potentially improve residual kidney function in patients with end-stage renal failure.

Methods: In rats subtotal nephrectomy was followed by coronary ligation (wk 8) [Borgartz, AJP, 2012]. In wk 11 we administered losartan (RAS), or PDTC, tempol and meldonium (Inflammation-NO/Ros) or all of these plus metoprolol (all-CRC) until wk 16.

Results: Tubulo-interstitial (TI) fibrosis decreased in all treated groups (fig 1A). However, renal function was not significantly affected by any treatment. Systolic dysfunction stabilized in all treated groups, but declined further in vehicle-treated rats (fig 1B). Cardiac fibrosis improved in all treated groups without significant additive effect of targeting all CRC (fig 1C). TI and cardiac fibrosis correlated (fig 1D). Only all-CRC reduced MAP. Diastolic hemodynamics and ventricular and cardiomyocyte size were not affected by any treatment. Reducing TI injury and renal and cardiac CTGF mRNA expression was most effective by targeting all CRC.

Conclusions: Pharmacological targeting of cardiorenal connectors in this model of chronic renocardiac syndrome ameliorated the severity of cardiac and renal fibrosis and prevented further decline in systolic dysfunction.
production is observed in diseased heart and vascular tissue, and is associated with the activation of pro-fibrotic cascades, the involvement of renal FGF23 synthesis and potential fibrogenic effects warranted investigation.

**Methods**: Kidneys were harvested from FVB mice at day 0 or after 3 or 9 days post-unilateral ureteric obstruction (UO) (n=6). Paraffin-embedded sections were stained for FGF23 and with lectins to identify specific nephron segments. Total RNA was extracted from whole kidney tissue and laser-capture microdissected glomerular and tubular regions, and analysed by qPCR. Rat renal fibroblasts were cultured with exogenous recombiant human FGF23 and stained for α-smooth muscle actin (aSMA) to assess myofibroblast differentiation.

**Results**: Generalised-low level FGF23 protein staining was observed in proximal tubules at day 0, with more intense focal staining at days 3 and 9 post-UO. Local FGF23 synthesis was confirmed by qPCR of whole kidney extracts, and specifically, in proximal tubular cells, but not glomeruli. Normalised FGF23 expression increased 11-fold in day 3 UO relative to day 0 (both p<0.01). Treatment of rat UO fibroblasts with 10ng/ml FGF23 resulted in 4-fold increase in aSMA staining over 72h, equivalent to the effect of 1ng/ml transforming growth factor-β (both p<0.01).

**Conclusions**: Local renal FGF23 synthesis in proximal tubular cells is enhanced by tubulointerstitial injury and may augment myofibroblast differentiation.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO425

Quantitating Intracellular Oxygen Tension in Kidney by Phosphorescence Lifetime Measurement

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**Background**: Hypoxia plays critical roles in the progression of chronic kidney disease, since intracellular reactions to hypoxia depend on intracellular oxygen (O2) tension. However, existing techniques to detect intracellular hypoxia cannot quantify O2 tension.**

**Methods**: Phosphorescence lifetime (PL) measurement is reported to be useful to quantify O2 tension in vivo, however, most phosphorescent probes distribute extracellularly. Here we used BTPDM1, a lipophilic phosphore probe, to quantify intracellular hypoxia in the kidney. We measured PL in Human Kidney 2 (HK-2) cells and murine kidney after BTPDM1 administration.

**Results**: We first made a calibration curve between PL and partial pressure of O2 (pO2) in HK-2 cells. Then we confirmed that BTPDM1 distributed in tubular cells in vivo. Next we measured PL of the murine kidney in normal condition, renal ischemia, hypoxemia and anemia. PL were calculated to be 1.8±0.2µs, 4.0±0.3µs, 2.8±0.2µs, 2.2±0.2µs, respectively. We also investigated chronic kidney damaged model mice of 7 days after 30 minutes unilateral ischemia-reperfusion (I/R) injury of kidney. PL of I/R injured kidney was lower than contralateral kidney (2.2±0.2µs vs 1.8±0.1µs). We also found an increase in pimonidazole adduct protein and a decrease in peritubular capillary density in I/R injured kidneys. We quantitated in vivo intracellular pO2 by extrapolating the calibration curve in HK-2 cells. The intracellular pO2 of normal kidney tubule was estimated to be 50mHg, which was compatible with published value obtained by needle O2 electrode.

**Conclusions**: Our novel technique allowed accurate estimation of intracellular O2 tension of the normal and diseased kidney in vivo for the first time.

SA-PO426

Resveratrol Increases Expression of Heme Oxygenase-1 via Nrf2 Signaling to Ameliorate Renal Damage by Anti-Complement, Anti-Oxidative, and Anti-Apoptotic Effects in a Murine Model of Membranous Nephropathy

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**Background**: Idiopathic membranous nephropathy (MN) is an autoimmune-mediated glomerulonephritis and a common cause of nephrotic syndrome in adults. There are limited available treatments for MN. We assessed the efficacy of resveratrol (RSV) therapy for treating MN in a model of this disease.

**Methods**: Murine MN was experimentally induced by cationic bovine serum albumin, with phosphate-buffered saline used in control mice. MN mice were untreated or given RSV. Disease severity and pathogenesis was assessed by determination of metabolic and histopathological parameters, profile of reactive oxygen species, apoptosis, production of heme oxygenase-1 (HO1) and signalings.

**Results**: MN mice given RSV had significantly reduced proteinuria and a marked amelioration of glomerular lesions. RSV also significantly attenuated immunofluorescent staining of glomeruli in vivo and MC in vitro. MGF is a stimulus to VEGF and TGFbeta1 expression in vivo in these mice. MGF expression is increased both in glomeruli in vivo and MC in vitro. MGF is a stimulus to VEGF and TGFbeta1 as observed here. These growth factors are associated with excess ECM production, and these results are consis tent with the reduction of ECM production and 3H2-deoxyglucose uptake rates in the kidneys of MN mice. We also found an increase in pimonidazole adduct protein and a decrease in peritubular capillary density in I/R injured kidneys. We quantitated in vivo intracellular pO2 by extrapolating the calibration curve in HK-2 cells. The intracellular pO2 of normal kidney tubule was estimated to be 50mHg, which was compatible with published value obtained by needle O2 electrode.

**Conclusions**: Our novel technique allowed accurate estimation of intracellular O2 tension of the normal and diseased kidney in vivo for the first time.

SA-PO427

FVB Os/+ Mesangial Cells Exhibit Enhanced mTOR and Growth Factor Expression, Modeling the FVB Os/+ Glomerulosclerosis Mouse

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**Background**: We previously reported FVB Os/+ mice which exhibit rapidy progressive glomerulosclerosis beginning within the first 2 weeks after birth. Here we examine primary culture mesangial cells (MC) from FVB Os/+ mice and FVB Os/+ control mice to examine the potential of FVB Os/+ MC and identify cellular mechanisms which may contribute to glomerulosclerosis (GS) in vivo. FVB Os/+ MC have excess ECM production.

**Methods**: Primary culture MC were studied between passages 5 -12. Western analyses were performed with specific antibodies against selected proteins to examine mTOR, phospho-S6 Kinase, and growth factor expression important to excess extracellular matrix (ECM) production. GLUT1 glucose transporter expression and SH2-deoxyglucose uptake rates were also determined. Plotted for comparison in a graph. FVB Os/+ MC also had increased VEGF (1.6-fold) and TGF beta (2.7-fold), which likely contribute to the excess ECM production of these cells. The increased VEGF in vitro stimulates increased VEGF in FVB Os/+ glomerulus in vivo. MGF was increased in FVB Os/+ MC (2.7 fold), mimicking increased glomerular MGF in vivo. We previously found MGF stimulates VEGF and TGFβ1 in MC. FVB Os/+ MC carry the Os mutation which impairs cell division, explaining their slow proliferation. Consistent with this, phospho-ERK1/2 was reduced 66%. In spite of increased mTOR (3.8-fold) and downstream phospho-S6 kinase (5.2-fold), the cells could not proliferate normally.

**Conclusions**: FVB Os/+ MC exhibit growth factor expression simulating glomerular growth factor expression in vivo in these mice. MGF expression is increased both in glomeruli in vivo and MC in vitro. MGF is a stimulus to VEGF and TGFbeta1 expression as observed here. These growth factors are associated with excess ECM production in FVB Os/+ MC, despite suppressed Erk1/2, indicating another pathway is important to excess ECM production.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO428

Role of Sodium-Glucose Linked Cotransporter-2 Inhibitor in the Kidneys of Salt Sensitive Hypertension

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**Background**: Sodium-glucose linked cotransporter-2 (SGLT2) is expressed in the apical side of the proximal tubules and can transport not only glucose but also sodium. Because salt is an aggravated factor for the salt sensitive hypertensive renal injury model, SGLT2 expression may be related to the progression of renal injury due to salt sensitive hypertension. The aim of this study is to reveal the role of SGLT2 inhibitor in angiotensin II (AII) induced renal injury.

**Methods**: Male C57BL6/wild-type mice were divided into three groups: The Ang II group was systemically infused with Ang II for 16 days. The SGLT2 inhibitor (SGLT2-I) group was given an oral dose of the dapagliflozin SGLT2 inhibitor of 1mg/kg/daily in addition to an injection of Ang II. The control group was injected with a vehicle.

**Results**: In both the Ang II and the SGLT2-I groups, the degree of hypertension, the glycemic levels in blood and the body weight were similar. Renal gene expressions of angiotensinogen in the SGLT2-I group were significantly increased both in the AII and the SGLT2-I groups than the control group. Renal gene expression of the angiotensinogen in the SGLT2 inhibitor group tended to be lower than that in the AII group. The degree of macrophage infiltration and urinary albumin levels tended to be lower in the SGLT2-I group than in the AII group. These results suggested that SGLT2 inhibitor may attenuate the renal damage due to salt sensitive hypertension via inhibiting the activation of renal renin angiotensin system.

**Conclusions**: In conclusion, SGLT2 inhibitor may be a useful treatment of hypertensive renal disease.
The Renoprotective Effect of Nuclear 1 Factor Related Factor 2 (Nrf2) Activator, Bardoxolone Methyl, in Aldosterone and High Salt-Induced Renal Injury

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Background: Activation of nuclear 1 factor related factor 2 (Nrf2) is reported to have anti-oxidant and anti-inflammatory effects. In the aldosterone (Ald) and high salt-induced renal injury model using mice, we previously reported that severe tubulointerstitial damage was provoked by oxidative stress. The aim of this study is to reveal the renoprotective effect of the Nrf2 activator in this model.

Methods: To evaluate the degree of tubulointerstitial damage using the urinary liver type fatty acid binding protein (L-FABP), known as a biomarker of the tubulointerstitial damage, we used human L-FABP chromosomal transgenic (L-FABP⁺) mice. Male L-FABP⁺ mice were divided into three groups: The Ald group received systemic aldosterone infusions via an osmotic minipump and were given 1% NaCl water for 14 days. The Ald-Nrf2 group was given Bardoxolone Methyl of the Nrf2 activator intraperitoneally at a dose of 10mg/kg/day in addition to an injection of aldosterone and salt. The control group was given only a vehicle.

Results: The gene expression of MCP-1, the gene expression of RANTES, the gene expression of collagen type I and type III and the degree of macrophage infiltration were significantly greater in the aldosterone group compared to those in the control and renal inflammatory reaction and renal fibrosis were significantly attenuated in the Ald-Nrf2 group. The degree of renal L-FABP gene expression and urinary L-FABP levels increased in the Ald group compared to the control and decreased in the Ald-Nrf2 group.

Conclusions: The Nrf2 activator, Bardoxolone Methyl, could attenuate renal oxidative stress induced by aldosterone and high salt, and consequently, renal inflammatory reaction and the production of renal collagen were prevented. Bardoxolone Methyl may be a useful treatment for renal disease.

Detection of Mesangial Tissue Transglutaminase Activity in Human Kidney Biopsy Specimens

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Background: Tissue transglutaminase (TG2) is a protein-cross-linking enzyme that plays an important role in tubulointerstitial fibrosis in animal models of chronic kidney disease and diabetic nephropathy. However, its pathological significance in human glomerular diseases remains unclear. TG2 transforms into catalytically active TG2 through an unknown mechanism, and this accumulation aggravates kidney injury.

Methods: A total of 241 renal biopsy specimens obtained between January 2010 and December 2013 were assessed for TG2 activity by immunofluorescence microscopy with FITC-labeled highly reactive TG2 substrate peptides. The presence of the active form of TG2 was assessed by immunohistochemistry.

Results: Fifty-five of 65 (56%) patients with IgAN, 23 of 40 (58%) patients with lupus nephritis (LN), and 7 of 11 (64%) patients with secondary IgAN, including 8 IgA nephropathy (IgA), showed mesangial TG2 activity. Male Tgm2e (n=24) were fed a 0.2% w/w adenosine-containing diet. Two weeks later from the start of the diet, renal dysfunction of these mice were confirmed and were divided into the four groups: the adenine group was given only the diet containing adenine. The Fexubostat (Fe) group and the Topiroxostat high (Top-H) or low (Top-L) groups were given the diet containing each Fe (3mg/kg), Top-H (3mg/kg), Top-L (1mg/kg) in addition to adenine for another 2 weeks. Thereafter, adenosine-containing diet was stopped, only each medication was continued for additional 2 weeks and the kidneys in each group were removed.

Results: Renal dysfunction, the degree of macrophage infiltration, tubulointerstitial damage and renal fibrosis were significantly attenuated in the kidneys of the Feb, the Top-L and the Top-H groups compared to those in the adenine group. Serum uric acid levels and renal xanthine oxidoreductase activity in the Feb, the Top-H and the Top-L groups were significantly lower than those in the adenine group. Those levels in the Top-H group were significantly lower than those in the Feb group. Urinary excretion levels of L-FABP in both the Top-H and Top-L groups were significantly lower than those in both the adenine and Feb groups.

Conclusions: In conclusion, Topiroxostat attenuated the renal damage induced by hyperuricemia and may be a useful treatment for hyperuricemic renal damage. Funding: Private Foundation Support

Accumulation of Indoxyl Sulfate in Renal Tubular Cells Aggravates Kidney Injury in Rats with 5/6 Nephrectomy

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Background: Indoxyl sulfate (IS), a representative uromic toxin, is detected in renal tubular cells of CKD patients and 5/6 nephrectomized rats administrated with IS. It has been suggested that the retention of IS is induced through organic anion transporters in the basolateral membrane of renal tubular epithelial cells and this retention leads to nephrotoxicity. However, the mechanism for IS accumulation in renal tubules remains unclear. To reveal the correlation between IS accumulation and renal dysfunction in 5/6 nephrectomized rats, we investigated the expression of transporters in the apical or basolateral membrane and of markers for renal injury, and a content of IS in renal tubular epithelial cells using a novel antibody against IS.

Methods: To study the serum concentration of IS, we used high performance liquid chromatography (HPLC) and our newly developed enzyme-linked immunosorbent assay (ELISA). The renal sections were stained with the antibody for IS. The expression of transporters in renal tubular cells and the markers for renal injury such as Kidney Injury Molecule-1 (KIM-1) were detected by immunohistochemistry.

Results: Serum level of IS was identified to be increased in the 5/6 nephrectomized rats compared to the normal rats by the newly ELISA. The new system could sensitively detect the low concentration of IS. The value determined by ELISA is in a good correlation with HPLC. Immunohistochemistry showed a significant IS staining in renal sections of the model rats. We found the presence of IS in hyper tubular cells, where the expression of a transporter in the apical membrane mediating IS secretion was decreased, while the expression of a transporter in the basolateral membrane was retained. KIM-1, the marker for early kidney injury, was highly expressed in some tubules, but not in the IS positive cells.

Conclusions: Our findings suggest that IS is accumulated in renal tubular cells at the later stage of renal injury due to unbalance expression of transporters between in the apical membrane and in the basolateral membrane, and this accumulation aggravates kidney injury. Funding: Pharmaceutical Company Support - KUREHA corporation

IL-15 as a Potential New Therapeutic Treatment for Renal Fibrosis

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Background: The human epithelial cells of various tissues produce interleukin-15 (IL-15), which acts not only on immune cells, but also on epithelial cells, mainly via its anti-apoptotic action. Thus, human and mouse renal tubular epithelial cells (RPTEC) constitutively secrete IL-15. Our group recently reported that IL-15 preserves epithelial phenotype in human kidney tubular cells since IL-15 is sufficient to induce MCT commitment of RPTEC. Therefore, the goal of our study is to explore the renoprotective potential of IL-15 in vitro and in vivo in renal fibrosis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**SA-PO434**

Loss of the Vascular Class 3 Semaphorin, Semaphorin 3G, Leads to Attenuated Fibrosis and Reduced Tubular Injury by Unilateral Ureteral Obstruction in Mice

**Methods:** Our study sought to examine if IL-15 could inhibit EMT in tubular epithelial cells by reducing secreted cytokines that contribute to tubulointerstitial fibrosis. We used the unilateral ureteral obstruction model (UO) in mice. We also analyzed IL-15 expression in various human nephropathies.

**Results:** IL-15 expression decreased in human renal disease and in mice during UO (p=0.05, n=19). IL-15 treatment coupled with its soluble receptor (IL-15Rα), prevents interstitial fibrosis during UO (10.7 ± 1.1% in control group, vs 8.2 ± 0.7% in IL-15 treated mice and 6.4 ± 0.6% in IL-15/IL-15Rα treated mice, p<0.01, n=7 mice/group). Quantified by Sirius Red and Western Blot, through two different mechanisms. We found a direct inhibition of IL-15 on collagen synthesis, in both HCC (collagen IV) and myofibroblasts (collagen I and III).

**Conclusions:** In conclusion, IL-15 can attenuate TGFβ-induced EMT by acting directly through a reduction of collagen synthesis, both on myofibroblasts, the main effector of fibrosis, and tubular cell. IL-15 also modulates macrophages infiltration in vivo in UO. Therefore IL-15 could be a novel therapeutic player in renal diseases.

**SA-PO435**

Leukemia Inhibitory Factor Attenuates Tubulointerstitial Fibrosis in Unilateral Ureteral Obstruction

**Background:** Tubulointerstitial fibrosis is a common chronic kidney disease which is often sustained by chronic inflammation. CD4+ T-cells play an important role in the formation of renal fibrosis, its precise mechanisms are still unclear. Semaphorin 3G (Sema3G) belongs to a class 3 family of secreted semaphorin. Various cytokines are known to be involved in the formation of renal fibrosis, its precise mechanism is still unclear.

**Methods:** To understand the role of Sema3G in renal fibrosis, Sema3G knockout mice and control mice are subjected to unilateral ureteral obstruction (UUO).

**Results:** Histologically, UUO kidneys does not show obvious difference between control and Sema3G KO mice. However, although mRNA expression of Tgfα and Sna1, a key regulator of Tgfb-induced fibrosis, increases by UUO in controls, these increases are attenuated in Sema3G KO UUO kidneys (for Tgfα, 55% suppression compared to controls, p<0.05; and for Sna1, 39% suppression, p<0.01 at day 7), suggesting that Sema3G KO mice are protected from tubular injury.

**Conclusions:** Together, these data demonstrate that endothelial Sema3G acts on adjacent tubular/interstitial cells and promotes fibrosis by UUO. Identification of the mechanism of this interaction would provide new therapeutic targets for CKD and renal fibrosis.

**Funding:** Government Support - Non-U.S.

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

**SA-PO436**

**Methods:** We observed that dendritic cell (DC) (CD11c) and myeloid cells (CD11b) infiltrated the renal interstitium in the early phase of acute tubular damage and a later phase of IF. To evaluate the role of TLR4 in renal inflammation-fibrosis, we analyzed the degree of inflammation that is dependent on TLR4 in WT and TLR4 mutant mice subjected to LPS. We further compared IF by Masson trichrome stain. Changes in IF (after adjusting for day 2 log BUN) were analyzed by regression analysis.

**Results:** Compared to control mice, CKO mice showed significantly higher serum creatinine at 40 and 60 days. Anti-dsDNA antibody was detected at low levels at 8 weeks and markedly elevated at 20 and 40 weeks. At 40 weeks, CKO mice showed severe proliferative glomerulonephritis and tubulointerstitial nephritis by light microscopy with mesangial IgG and C3 depositions by IF staining. Electron microscopy revealed electron dense depositions in mesangial area, but few in subendothelial or subepithelial area. Immunohistochemical staining showed marked accumulation of DCs (CD11c+), macrophages (F4/80+) and helper T cells (CD4+) at periglomerular and tubulointerstitial area. Infiltration of numerous DCs was also observed within glomeruli. Flow cytometric analysis of the CKO kidney showed the inflammatory cells increased with increasing age. Despite the prominent morphological changes, there was no significant increase of albuminuria, even at 40 weeks.

**Conclusions:** The DC-specific ablation of Shp-1 in mice resulted in development of unique autoimmune glomerulo- and tubulointerstitial nephritis, which is distinct from typical lupus nephritis characterized by wire-loop lesions and heavy proteinuria.

**Funding:** Government Support - Non-U.S.

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**Underline represents presenting author.**
SA-PO438
A New Mouse Model of Glomerular Foam Cell Accumulation in Disease
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Background: Foam cells are lipid-laden cells of monocyte/macrophage origin which have a key role in the development of atherosclerosis. Similar foam cells are found in human kidney biopsies in various diseases (e.g. type 2 diabetes and focal segmental glomerulosclerosis (FSGS), diabetic nephropathy, and the interstitium in nephrotic states). The pathophysiologic significance of foam cells in the kidney is poorly understood, in part due to lack of good animal models. We sought to develop a robust animal model for foam cell accumulation in the kidney to test their pathogenic significance.

Methods: Adult Wistar rats were injected with anti-Thy-1.1 antibody to induce Nephrotic nephritis (NTN) in the HPMC-Tween treated group. Untreated age-matched controls. Each organ including kidney was harvested for histologic evaluation. Immunohistochemical staining (IHC) for Mac2 was performed to quantify the state of monocyte/macrophage infiltration and urinalysis was conducted to calculate the urine albumin-creatinine ratio (ACR) and total albumin excretion.

Conclusions: These experiments show that DAC treatment had a protective effect on NTN phenotypes in WKY rats with a reduction in DNA cytosine methylation in both nephritic glomeruli and macrophages. These results suggest that DNA methylation may be involved in the pathogenesis of CRGN and may represent a target for intervention.

Funding: Government Support - Non-U.S.

SA-PO441
Macrophages Present an Essential Source of Anti-Inflammatory Annexin A1 Signals During the Course of Acute Anti-Thy-1.1 Nephritis
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Background: Macrophage subpopulations exert distinctive effects during inflammatory kidney disease and may either aggravate kidney damage or foster renal repair. The anti-inflammatory protein annexin A1 (AnxA1) has been shown to shift macrophage polarization towards the anti-inflammatory M2 phenotype. Cellular sources and regulation of intrinsic AnxA1 signals during renal inflammation remain to be elucidated.

Methods: Adult Wistar rats were injected with anti-Thy-1.1 antibody to induce mesangiocapillary glomerulonephritis and examined after 24h (initiation phase), 5d (proliferation phase), and 15d (resolution phase). Regulation of AnxA1 was studied by real-time PCR and Western blot. AnxA1 levels were also determined in vitro in co-cultures of THP-1 macrophages, mesangial cells, and T cells. Quantification of AnxA1 in cells was performed by flow cytometry.

Results: AnxA1 expression was significantly increased in mesangial cells and macrophages in the proliferative phase of nephritis. In vitro co-culture experiments demonstrated that AnxA1 expression was induced by T cell stimulation, suggesting an important role for T cells in the regulation of AnxA1 during renal inflammation.

Conclusions: These data provide evidence for a role of T cells and macrophages in the regulation of AnxA1 expression during acute anti-Thy-1.1 nephritis. Further studies are needed to elucidate the mechanisms underlying AnxA1 expression in vivo.

Funding: German Research Council - EMK, Charité · Universitätsmedizin Berlin, Berlin, Germany.

SA-PO440
5-Aza-2-Deoxycytidine Reduces Nephrotic Nephritis and DNA Cytosine Methylation in Nephritic Glomeruli and Macrophages In Vitro
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Background: Nephrotic nephritis (NTN) is a macrophage dependent rat model of crescentic glomerulonephritis (CRGN). We investigated whether DNA cytosine methylation could determine dysregulation of macrophage activity and contribute to CRGN susceptibility, by examining the effect of 5-aza-2-deoxycytidine (DAC), an inhibitor of DNA methylation, on NTN phenotypes and DNA methylation in both nephritic glomeruli and bone marrow derived macrophages.

Methods: NTN was induced in male WKY rats. 6 rats were treated with intraperitoneal DAC and 6 controls with vehicle only. Treatment was given every three days prior to sacrifice at 10 days and then NTN phenotypes assayed. The effect of DAC on DNA methylation was examined by multiplexed PCR sequencing of bisulfite converted DNA in both nephritic glomeruli from NTN animals, and in WKY bone marrow derived macrophages treated in vitro with DAC.

Results: DAC treated animals had fewer glomerular crescents, less proteinuria and less glomerular macrophage infiltration (ED1 staining).

DNA methylation in nephritic glomeruli was decreased across 200 cytosine bases in DAC treated samples compared to controls (P = 0.049, Wilcoxon rank sum test). This decrease was driven by 39 cytosines that showed demethylation in DAC treated animals. In vitro sequencing in macrophages showed diverse methylation changes after DAC treatment depending on length of exposure and dose.

Conclusions: These experiments show that DAC treatment had a protective effect on NTN phenotypes in WKY rats with a reduction in DNA cytosine methylation in both nephritic glomeruli and macrophages. These results suggest that DNA methylation may be involved in the pathogenesis of CRGN and may represent a target for intervention.

Funding: Government Support - Non-U.S.
SA-PO442
Reduced Mitochondrial Energy Production in the Kidney Induces Focal Segmental Glomerulosclerosis in Low-Birth-Weight Rats at Adulthood
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Background: Intraglomerular hypertension has been linked with the pathogenesis of focal segmental glomerulosclerosis (FSGS) lesions in low-birth-weight (LBW)-related nephropathy, which is associated with a decreased number of nephrons. However, other mechanisms may participate in the pathogenesis of LBW-related nephropathy. Here, we investigated innate factors that could induce LBW-related nephropathy at adulthood.

Methods: LBW rats (N = 7) were obtained by intraperitoneally injecting pregnant rats with dexamethasone. Normal-birth-weight (NBW) rats (N = 7) were obtained by saline injection. At 4 weeks of age, the left kidney was removed and used for histological analysis (immuno-)histological analyses for crystal density, tissue cellularity, tubular dilation, inflammatory infiltration, and fibrosis, and vascularization.

Results: At 4 weeks of age, glomerular numbers in LBW rats were significantly lower than NBW rats (p < 0.01). However, there were no scrotal lesions, and neither group showed any other pathological changes at this age. At 9 weeks of age, FSGS lesions were observed in 7.4% of glomeruli in LBW rats, but only 0.5% of glomeruli had lesions in NBW rats. The pathological changes in LBW rats at 9 weeks of age resembled that of human LBW-related nephropathy. Quantitative proteomics using the renal cortex from 4-week-old rats revealed that 685 proteins decreased in LBW rats compared with NBW rats, and among them, 97 proteins (14.2%) were mitochondrial proteins. In such reduced kidney disease (CKD), but direct evidence that prolonged exposure to tissue Hyp initiates renal IL-1β or TLR-4 in S. Unexpectedly, Hyp attenuated IL-1β, TLR-4, and urothelial cancer complications in countries using traditional herbal medicine. Early detection of renal tubular injury could be useful in individuals at risk of exposure to AA.

Mean ± SE, *p < 0.05 vs. respective S, #p < 0.05 vs. respective Nor.

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SA-PO444
Methylation Decreases Expression of Erythropoietin in Fibrosing Kidney Disease
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Background: Renal erythropoietin-producing cells remain in atrophic kidneys and are capable of producing erythropoietin in dialysis patients who take the stabilizer of hypoxia-inducible factors. The mechanism of decreased response of renal erythropoietin-producing cells to anemic stimulation in chronic kidney disease remains unclear.

Methods: We use genetically modified mice who report pericytes/myofibroblasts and express pericyte-specific Cre recombinase to perform in vivo study. We also isolate pericytes/myofibroblasts from these mice for in vitro analysis of epigenetic modification and erythropoietin expression.

Results: Here we show that Foxd1+ progenitor-depleted;Col1a1-GFP+;PDGFRbeta+ kidney pericytes are erythropoietin-producing cells regulated by hypoxia-inducible factor 2α (HIF-2α) and decrease such a function upon their transition to myofibroblasts in fibrosing kidney disease. Hypermethylation of erythropoietin 5′- untranslated region is demonstrated and associated with decreased expression of erythropoietin in kidney myofibroblasts. Demethylation with 5-azacytidine or knockdown of upregulated DNA methyltransferase 1 in kidney myofibroblasts is found to increase expression of erythropoietin in fibrosing kidney disease.

Conclusions: These studies demonstrate that epigenetic modifications may provide a molecular basis for decreased response of renal erythropoietin-producing cells to anemic stimulation in fibrosing kidney disease.

Funding: Government Support - Non-U.S.

SA-PO445
Multiparametric Magnetic Resonance Imaging for Assessing Renal Histopathology in a Mouse Model of CKD
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Background: Multiparametric magnetic resonance imaging (MRI) allows non-invasive assessment of renal pathologies, especially in patients with chronic kidney disease (CKD) as is does not require contrast agent administration. We aimed to establish an imaging protocol for multiparametric MRI in an experimental CKD mouse model and correlate radiological and histopathological parameters.

Methods: CKD was induced in male C57BL/6 mice (n=8) by feeding an adinidine-supplemented diet for 3 weeks resulting in deposition of dicyruxiadecrine crystals, tubular dilation, capillary loss, tubulointerstitial inflammation and fibrosis. Untreated animals (n=8) served as controls. Kidneys were fixed in paraformaldehyde and subjected to MRI in a 7-Tesla scanner ex vivo. Volumetry of renal cortex and medulla was performed on T2 weighted sequences. MRI parameters (apparent diffusion coefficient (ADC), fractional anisotropy (FA), T1, T2, T2* relaxation times) were determined for 3 regions of interest in both cortex and medulla, whereas ADC was increased only in the cortex of diseased kidneys and correlated with (immuno-)histological analyses for crystal density, tissue cellularity, tubular dilation, inflammatory infiltration, fibrosis, and vascularization.

Results: CKD resulted in significant volumetric augmentation of the medulla. T1 times decreased in control and diseased kidneys, T2 and T2* times were significantly increased in both cortex and medulla, whereas ADC was only increased in the cortex of diseased kidneys in comparison to controls. In contrast, FA was significantly reduced in diseased cortex and medulla. T2 time correlated with the relative area of fibrosis (Francois’ rho 0.71 or 0.79 for cortex or medulla), infiltrated macrophages (0.69, 0.81), and tubular lumen (0.74).

Conclusions: Multiparametric MRI enabled characterization and diagnosis of chronic changes in the presented CKD model and showed correlation of T2 times with fibrosis, inflammatory infiltration, and tubular dilation. These results may help to broaden our understanding of MRI findings in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO446
Nuclear Magnetic Resonance Based Metabonomic Profiles Produced by Aristolochic Acids: Comparison with Well-Known Tubulotoxic Agents
Marie Colet,1 Jean-Noël de Roziers,1 Françoise,3 Eric De prez,2 Jean-Marie Colet,1 Joelle L. Nortier,2 "1Lab Human Biology & Toxicology, UMONS; 2Lab Experimental Nephrology, ULB; 3Lab Histology, UMONS.

Background: Aristolochic acids (AA) are powerful nephrotoxic and carcinogenic products derived from Aristolochiaceae responsible for acute to chronic renal failure and urothelial cancer complications in countries using traditional herbal medicine. Early detection of renal tubular injury could be useful in individuals at risk of exposure to AA.

Methods: The Consortium of Metabonomic in Toxicology (COMET) has developed predictive models of renal toxicity based on the NMR-based metabonomic evaluation of urine and serum samples collected from rats acutely exposed to various well-characterized nephrotoxins. Using this COMET protocol, we studied the metabonomic urine profile of rats injected with aristolochic acid or AA and other compounds (72, 100mg/kg). We then compared it to those obtained with 3 molecules known for their toxicity on the proximal tubule, i.e l(isoflavone (I: 7, 70mg/kg), genticamin (Gent: 40, 400mg/kg) and cisplatin (Cis: 0.5, 5mg/kg), respectively.

Funding: Government Support - Non-U.S.
Results: Metabolic results obtained in AA rats demonstrated a urinary increase in medullary rCBF (turbine, brain, glycine) in osmotic (lactate) and in reabsorptive capacity of the tubular epithelium (glucose), and a significant reduction of Krebs’ cycle components (alpha-ketoglutarate, succinate, citrate), suggesting a mitochondrial injury. The comparison of these AA profiles with those obtained with Ido, Gentamicin, and Cis revealed significant similarities in 2D plots. However, the 3D modelization approach showed very close score plots shared by AA, Ido and Cis and a different behaviour exhibited by Genta samples. Conclusions: This metabonomic study confirms the mode of action of AA toward the proximal tubule and provides an original signature of induced mitochondrial insult. This approach could bring new insight in understanding the toxicity pathways of AA within the kidney. Moreover, it could be a useful tool of noninvasive screening in populations at risk of AA intoxication.

SA-PO447
Establishment of a 3-Step Method to Obtain the Absolute Number of Nephrons in Mice Xiaogang Chg., Jian-Kang Chen. Depts of Cellular Biology & Anatomy and Medicine, Georgia Regents Univ, Augusta, GA.

Background: Low nephron number is implicated in hypertension and kidney disease. Existing methods to determine nephron number have various limitations. While using the Cre reporter mice expressing membrane-Tomato/membrane-Green fluorescent protein (mT/mG) for other studies, we fortunately noted that the Tomato fluorescence remarkably visualized all glomeruli in the kidneys, which prompted us to establish a 3-step (Separate-Press-Count) method to obtain the exact nephron number in mice.

Methods: One homozygous mT/mG mouse (S232, available from the Jackson Laboratory, Stock Number: 007576) was bred with FVB/NJ mice. This produced ~11 heterozygous pups per litter. After the pups reached 6 weeks of age, they were weighed and euthanized. Each kidney was decapsulated, weighed, and blantly separated into 35-45 pieces (~2-3 mm3) each using forceps with non-serrated but blunted tips. Each piece was pressed between a microscope slide with grids and a coverslip, followed by counting of every single glomerulus under a fluorescence microscopy.

Results: The nephron number in male mice ranged from 10421 to 15577 (mean = 12977 ± 2136) for left kidney and 10374 to 15691 (mean = 13271 ± 2414) for right kidney (n=6) while that of female mice ranged from 13890 to 16277 (mean = 15184 ± 993) for left kidney and 14547 to 16165 (mean = 15555 ± 741) for right kidney (n=5). Thus, the mean total nephron number in male mice (25562 ± 4330) is lower than that of female mice (30739 ± 1443). This is still true when expressed as mean nephron number per gram of body weight (mG): that of male 1025 ± 179 vs. female 1362 ± 90 (n=5, p<0.001), 5.6 nephrons (Nn) in male mice decreased N/Gbw down to 156 ± 17, increased blood pressure (BP) up to 142 ± 7 mmHg, elevated BUN level up to 292 ± 99 (n=5), and caused 37.5% mice to die within 2 weeks while the remaining 5.6 N/Gn mice with >241 N/Gbw had 130 ± 8 mmHg BP and 73 ± 25 mmHg BUN and were still alive even 4 weeks after 5/6 Nx.

Conclusions: We have established a new simple method to count the absolute nephron number and are using it to define the minimum number of nephrons per gram of body weight that can maintain the normal blood pressure and kidney function in mice.

Funding: NIDDK Support

SA-PO448

Background: One of the many unresolved questions regarding the permeability of the glomerular filtration barrier is the reason for the difference in permeability between albumin and polysaccharide probe molecules such as Ficoll. The difference in sieving coefficients between albumin and a Ficoll molecule of the same molecular size (~36 A) is ~2-3 orders of magnitude. Although this large difference in permeability has been attributed mainly to charge effects, we have previously shown that this would require a supraphysiological amount of charge on the filtration barrier, being about ~10 times more (~36 Å) for other studies, we fortunately noted that the Tomato fluorescence remarkably visualized all glomeruli in the kidneys, which prompted us to establish a 3-step (Separate-Press-Count) method to obtain the exact nephron number in mice.

Methods: The classic heteroporous model by Deen, Bridges, Brenner and Myers (Deen et al, AJP Renal Physiology, 1985) was extended by introducing size distributions on the selective elements of the barrier. This is well in line with experimental data, which has been established; however etv4 is also expressed in the metanephric mesenchyme. We asked what role Etv4 plays during nephrogenesis.

Methods: To inhibit etv4 function in the metanephric mesenchyme, we crossed mice with a loxP-flanked dominant-negative etv4 (R26/+;Flp;DNT-etv4) with a metanephric mesenchyme-specific sx2-cre mice (sx2-TGC m/+); cre-negative littermates served as control.

Results: Six2cre-DN-Etv4 mice express DN-etv4 in the nephron progenitor population starting dpc10.5. Cre-positive mice have lower body weight and fail to thrive. At four weeks, they have a reduced nephron number (~42 ± 2 vs. ~80 ± 6 glomeruli per g tissue, p<0.001). They develop kidney failure (at 4 weeks: BUN 103.8±17.8 mg/dl, p< 0.001) and proteinuria (21.29±7.23 g Albumin/g Creatinine vs. 0.14±0.03 g Albumin/g Creatinine in urine, p<0.05). Their kidneys show all features of chronic kidney failure proteinosis, glomerulosclerosis, fibrosis) and they die at 3-5 weeks of kidney failure.

Conclusions: Expression of etv4 in the metanephric mesenchyme is required for normal kidney development, and expression of DN-etv4 in the sx2+ population leads to defective kidney development with reduced nephron number and progressive chronic kidney failure at 3-5 weeks of age. Titration of DN-etv4 expression in metanephric mesenchyme may provide a novel genetic model for low nephron endowment and progressive CKD.

Funding: NIDDK Support

SA-PO451
NO Depletion by L-NAMe Causes Increases in Rat Glomerular Permeability In Vivo – Reversal with Temporal and L-Arginine, but Not with the Potent NO-Donor DEA-NONOate Bengt Rippe, Julia Dolinina, Kristinn Sverrisson, Anna Rippe. Dept of Nephrology, Lund Univ, Lund, Sweden.

Background: There is increasing evidence that the permeability of the glomerular filtration barrier (GFB) is regulated by a balance between the bioavailability of nitric oxide (NO) and the presence of reactive oxygen species (ROS). It has been postulated that normal or moderately elevated NO levels protect the GFB from permeability increases, while ROS, through reducing the bioavailability of NO, have the opposite effect.

Methods: In anesthetized Wistar rats, the left ureter was cannulated for urine collection, while simultaneously blood access was achieved. To test the tentative antagonism between NO and ROS, rats were systemically infused with either L-NAME (6 mg/kg/min) or L-NAMe together with the superoxide scavenger tempol (1 mg/kg/min), or L-NAMe together with L-arginine (290 mg/kg/min). Furthermore, we tested whether the potent NO donor, DEA-NONOate, could reverse the permeability effects of L-NAMe. To measure glomerular sieving coefficients (S) to Ficollic, rats were infused with fluorescein
isochoicancat (FTC)-Ficol 7/400 (mol.ruclus 10-80A). Plasma and urine samples were analyzed by high performance liquid chromatography (HPLC) for determination of 0 for Ficolll repeatedly during up to 2 hours. 

**Results:** L-NAME increased 0 for Ficoll in 0.27 to 1.0 x 10^-6 to 5.9 x 10^-6 x 27 (n=6; p<0.05) in 15 min. Tempol (n=6) completely abrogated these increases in glomerular permeability. Furthermore, the 0 for Ficoll, being 7.0 (2.1) x 10^-15 at 15 min, which was also seen with L-arginine. However, DEA-NAMEOate did not reverse the permeability effects following L-NAME. 

**Conclusions:** NO depletion in vivo by L-NAME caused increases in glomerular permeability, which could be reversed by either the ROS antagonist, tempol, or by L-arginine. By contrast, the potent NO-donor, DEA-NAMEOate, did not ameliorate the permeability effects of L-NAME. It is concluded that moderate levels of elevated NO production act to protect the permeability of the GFB, whereas very high levels of NO, as produced following systemic DEA-NAMEOate infusion, may actually be detrimental to the GFB.

**Funding:** Government Support - Non-U.S.

SA-PO452 Down-Regulation Of Renal Tubular Wnt/β-Catenin Signaling Induces Tubular Cell Death in Proteinuric Nephropathy

**Methods:** Wnt/β-catenin expression was measured in control/ human serum albumin (HSA)-treated human kidney 2 (HK-2) cells and kidney cortical lysates of protein-overloaded mice given 4- or 8- week BSA injection by Western blotting and IHC staining. Genetic knockdown of β-catenin in HK-2 cells was achieved using siRNA transfection. Apoptotic phenotypes were evaluated by qPCR, Western blotting, IHC staining/ activity assay and TUNEL assay. 

**Results:** Upon 4-day/BSA stimulation, protein levels of active nuclear β-catenin in HK-2 cells declined by 67±0.04 (p=0.05) versus control. Similarly, Bax/Bcl-2 gene expression ratio increased significantly. HSA treatment with or without β-catenin siRNA transfection in HK-2 cells up-regulated Bax/Bcl-2 gene expression ratio by 116±0.02 (p<0.05) and 52.0±0.05 (p=0.05), respectively. Similarly, TUNEL and caspase-3 activity was also increased by silencing β-catenin. In protein-overloaded mice, dynamic expression of β-catenin was observed at the early stage and associated with up-regulation of NGL and KIM-1 gene expressions. 

**Conclusions:** Protein-overload promotes renal tubular apoptosis via abrogation of Wnt/β-catenin signaling in vitro and in vivo. Funding supports: Hong Kong Society of Nephrology Research Grant (2013), and the National Basic Research Program of China 973 program no. 2012CB176000 (no. 2012CB517606).

**SA-PO453 Endothelin-1 Induces Proteinuria by Heperanase-Mediated Disruption of the Endothelial Glyocalyx**

**Methods:** Endothelin-1-stimulated podocytes increased transendothelial albumin passage, which is HPSE-dependent. Experimental type 1 diabetes in wild type (WT) mice revealed proteinuria and renal damage, accompanied with an increased glomerular HPSE expression and a reduced glomerular HS expression. Proteinuria and renal damage were reduced in the diabetic podocyte-specific endothelin receptor knockout (podETRKO) mice, which showed a normal HPSE and HS expression. Importantly, glyocalyx thickness was reduced after induction of diabetes in the WT mice, but preserved in the diabetic podETRKO mice. 

**Conclusions:** Our data show that endothelin-1 induces HPSE expression in the podocyte in experimental DN. Furthermore, these results suggest that HPSE cleaves HS in the endothelial glyocalyx, which results in a reduced glyocalyx thickness and the development of proteinuria.

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

**Underline represents presenting author.”

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**SA-PO454 Endothelin-1 Increases Glomerular Permeability in Sickle Cell Mice Malgorzata Kasztan, 1 Chiao-Wang Sun, 2 David M. Pollock. 1 Cardia-Renal Physiology&Medicine, Univ of Alabama at Birmingham, Birmingham, AL; 2Biochemistry&Molecular Biology, Univ of Alabama at Birmingham, Birmingham, AL.** 

**Background:** Sickle cell disease (SCD) leads to nephropathy manifested by increased glomerular permeability (P_{alb}) and albuminuria/proteinuria. The endothelium-derived peptide endothelin-1 (ET-1), with its powerful vasoconstrictor and pro-inflammatory effects mediated primarily through ET, receptors, is elevated in SCD patients and may contribute to the development of sickle cell glomerulopathy. Therefore, the aim of the study was to determine whether ET-1 contributes to increased glomerular permeability to albumin in SCD and if ET-1 receptors blockage alters albuminuria in the SCD. Furthermore, because our preliminary studies showed sex differences in the vasconstrictor response to ET-1 in sickle cell mice the study was designed to determine if sex differences exist in this response. 

**Methods:** Experiments utilized 12 week old humanized sickle cell mice (HSSS) and generated controls (HAA) recently developed by the Towery’s lab. Ambrisentan (ETa antagonist), A-18206 (ETa antagonist) or vehicle was administered during drinking water (10mg/kg/day) for 2 weeks. Glomeruli were isolated for direct permeability measurements as a volume response of glomerular capillaries to an oncopressive medium generated by defined concentrations of albumin. 

**Results:** P_{alb} was significantly higher in glomeruli from sickle mice (both in males and females) than control mice (0.5±0.07 and 0.47±0.06 vs. 0.13±0.02 and 0.10±0.02, respectively). Ambrisentan treatment significantly reduced the elevated P_{alb} in glomeruli from male (0.24±0.05 vs. 0.50±0.07) and female (0.20±0.03 vs. 0.47±0.06) HSBS mice. ET_{a} receptors antagonism with A-18206 also significantly decreased the P_{alb} in glomeruli from male (0.28±0.06 vs. 0.50±0.07) and female (0.24±0.03 vs. 0.47±0.06) HSBS mice. Treatment with both antagonists did not alter P_{alb} in HAA mice. 

**Conclusions:** These data suggest that ET1 treatment may play an important role in the development of sickle cell nephropathy and support the use of chronic ETa antagonism as a prospective treatment for sickle cell nephropathy. 

**Funding:** Other NIH Support - NHI/HLB01 (U11 HL11764-01)
choline in their drinking water. Mice with total CHOP knockdown were used to test the role of CHOP in the development of CKD to assess changes in blood pressure and 24h total urinary protein and albumin measurements. On day 21 post-implantation, mice were sacrificed and PASM staining was used to evaluate renal interstitial cast formation and glomerular damage.

**Results:** In response to the CKD model, both CHOP−/− and wild type (WT) mice experienced significant increases in systolic and diastolic blood pressure. However, CHOP−/− mice showed significantly lower proteinuria and albuminuria. In addition, CHOP deficiency significantly decreased interstitial cast formation and glomerular damage in response to the model compared to WT.

**Conclusions:** CHOP deficiency resulted in a decrease in proteinuria and renal tissue damage. Along with inducing apoptosis, CHOP has been shown to interact with inflammatory pathways resulting in NFκB activation. Further tests will evaluate the effect of CHOP deficiency in inflammatory, fibrotic and apoptotic response in our model. Our findings could lead to the development novel therapeutics to halt the progression of CKD.

**Funding:** Government Support – MOP-133484.

**Funding:** Government Support - Non-U.S.

**SA-PO457**

**Caveolin-1 Is Crucial in the Pathogenesis and Progression of Light Chain Deposition Disease but Not in Al-Alamyloidosis**

**Jiaxin Peng, Paola Guo, John P. Hwang, and Shuling Zhou**

**Background:** In vitro models of glomerulopathic light chains (GLCs), including light chain deposition disease (LCDD) and light chain amyloidosis (AL-Am) have provided solid platforms to study the pathogenesis of these diseases and how initiation and progression takes place. C-fos and NF-κB have been found to be important signaling mechanisms in the initiation phase of these two disorders. The role of caveolin-1 in the initiation / progression phases was explored in this study using human and mouse caveolin-1 knock-out (KO) and wild type (WT) mouse MCs.

**Methods:** Human and Caveolin-1 KO and WT mouse MCs were grown on dishes (2D) and Matrigel (3D), and incubated with GLCs 10 μg/ml purified from the urine of renal biopsy-poorly treated patients with LCDD and AL-Am. Downstream effects were tested by determining whether c-fos and NF-κB transcriptional activity occurred and whether the promotion of expression and amounts of α-hemoglobin (αHb) fibril formation were observed in WT caveolin-1 MCs.

**Results:** When LCDD GLCs were incubated with caveolin-1 KO cells, no c-fos or NF-κB transcriptional activity was observed and similar amounts of amyloid fibril formation occurred when WT and caveolin-1 KO MCs were incubated with AL-Am GLCs.

**Conclusions:** Caveolin-1 (through activation of c-fos and NF-κB) plays a crucial role in signaling in LCDD and subsequent downstream effects. The absence of caveolin-1 at the surface of MCs abolishes downstream effects in LCDD but not in AL-Am. While amyloid production still occurs when MCs are incubated with Am-AL GLCs, the production of excess extracellular matrix is abolished when LCDD GLCs are incubated with caveolin-1 KO MCs.

**Funding:** Private Foundation Support

**SA-PO458**

**Inhibition of TRPC6 Channels Protects against Renal Fibrosis**

**Yueh-Lin Wu,1,2 Jian Xie,2 Chou-Long Huang,3 Taipei Medical Univ Hospital, Taiwan; UT southwestern Medical Center, Dallas, TX.**

**Background:** Fibrosis is an important process of tissue repair, yet excess leads to organ failure. In glomerular fibrosis, how initiation and progression takes place. C-fos and NF-κB have been found to be important signaling mechanisms in the initiation phase of these two disorders. The role of caveolin-1 in the initiation / progression phases was explored in this study using human and mouse caveolin-1 knock-out (KO) and wild type (WT) mouse MCs. In contrast, normal translocation was observed with WT caveolin-1 MCs. In contrast, normal translocation was observed with WT caveolin-1 MCs. In contrast, normal translocation was observed with WT caveolin-1 MCs. In contrast, normal translocation was observed with WT caveolin-1 MCs.

**Methods:** Human and Caveolin-1 KO and WT mouse MCs were grown on dishes (2D) and Matrigel (3D), and incubated with GLCs 10 μg/ml purified from the urine of renal biopsy-poorly treated patients with LCDD and AL-Am. Downstream effects were tested by determining whether c-fos and NF-κB transcriptional activity occurred and whether the promotion of expression and amounts of α-hemoglobin (αHb) fibril formation were observed in WT caveolin-1 MCs.

**Results:** When LCDD GLCs were incubated with caveolin-1 KO cells, no c-fos or NF-κB transcriptional activity was observed and similar amounts of amyloid fibril formation occurred when WT and caveolin-1 KO MCs were incubated with AL-Am GLCs.

**Conclusions:** Caveolin-1 (through activation of c-fos and NF-κB) plays a crucial role in signaling in LCDD and subsequent downstream effects. The absence of caveolin-1 at the surface of MCs abolishes downstream effects in LCDD but not in AL-Am. While amyloid production still occurs when MCs are incubated with Am-AL GLCs, the production of excess extracellular matrix is abolished when LCDD GLCs are incubated with caveolin-1 KO MCs.

**Funding:** Private Foundation Support

**SA-PO459**

**Histone Methyltransferase EZH2: A Novel Therapeutic Target for Renal Fibrosis**

**Xiaozhu Zhou, Muruguayu Ponnusamy, Evelyn Tolbert, George P. Bayliss, Shougang Zhuang.**

**Dept of Medicine, Rhode Island Hospital and Alpert Medical School, Brown University, Providence, RI.**

**Background:** EZH2 (Enhancer of Zeste Homolog 2) is a methyltransferase that induces histone H3 lysine 27 trimethylation (H3K27me3) and functions as an oncogenic factor in many cancer types. However, its role in renal fibrogenesis remains to be explored. In the course of this study, the potential role EZH2 plays in renal interstitial fibroblasts and development of renal fibrosis in a murine model of unilateral ureteral obstruction as well as mechanisms involved.

**Results:** Our results showed that EZH2 and H3K27me3 were highly expressed in the cultured renal fibroblasts and kidney from mice with unilateral ureteral obstruction. Pharmacological inhibition of EZH2 with 3-deazaneplanocin A (D3/3Nz) and GSK126, or silencing of EZH2 with its specific siRNA inhibited serum- and TGFβ1-induced activation of renal interstitial fibroblasts in vitro. Administration of 3-D3Nz ameliorated expression of extracellular matrix deposition and preserved kidney structure and function in the obstructed kidney. Mechanistically, 3-D3Nz inhibited expression of type I TGFβ receptor and phosphorylation of Smad3, along with preservation of Smad7 expression. 3-D3Nz was also effective in blocking phosphorylation of the EGFR and PDGFR receptors, and suppressing activation of STAT3 and ERK1/2 signaling pathways in the injured kidney. Moreover, 3-D3Nz treatment abolished injury-induced renal expression of αvβ6 integrin, Notch1 and Notch3. Finally, EZH2 inhibition increased expression of Pten, a protein tyrosine phosphatase associated with dephosphorylation of multiple tyrosine kinase receptors, in the kidney after ureteral ligation.

**Conclusions:** This study has identified EZH2 as an important epigenetic regulator of renal fibrosis and suggested that it could be a novel target for therapeutic interference in chronic kidney disease.

**Funding:** NIDDK Support

**SA-PO460**

**Targeting PHD2 for the Treatment of Anemia and Interstitial Fibrosis in Chronic Kidney Disease**

**Rachael Peralta, Xiaokun Xiao, Melanie Katz, Shuling Guo, Gene Hung, Sue Murray.**

**Anti-Cancer Drug Discovery, Iris Pharmaceuticals, Inc., Carlsbad, CA.**

**Background:** Anemia is a common manifestation of chronic kidney disease (CKD) and is associated with cardiovascular disease. The predominant cause of anemia in CKD is erythropoietin (EPO) deficiency. EPO is a hormone produced primarily by adult kidneys and is essential for the production of red blood cells. It has been shown in many animal models that EPO protects the kidney against interstitial fibrosis. Proxil hydroxylation of domain 2 (PHD2) is a primary regulator of hypoxia-inducible factors (HIFs) that regulate genes involved in cellular adaptation to reduced oxygen availability. When PHD2 is reduced, HIFa is stabilized and upregulates several genes to promote survival in low-oxygen conditions. Systemic PHD2 inactivation has been found to increase renal EPO production and stimulate red blood cell synthesis, which can improve anemia in CKD patients (Minamishima et al, Science 2010).

**Results:** Using antisense oligonucleotides (ASOs) designed against the PHD2 mRNA, we have demonstrated a 60% reduction of kidney PHD2 expression after 4 weeks of treatment in adenine (7 mg/70 g bw/week) compared to the saline group. In addition, we observed increases in EPO mRNA expression in the kidney interstitial fibroblasts by RT-PCR (~550-fold) and in-situ analysis. We sought to demonstrate an improvement in anemia and renal fibrosis using our PHD2 ASO. We developed an adenine-induced mouse model of CKD that developed severe anemia and interstitial fibrosis. After simultaneous administration of the 0.2% adenine diet and the PHD2 ASO (12 mg/12 weeks) for 12 weeks, we observed significant increases in kidney EPO mRNA (~35-fold) and plasma EPO levels (~12-fold) compared to the control ASO group. Histological analysis showed improved fibrosis based on reduced Sirius Red staining. There were also improvements in anemia based on whole blood analysis of hemoglobin and hematocrit levels.

**Conclusions:** These data indicate that reducing PHD2 with ASOs may be a viable option for treating CKD patients with severe anemia and renal fibrosis.

**Funding:** Pharmaceutical Company Support - Iris Pharmaceuticals, Inc.

**SA-PO461**

**Fibronectin Assembly Mediates KIM-1 Induced TGFβ-Dependent Kidney Fibrosis**

**Venkata Sambisetty, Cuiyan Xin, Sandhya Padmanabhan, Bhargavi Chandrasekhar, Akinwande A. Akinfolarin, Joseph V. Bonventre.**

**Dept of Cellular, Molecular & Nutritional Div, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.**

**Background:** Cell-extracellular matrix interactions play a crucial role in kidney fibrosis. Localized activation of TGFβ is critical for excretion of its cellular effects. Kidney injury molecule-1 (KIM-1) is upregulated in dedifferentiated proximal tubular cells (PTECs) following kidney injury and has been shown to induce kidney fibrosis in vivo. Here, we report that KIM-1 mediates fibrosis by up-regulating the critical components of the TGFβ activation machinery including fibronectin and corresponding integrins uniquely in vivo. In blocking fibronectin assembly reduces kidney fibrosis.

**Methods:** Full-length KIM-1 or the KIM-1 mutant was overexpressed in LLC-PK1 and HEK cell lines and fibronectin and integrin levels were evaluated. Active TGFβ was measured using a bioassay. Mice were subjected to ischemia/reperfusion injury (IRI) or

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

**Underlines represent presenting author.**

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unilateral ureteral obstruction (UUO). In the UUO model, mice were treated with fibronectin blocking peptide or control peptide to evaluate the effects of inhibition of fibronectin assembly on fibrosis.

**Results:** KIM-1 expressing PTECs produced significantly increased levels of fibronectin and fibronectin receptors. These increases were abrogated when phosphorytrosine-350 of KIM-1 was mutated or KIM-1 was deleted. KIM-1 expressing cells displayed higher levels of total and activated TGFβ as compared to control cells. In vivo, KIM-1 expressing tubular epithelial cells were characterized by high fibronectin staining after ischemia/reperfusion injury or UUO. Blocking fibronectin assembly with a blocking peptide decreased fibrosis in the UUO model.

**Conclusions:** KIM-1 induced localized activation of TGFβthrough up-regulation of TGFβ, fibronectin and integrin receptors. Blocking fibronectin assembly reduced fibrosis in response to UUO in vivo. This mechanism can contribute to the fibrosis associated with chronic expression of KIM-1 and may be a common feature of chronic kidney disease. Blocking fibronectin assembly may be therapeutically beneficial to prevent or reduce kidney fibrosis.

**Funding:** NIDDK Support

**SA-PO462**

**Complement Modulation by C1-Inhibitor Hampered Pericyte (PC) to Myofibroblast Trans-Differentiation (TDF) and Vascular Rarefaction in Ischemia/Reperfusion (I/R) Injury** Giuseppe Castellano,1 Rossana Franzin,1 Chiara Divella,1 Alessandra Stasi,1 Angelica Intini,1 Margherita Gigante,1 Marco Fiorentino,1 G. Lucarelli,1 M. Battaglia,1 Giuseppe Grandaliano,1 Loretto Gesualdo1 1Nephrology and Urology Unit, Univ of Bari;2Dept Medical and Surgical Science, Univ of Foggia, Italy.

**Background:** Preservation of endothelium-Pericyte (PC) interaction is critical to counteract renal fibrosis during chronic kidney disease; no data are available on PC involvement in AKI. We investigated whether Complement might modulate PC activation in I/R.

**Methods:** Ten pigs underwent to 30 min of renal warm I, followed by 24h of R. Five pigs were treated with C1-Inhibitor (C1-Inh, 500U/Kg). Biopsies were analyzed by IHC and IF for PDGFRβ, Caspase3 and aSMA. FACS, Ann-V-IP and IF were performed on human PC (PDGFRβ cells) stimulated with CsA (1x10⁻⁴ M) for 24h in vitro.

**Results:** I/R induced PC to myofibroblasts TDF by reducing PDGFRβ without PC apoptosis (PDGFRβ/Caspase3) in vivo. TDF was accompanied by a significant decrease in capillary lumen area (Fig1A: %T0:11.3±2.1; T24:3.9±2.3; p<0.05) and aSMA up regulation (Fig1B): C1-Inh preserved PDGFRβ expression in PC and restored peritubular capillary area (T24C1-Inh:12.06±3.5 vs T24). In accordance, C5a induced PC proliferation and Collagen I production without apoptosis (Ann V) in vitro. CsA induced PC to myofibroblasts TDF, with PDGFRβ down-regulation (Fig1C: %Bas: 15.2i±3.6; CsA:3.6±2.3; TGFβ:2.08±1.04 p<0.05) and remodeling of aSMA stress fibers, with contractile phenotype. Finally, CsA significantly up-regulated iId2 factor in PC, which is pivotal for cellular de-differentiation.

**Conclusions:** Complement might contribute to PC to Myofibroblasts TDF in I/R injury, leading to vascular rarefaction and renal fibrosis. C1-Inh may be an effective strategy to prevent renal development in transplanted kidney.

**Funding:** NIDDK Support

**SA-PO463**

Establishment of a Novel Mouse Strain to Trace Erythropoietin Producing Cells at Desired Time Points Keiichi Kaneko, Motoko Yanagita. Nephrology, Kyoto Univ, Kyoto, Japan.

**Background:** We previously reported that resident fibroblasts including Erythropoietin (Epo) producing cells were labeled with myelin proteolipid protein and transdifferentiated into myofibroblasts during fibrosis with concomitant loss of Epo production. However, the previous method could not distinguish between Epo-producing cells and other resident fibroblasts and the behavior of Epo-producing cells remains unclear. Recently, Epo-Cre mice were generated which enabled the lineage tracing of Epo-Cre labeled cells during fibrosis development and the history of Epo production. Using the mouse strain, the transdifferentiation of Epo-Cre labeled cells into myofibroblasts during fibrosis has been demonstrated. Because Epo-Cre mice labeled the cells with the history of Epo production from fetal period to adult life, we tried to narrow down the period of labeling and to trace the certain cell population with the current Epo-producing ability at desired time points.

**Methods:** We generated a novel mouse strain in which inducible form of Cre is knocked-in at the locus of Epo gene (Epo-CreERT2 mice). Epo-CreERT2 mice were crossed with B26f1Tomato mice. Tamoxifen was administered to induce inducible form of Cre, EpoERT2.

**Results:** Epo-CreERT2 labeled cells were located in the interstitium of the cortical and corticomedullary region of the kidney, and the numbers increased with the induction of anemia. Epo-CreERT2 labeled cells expressed PDGFRβ and CD73, suggesting that Epo-CreERT2 labeled cells are resident fibroblasts and are likely to be Epo-producing cells. After unilateral ureteral obstruction (UUO), Epo-CreERT2 labeled cells transdifferentiated into myofibroblasts. The ratio of Epo-CreERT2 labeled cells transdifferentiated into myofibroblasts was 68 % at day 3 and 86 % at day 5 of UUO. The numbers of Epo-CreERT2 labeled cells were increased 1.9-fold at day 3 and 2.1-fold at day 5 of UUO.

**Conclusions:** We generated a novel mouse strain and succeeded in labeling Epo-producing cells at desired time points. We demonstrated that Epo-producing cells transdifferentiated into myofibroblasts and were increased in fibrotic kidney. We aim to elucidate the mechanism of injury and repair of Epo-producing cells with this strain, Epo-CreERT2 mice.

**SA-PO464**

**Role of P13 Kinase γ in Recruitment of Bone Marrow-Derived Fibroblasts and Development of Renal Fibrosis** Yumaho Wu, Hua Liang, William E. Mitch, Yanlin Wang. Medicine, Baylor College of Medicine, Houston, TX.

**Background:** Renal fibrosis is a prominent pathological feature of chronic kidney disease leading to progressive loss of renal function. Although activated fibroblasts are responsible for the production and deposition of the extracellular matrix, the origin of activated fibroblasts mediating renal fibrosis remains debatable. Recent studies have shown bone marrow-derived fibroblasts contributed significantly to the pathogenesis of renal fibrosis. We previously showed that CNXCL16 plays a critical role in recruiting bone marrow-derived fibroblasts into kidney. However, the signaling mechanisms are not known. In the present study, we examined the role of P13 kinase γ (PI3Kγ) in the recruitment of bone marrow-derived fibroblasts and development of renal fibrosis. We have previously shown that CXCL16 plays a critical role in recruiting bone marrow-derived fibroblasts and the development of fibrosis using a mouse model of follic acid-induced nephropathy in wild-type (WT) and PI3Kγ-knockout (KO) mice in vivo and migration of cultured mouse monocyte treated with CXCL16 in vitro.

**Results:** Compared with WT mice, PI3Kγ-KO mice exhibited significant preservation of kidney function as measured by serum urea nitrogen and displayed significantly fewer bone marrow-derived fibroblasts dual positive for CD45 and PDGFRβ in the kidney 2 weeks after follic acid treatment. Furthermore, PI3Kγ-KO mice exhibited fewer α-smooth muscle actin (α-SMA) positive myofibroblasts and expressed less α-SMA protein in the kidney following follic acid treatment. Consistent with these findings, PI3Kγ-deficiency significantly reduced total collagen deposition and suppressed expression of extracellular matrix proteins (collagen 1 and fibronectin). In cultured mouse monocytes, CXCL16 activated PI3Kγ and induced bone marrow migration, which was abolished in the absence of PI3Kγ.

**Conclusions:** These data indicate that PI3Kγ plays a pivotal role in recruiting bone marrow-derived fibroblasts into the kidney and developing renal fibrosis. Inhibition of PI3Kγ signaling may represent a novel therapeutic strategy for chronic kidney disease.

**Funding:** NIDDK Support

**SA-PO465**

**Inhibition of K-Ras prior to Induction of Acute Kidney Reduces Long-Term Progression to Chronic Kidney Disease in a Murine Model of Aristolochic Acid Nephropathy** Sujit Kumar Saha, Bruce M. Hendry, Claire C. Sharpe. Dept of Renal Sciences, King's College London, London, United Kingdom.

**Background:** Acute kidney injury (AKI) is recognised to be an early harbinger of chronic kidney disease (CKD). We have previously shown that K-Ras expression and activation are up-regulated in renal fibrosis and reducing K-Ras expression can prevent scarring. In this study our aim was to test whether transiently reducing K-Ras expression in the peri-AKI period can reduce progression to CKD.

**Methods:** CD1 mice received i.p. injections of either 3.5mg/kg Aristolochic Acid (AA) or normal saline on Day 1 and on Day 5. A treatment group were also given a single...
subcutaneous injection of 100mg/kg of mouse K-Ras antisense oligonucleotide (ASO) 2 days prior to the first AA injection. A vehicle group was given a subcutaneous injection of saline 2 days prior to the first AA injection. Renal function at multiple time points was assessed through a blood urea nitrogen (BUN) assay. The degree of fibrosis was ascertained through Picrosirius Red (PSR) and Masson Trichrome (MT) staining to quantify collagen deposition. The expression of K-Ras was determined by Q-PCR.

Results: CD1 mice given AA suffered an AKI with a 4.6 fold rise in BUN at Day 12 that returned to baseline by Day 30. However by Day 80, the AA mice had a 57% higher BUN than control mice, demonstrating later onset CKD. AA mice treated with mouse K-Ras ASO pre-AKI suffered a similar AKI but BUN at Day 80 was 48% lower than untreated AA mice and was comparable with healthy controls. PSR and MT staining demonstrated a 5 fold increase in collagen deposition by Day 80 in AA mice which was reduced by 30% in ASO-treated animals. K-Ras expression was consistently unregulated in the untreated AA mice throughout the chronic phase but the transient treatment with ASO prior to the acute injury resulted in normalisation of K-Ras mRNA by Day 80.

Conclusions: Transiently reducing K-Ras expression in the peri-AKI period in a murine model of aristolochic acid nephropathy reduces downstream fibrosis and prevents the decline in renal excretory function. Targeting K-Ras may provide a future therapeutic option for preventing renal fibrosis and CKD following AKI.

SA-PO466
Non-Osmotic Sodium Storage Affects Glomerular Endothelial Cell Permeability
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Background: High dietary NaCl intake may affect glomerular permeability via pressure effects or via direct effects. In this respect, the Na+ buffering capacity of heparan sulfate glycosaminoglycans (HS-GAGs) in the endothelial surface layer (ESL) is of interest. The objective of this study is to investigate the interplay between Na+ and HS-GAGs and their effects on glomerular permeability.

Methods: Human glomerular endothelial cell (GEnCi) permeability to macromolecules was tested by measuring FITC-labeled albumin passage. Electrical resistance of a GEnCi monolayer, reflecting ESL Na+ content, was assessed with the ECIS® system at 4000 Hz. We studied the expression of gene coding enzymes involved in heparan sulfate (EXT-1, EXT-2) and chondroitin sulfate (CHSY) synthesis using real-time qPCR. Measurements were performed at different NaCl concentrations (125/150/175 mM NaCl ± HS degradation enzyme heparinase, 0.7 U/mL). We added mannitol to keep osmolality constant.

Results: Relative to 125 mM, EXT-1 and EXT-2 expression was higher after stimulation with 150 mM NaCl while CHSY expression remained unchanged (Fig A). Albumin permeability decreased after 2 and 5 days stimulation with 150 and 175 mM NaCl (Fig B). ECIS experiments showed that NaCl addition led to a concentration-dependent decrease in resistance (Fig C). NaCl did not alter resistance in the absence of cells. Heparinase increased resistance when added to 125 and 150 mM NaCl (Fig D). Mannitol did not alter permeability or resistance.

Conclusions: High NaCl stimulates HS-GAG synthesis of the glomerular endothelium, which may facilitate more Na+ binding. Subsequent higher ESL Na+ content may seal the glomerular barrier as suggested by both lower permeability and lower resistance.

Funding: LifeLabs Foundation Support, Government Support - Non-U.S.

SA-PO467
Precision-Cut Human Kidney Slices as a Model to Elucidate the Pathogenesis of Renal Fibrosis
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Background: Renal fibrosis is a major problem in chronic kidney disease and chronic renal transplanted failure. Unraveling the mechanisms underlying the initiation and progression of renal fibrosis is of key importance to identify new therapeutic targets. However, suitable human in vivo models for renal fibrosis are lacking. Here, we explored precision-cut human kidney slices (PCKS) as a model for human renal disease.

Methods: PCKS were prepared from human cortical kidney tissue obtained from tumor-nephrectomies and cultured up to 96th. Morphology, cell viability (ATP levels, LDH leakage) and metabolic functionality (UDP-glucuronosyltransferase and transporter activity) were determined to assess PCKS integrity. Furthermore, inflammation- and fibrosis-related gene expression was characterized. To validate the model, renal fibrogenesis was induced using transforming-growth factor b1 (TGF-b1).

Results: Preparation of PCKS induced an inflammatory tissue response, while long-term incubation (96h) induced fibrogenesis as seen by increased expression of collagen type 1a1 (COL1A1) and fibropectin (FN1). Importantly, PCKS remained functional for more than 48h as evidenced by active glucuronidase and phospholipasef epoxide uptake. Moreover, treatment with TGF-b1 augmented fibrosis, as illustrated by at least 1.8-fold increase of multiple fibrosis markers including COL1A1, FN1, plasminogen activator inhibitor-1 and a-smooth muscle actin.

Conclusions: With extensive characterization, PCKS appear to be an excellent model to investigate renal pathology e.g. renal fibrosis. Moreover, the human origin of PCKS makes this ex vivo model very suitable for translational research.

Funding: NIDDK Support, Veterans Administration Support

SA-PO468
Centrality of Bone Marrow-Derived Fibroblasts in Magnetic Resonance Imaging Contrast-Induced Systemic Fibrosis
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Background: So-called “nephrogenic” systemic fibrosis is a ghastly sclerotic condition that occurs only in conditions of low renal function (acute kidney injury or severe chronic kidney disease) and gadolinium-based contrast exposure. Nothing is known about the pathology.

Methods: Experiments were designed to test if bone marrow from magnetic resonance imaging contrast–treated donors is stimulated to induce fibrosis, and to what degree these cells can be primed to home to affected organs. Male Fisher 344 rats that express human placental alkaline phosphatase (hPLAP) were divided into two groups, one served as control, the other treated with the glycosaminoglycan-type grade gadodiamide (Osmianc, General Electric) 2.5 mol/kg IP daily, aiming for dosing over 4 weeks or evidence of systemic fibrosis. Rats with 5/6 nephrectomies were lethally–irradiated (900 Rad) followed by salvage bone marrow transplant from the control or contrast–treated donors. After an engraftment period, these recipients were divided into control and contrast–treated groups.

Results: Regardless of bone marrow source, contrast–treated recipients demonstrated severe skin fibrosis. Fibronectin was similarly increased by immunofluorescence and immunoblot, but a synergistic effect evident in recipients of contrast–treated animals. The fibroblast precursor (“fibrocyte”) markers, CD45RO and procollagen I, were increased in the contrast–treated recipients. Recipients of marrow from contrast–treated donors demonstrated greater dermal CD34 without histologic evidence of fibrosis.

Conclusions: Bone marrow from contrast–treated animals did not induce systemic fibrosis, therefore target organs (such as the skin) appear central to the process. However, given the synergistic effect, “primed” fibroblast precursors do have an increased affinity for diseased lesions. Clinically, this may explain why repeat administrations of gadolinium–based contrast correlate with chronicity.

Funding: NIDDK Support, Veterans Administration Support

SA-PO469
SOCS2 Plays No Major Role in the Mouse Remnant Kidney Model of Fibrosis
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Background: SOCS2, a key negative regulator of GH stimulated JAK/STA T5 signaling, is overexpressed in muscle, bone and liver of uremic rats and is presumably a cause of uremic GH resistance and growth retardation. SOCS2 deficient mice are GH sensitive, exhibit gigantism and accumulate collagen in skin, trachea and lungs (Reiser K et al, AJP 2004). Since GH overexpression is one of the key causes renal fibrosis, we tested whether SOCS2 deletion, by decreasing GH sensitivity, accelerates renal kidney fibrosis.

Methods: SOCS2 Plays No Major Role in the Mouse Remnant Kidney Model of Fibrosis
β-arrestin2, Downstream of Angiotensin II Type I Receptor Biased Signaling Pathway, Plays an Important Role in Renal Fibrosis

**Methods:** We used a combination of molecular and cellular approaches to investigate the role of β-arrestin2 in renal fibrosis. We generated a mouse model where β-arrestin2 is selectively expressed in the renal proximal tubule (β-arrestin2-RRTPC). We then subjected these mice to unilateral ureteral obstruction (UUO) and renal ischemia/reperfusion injury (IRI) to induce renal fibrosis. In addition, we performed in vitro experiments using NRK-49F cells treated with SII, which activates the β-arrestin pathway.

**Results:**

1. **SII-induced β-arrestin2 phosphorylation**: We found that SII induced the binding of β-arrestin2 to the AT1R, but not β-arrestin1.

2. **SII-induced collagen synthesis**: SII increased the synthesis of collagen I and fibronectin in NRK-49F cells.

3. **Transfection of β-arrestin2 enhanced SII-induced fibronectin expression**: Transfection of β-arrestin2 enhanced SII-induced fibronectin expression in NRK-49F cells.

4. **Role of β-arrestin2 in renal fibrosis**: Deletion of β-arrestin2 in the renal proximal tubule (β-arrestin2-RRTPC) resulted in decreased renal fibrosis compared to wild-type mice.

**Conclusions:** Our results suggest that β-arrestin2 plays a critical role in renal fibrosis by promoting collagen synthesis and fibronectin expression. This target is a potential therapeutic intervention for renal fibrosis.

**Funding:** This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant DK106704.

**SA-PO471**

**Deletion of ATR, a Master Molecule of DNA Damage Response, in the Proximal Tubule Exacerbates Kidney Injury and Increases Fibrosis**

**Methods:** To investigate the role of ATR (ATM: ataxia telangiectasia and Rad3-related) in renal fibrosis, we generated RPTC-/- mice and subjected them to models of kidney injury, such as unilateral ureteral obstruction (UUO) and renal ischemia/reperfusion injury (IRI).

**Results:**

1. **Lowered renal function in ATR-/- mice**: RPTC-/- mice exhibited decreased renal function compared to wild-type controls.

2. **Increased histological damage in ATR-/- mice**: RPTC-/- mice had more severe histological damage compared to wild-type controls.

3. **Increased kidney fibrosis in ATR-/- mice**: RPTC-/- mice showed increased kidney fibrosis compared to wild-type controls.

**Conclusions:** The deletion of ATR in the renal proximal tubule exacerbates kidney injury and increases renal fibrosis.

**Funding:** This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant DK106704.

**SA-PO472**

**Role of Heparanase in Renal Epithelial-Mesenchymal Transition Induced by Ischemia/Reperfusion**

**Methods:** To study the role of heparanase in EMT, we used a mouse model of ischemia/reperfusion injury (IRI) and measured the expression of EMT markers.

**Results:**

1. **Increased heparanase expression**: Heparanase expression was increased in the kidneys of mice subjected to IRI.

2. **Impaired EMT induction**: Inhibition of heparanase reduced the induction of EMT markers.

**Conclusions:** Heparanase plays a role in promoting EMT during renal ischemia/reperfusion injury.

**Funding:** This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant DK106704.

**SA-PO473**

**Hydrogen Sulfide Deficiency in the Kidney and Brain in Aging Mice**

**Methods:** To study the role of H2S in aging, we used a mouse model of aging and measured the expression of H2S-related genes.

**Results:**

1. **Reduced H2S expression**: H2S expression was decreased in the kidneys and brains of old mice.

2. **Increased mTORC1 activation**: mTORC1 activation was increased in the kidneys and brains of old mice.

**Conclusions:** H2S deficiency in aging mice contributes to the increased mTORC1 activation.

**Funding:** This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant DK106704.

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

**Underline represents presenting author.**

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**Poster/Saturday**

**732A**
to mTORC1 activation; these pathways could be related to age-related changes including fibrosis. Insulin may mediate reduction in CBS, CSE and H2S and contribute to matrix accumulation in the aging kidney. 

**Funding:** Other NIH Support - NIA, Veterans Administration Support

SA-PO474

The Role of Ergothioneine/OCTN1 in CKD 

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**Background:** Chronic kidney disease (CKD) is a strong risk factor for end stage kidney disease, and closely complicates with other organ damages. Organic cation transporter 1 (OCTN1) is known as a specific transporter for ergothioneine (ERGO). ERGO is reported to have a strong antioxidant effect. We hypothesized that OCTN1 function and the reduction of ERGO were closely related to the progression of CKD.

**Methods:** To evaluate the effects of OCTN1 function in CKD, everted sac method was used in CKD model or control mice. Furthermore, the pathological changes and oxidative stress in the kidney of OCTN1-/- or OCTN1+/- were evaluated in the CKD model mice. Moreover, the amount of ERGO in red blood cells of was measured in CKD patients.

**Results:** The uptake of ERGO in everted sac significantly decreased in CKD mice than control mice. Interstitial fibrosis, that evaluated by azan stain, sirius red stain, and the accumulation in the aging kidney. 

**Conclusions:** The uptake of ERGO through OCTN1 decreased in CKD. The reduction of ERGO in CKD may participate in oxidative stress and progression of kidney injury.

SA-PO475

SIRT2-MDM2 Signaling Attributes to Fibroblasts Activation but Not Tubular Epithelial-Mesenchymal Transition During Tubulointerstitial Fibrosis 

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**Background:** Renal resident fibroblasts and tubular epithelial cells are the main sources for extracellular matrix producing myofibroblasts during tubulointerstitial fibrosis (TIF). Histone deacetylases (HDAC) inhibitors are shown to have an anti-fibrotic effect in skin, liver and lung. Sirtuin 2 (SIRT2), belonging to class III HDAC, mediates p53 deacetylation and subsequently sensitizes the sequestration of p53 by MDM2, thereby resulting in a p53 reduction and cell cycle progression. Up to now it is unclear the role of SIRT2 and its association with MDM2 during renal fibrosis.

**Methods:** Unilateral Ureteral Obstruction (UUO) animal model was constructed on B57CL/6 mice. In vitro study cultured tubular epithelial cell line NRK-52E (TEC) and renal fibroblast cell line NRK-49F were employed. The expression of MDM2 and SIRT2 was regulated by its pharmacologic inhibitors or transfection of Lentiviral shRNA.

**Results:** It showed the protein level of SIRT2 was elevated markedly in UUO mice as well as the fibroblasts treated with TGF-b1. Nevertheless, in TECs the abundance of SIRT2 was not altered under TGF-b1 exposure. Additionally, AGK2, a specific SIRT2 inhibitor, attenuated the severity of TIF in UUO mice and the fibroblast activation triggered by TGF-b1. Next in fibroblast we found MDM2, a p53 inhibitor, was upregulated simultaneously under TGF-b1 stimulation. Interestingly, the increased MDM2 level can be minimized by pharmacologic or genetic blocking of SIRT2 which was not interfered by the specific inhibitor of the interaction between MDM2 and p53. Thus, it indicated SIRT2 regulating MDM2 was p53 independent. Moreover, genetic deletion of MDM2 by shRNA transfection didn’t affect the expression of SIRT2, although which could alleviate fibroblast activation.

**Conclusions:** Our current study suggests that besides p53, SIRT2 also could modulate MDM2 during fibroblasts activation, and targeting SIRT2-MDM2 signaling may be a potential strategy for the treatment of renal fibrosis.

**Funding:** Government Support - Non-U.S.

SA-PO476

The Role of ePLA2, in Experimental Renal Fibrosis 

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**Background:** Chronic kidney disease (CKD) is characterized by progressive renal fibrosis involving poorly defined signaling events between renal epithelial cells, fibroblasts, and inflammatory cells. Cystosolic phospholipase A2 (cPLA2) is abundant in renal epithelium and inflammatory cells and serves as the rate-limiting enzyme in eicosanoid production. Since eicosanoids regulate many biological processes important in renal injury, we aimed to investigate the role of cPLA2 in the progression of renal fibrosis in a mouse model.

**Methods:** Wild-type (WT) and cPLA2 globally deficient (KO) C57BL/6 mice were subjected to unilateral ureteral obstruction (UUO). In separate experiments WT mice were lethally irradiated and transplanted with either WT bone marrow or cPLA2-deficient bone marrow. We then performed UUO 5-6 weeks after bone marrow transplantation. After UUO, we collected unfractioned and injured kidneys for RNA, protein, flow cytometry, and histologic analysis, and preparation of single cell suspensions for flow cytometry.

**Results:** Compared with WT, cPLA2 KO animals had a 1.5-2.0 fold increase in histologic fibrosis at 14 days after UUO. In addition, the KO animals had elevated levels of renal injury proteins such as collagen and fibrinectin, pro-fibrotic chemokines such as fractalkine, and inflammatory markers such as MCP-1 after UUO as compared with WT animals at 7 days. By flow cytometry, cPLA2 KO animals had significantly more infiltration of CD45+; CD11b positive-Ly6C negative cells than WT animals after UUO. Additionally, adoptive bone marrow transplant from cPLA2 KO mice into WT mice yielded worsening of histologic fibrosis after UUO as compared with transplants derived from WT animals.

**Conclusions:** Depletion of cPLA2 and/or its products, predominantly from circulating myeloid cells, contribute to the development of experimental fibrosis using a UUO model in mice.

**Funding:** Other NIH Support - 1 F32 DK104475-0

SA-PO477

Delayed Administration of Suramin Attenuates Peritubular Fibrosis in Rats 

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**Background:** Peritubular fibrosis is one of the most serious complications in patients with peritoneal dialysis (PD) and lacks effective treatments. Our recent study showed that treatment with suramin, a compound that inhibits the interaction of multiple cytokines with their receptors, attenuated the development of peritoneal fibrosis in rats exposed to peritoneal fibrosis induced by chlorhexidine gluconate (CG). In the current study, we further assessed the therapeutic effect of suramin on the progression of peritoneal fibrosis in this model.

**Methods:** Rats were given a daily intraperitoneal injection of chlorhexidine gluconate (CG) for 3 weeks to induce peritoneal fibrosis followed by weekly administration of suramin at 20 mg/kg for an additional one or two weeks before kidneys were harvested.

**Results:** Delayed administration of suramin attenuated peritubular membrane thickening and collagen fibril deposition occurred after CG exposure. Suramin was also effective in reducing CG-induced expression of a-smooth muscle actin, fibronectin and collagen I. However, peritubular membrane thickening in CG exposed mice was not reversed by suramin. Moreover, delayed application of suramin suppressed CG-induced expression of several inflammatory cytokines in fibrotic peritoneum.

**Conclusions:** Our results indicate that suramin treatment inhibits the progression of peritoneal fibrosis via a mechanism involved in suppression of TGF-b1 and EGFR signaling pathways, and suggest that suramin holds a therapeutic potential for treatment of peritoneal fibrosis.

SA-PO478

MDM2 Mediates Tubulointerstitial Fibrosis and Fibroblasts Activation via p53-Independent Pathway 

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**Background:** MDM2 is an E3 ubiquitin ligase which plays essential roles in podocytes and tubular epithelial cells injury or repair by regulating cell cycle and mediating inflammatory process. MDM2 exerts its pathophysiological effects via p53 dependent or independent pathway. However whether MDM2 is implicated in tubulointerstitial fibrosis (TIF) and fibroblasts activation is still unknown.

**Methods:** Patients with TIF (secondary glomerulonephritis and interstitial nephritis were excluded) were enrolled in this study and Unilateral Ureteral Obstruction (UOO) animal model was constructed on B57CL/6 mice. In vitro study cultured renal fibroblast cell line NRK-49F was employed. The expression of MDM2 and Notch1 was regulated by its pharmacologic inhibitors or transfection of Lentiviral shRNA. PYR-41 was used as an inhibitor of ubiquitin E1 activating enzyme.

**Results:** Here, we found that unilateral UUO interstitial MDM2 was increased in patients with TIF as well as UUO mice. And interstitial MDM2 mainly originated from (myo) fibroblast. In vitro the expression of MDM2 was upregulated with fibroblasts activation under TGF-b1 stimulation, whereas was not amplified by MDM2 knocking down but by MDM2-p53 pathway inhibitor—Nutlin-3. Consistently, in UUO mice Nutlin-3 treatment cannot alleviate the interstitial fibrosis. Interestingly, we found Notch1, a molecule positively or negatively affecting the processes of proliferation, differentiation and apoptosis in a context-dependent manner, was reduced in cultured fibroblast treated with TGF-b1 which could be reversed by either genetic or pharmacologic blocking Notch1 signaling. Moreover, although pharmacologic or genetic blocking Notch1 signaling could trigger fibroblast activation it did not affect MDM2’s abundance.

**Conclusions:** Our current study suggests that MDM2-Notch1 signaling pathway, not the classic MDM2-p53 pathway, is involved in fibroblast activation in a ubiquitin dependent manner during tubulointerstitial fibrosis.

**Funding:** Government Support - Non-U.S.
The cAMP-epac Pathway Regulates Renal Fibrosis by Promoting Mitochondrial Biogenesis of Tubular Epithelial Cell
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Background: Thymosin β4 (Tβ4) is a G-actin sequestering protein with effects on angiogenesis, cell migration and matrix. Our previous data showed that exogenous Tβ4 treatment ameliorated ameloblastoma accumulation at day 14 after unilateral ureteral obstruction (UUO). In this study, we investigated whether knockdown of Tβ4 only on endothelial cells has effects on renal fibrosis.
Methods: We generated inducible endothelial cell Tβ4 knockdown mouse (Tβ4 KD) by mating Tβ4 sRNAlox mosaic mice with SCL Cre mice. SCL Cre negative mice were used as control (Cont). Tamoxifen was administrated to induce Tβ4 knockdown (+, qod, from 8d).
Results: Peritubular capillary density, assessed by CD31 staining, was significantly decreased in Tβ4 KD mice (Tβ4 KD 2.39±0.11 vs. Cont 3.20±0.08 %, P<0.001). Peritubular capillary permeability, measured by injecting Evans blue dye in vivo and assessing extravasated dye in the kidney, also was reduced in Tβ4 KD mice (Tβ4 KD 107.01±5.49 vs. Cont 161.85±16.32 mg/KW, P<0.05). Tβ4 KD had significantly decreased collagen I, assayed by IHC, vs. Cont (Tβ4 KD 15.24±0.57 vs. Cont 17.68±0.71 %, P<0.05), but no significant change in Sirius red positive area (Tβ4 KD 0.91±0.03 vs. Cont 1.14±0.15 %). Total collagen (Tβ4 KD 48.06±5.01 vs. Cont 53.50±2.34 mg/mg). Tβ4 KD had less EndoMT (α-SMA- and CD31- double positive cells/high power, Tβ4 KD 1.20±0.11 vs. Cont 1.74±0.17, P<0.05).
Conclusions: We conclude that endothelial cell thymosin β4 knockdown results in increased peritubular capillary density and function, with reduced collagen and EndoMT in UUO. We speculate that Tβ4 KD in endothelial cells may change endothelial function and modulate EndoMT.
Funding: NIDDK Support

Endostatin and Transglutaminase 2 Are Geroncic Proteins Involved in Fibrosis of Aging Kidney
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Background: Endostatin (EST), the C-terminal fragment of collagen XVIII and a potent anti-angiogenic factor, is highly enriched in aging kidneys. It has also been recently observed that a protective patterning protein, transglutaminase 2 (TG2), is described as an interactive partner of another profibrogenic factor, transglutaminase 2 (TG2), underlining its role in aging kidney. Moreover, a month-long delivery of EST peptide via implanted minipumps to aging kidney. Moreover, a month-long delivery of EST peptide via implanted minipumps has effects on renal fibrosis.
Methods: Studies were conducted in young and aging wild type mice, overexpressing EST and mice kidney of subcapsular injection of Tg2 or EST.
Results: In wild type mice, aging kidneys exhibited 2-4-fold increase in TG2 paralleled by the increased cross-linking of extracellular matrix proteins and striped fibrosis. Ex vivo aortic rings embedded in matrigel supplemented with TG2 showed suppressed angiogenesis and proteolytic degradation. Injection of TG2 in the intact kidney produces increased cross-linking within 48h. Transgenic microveurexpressing EST showed renal interstitial fibrosis already at the young age, suggesting that EST may contributes to interstitial fibrosis in the aging kidney. Moreover, a month-long delivery of EST peptide via implanted minipumps to mice kidney also showed increased renal fibrosis, which became more robust when superimposed on the early "wound healing" phase of folic acid (FA)-induced nephropathy, an "accelerated" response in the kidney, also was reduced in Tβ4 KD mice (Tβ4 KD 0.91±0.03 vs. Cont 1.14±0.15 %). Total collagen (Tβ4 KD 48.06±5.01 vs. Cont 53.50±2.34 mg/mg). Tβ4 KD had less EndoMT (α-SMA- and CD31- double positive cells/high power, Tβ4 KD 1.20±0.11 vs. Cont 1.74±0.17, P<0.05).
Conclusions: We conclude that endothelial cell thymosin β4 knockdown results in increased peritubular capillary density and function, with reduced collagen and EndoMT in UUO. We speculate that Tβ4 KD in endothelial cells may change endothelial function and modulate EndoMT.
Funding: NIDDK Support

Biomarkers of Collagen Type III and VI Turnover Can Predict Poor Recovery of Kidney Function in Kidney Transplant Recipients
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Background: Allograft dysfunction is a common complication after renal transplantation (Tx). The turnover of extracellular matrix proteins, collagen type III and type VI, contributes to renal repair mechanisms which accompany allograft dysfunction. Distorted turnover may lead to progressive fibrosis and to loss of renal function. The objective of our study was to evaluate the role of specific collagen type III and type VI cleavage fragments for early allograft dysfunction after kidney Tx.
Methods: 171 incident patients, receiving a kidney allograft were enrolled at Odense University Hospital. Plasma and urine samples were collected at the first postoperative days. C3M and Pro-C6 were measured in samples using novel ELISAs. Early allograft dysfunction was defined as eGFR less than 30 ml per minute per 1.73m2 29 days after Tx. The correlation of change of plasma creatinine (RCP) is the difference between plasma creatinine (pCrea) on the preoperative and first postoperative day divided by preoperative pCrea. Follow-up data on pCrea from a subset of patients was available at 6- and 12-months.
Results: Plasma Pro-C6 (pPro-C6) levels were significantly different in patients who received a deceased donor (DD), living donor (LD) and AB0 incompatible (AB0) donor kidney (p<0.001). pPro-C6 had a negative correlation with eGFR 29 days post Tx (p<0.001, r=-0.35) and a positive correlation with pCrea at 6- (p=0.0001, r=0.31) and 12 months (p<0.0001, r=0.32). With a cut-off of 0.3 for the RCPC, ROC curves showed that pPro-C6 predicted allograft dysfunction (p<0.0001, AUC=0.898). pCrea levels were significantly different in patients receiving a DD, LD and AB0 donor kidney, uC3M plasma Pro-C6 predicted allograft dysfunction (p<0.0001, AUC=0.898). uC3M levels were significantly different in patients receiving a DD, LD and AB0 donor kidney (p<0.0001, r=-0.35). Plasma C3M was associated with plasma CRP (p<0.0001, r=0.62).
Conclusions: The study indicates that specific collagen type III and type VI cleavage fragments, i.e. C3M and Pro-C6, are both markers for early and late allograft dysfunction after kidney Tx, and reflect the underlying pathophysiology.

Inhibitory Effect of Proximal Tubular Cells-Derived Neuropilin-1 in TGF Beta Signaling Pathway
Rui Chen, Xuejin He, Symon Ma, Jianxing Ma, Physiology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.
Background: Neuropilin-1 (NRP-1) is a co-receptor for multiple growth factors including class 3 semaphorins, VEGF, PDGF and TGF-β, and promotes signaling pathway involved in tumor growth, axonal chemorepellents, angiogenesis and liver fibrosis. In contrast, its function in the renal fibrosis has not been defined.
Methods: Primary renal proximal tubular cells (MRPTCs) were cultured from Nrp-1−/− mice. After infection of Nrp-1−/− cells with adenovirus expressing Cre resulted in Nrp-1 Knock-out (Nrp-1−/−) in the primary cells. Human proximal tubular cell line HKC-8, MEF cells and 3T3-L1 cells were used in this study. TGF-β-driven promoter transcriptional activity was measured by luciferase assay.
Results: NRP-1 was down-regulated by TGF-β in HKC8 and up-regulated in MEF cells and 3T3-1L cells, suggesting the different regulation mechanisms and functions of NRP-1 in proximal tubular cells and fibroblasts. Over-expression of NRP-1 suppressed TGF-β-induced phosphorylation of Smad2/3 and expression levels of fibronectin. HKC-8 cells over-expressing NRP-1 showed significantly decreased levels of both TGF-β receptor I and receptor II. The Nrp-1−/− cells showed higher TGF-β-induced Smad2/3 transcriptional activities and expression of fibronectin in Nrp-1−/− MRPTCs, compared with control adenovirus-infected Nrp-1−/− MRPtcs.
Conclusions: Proximal tubular cells-derived NRP1 inhibits the TGF beta signaling pathway. NRP1 functions are cell-type-specific in the kidney.
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Angiopoietin-1 Deficiency Increases Tubulointerstitial Fibrosis Krishnapriya Loganathan,1 Susan E. Quaggin,2 Marie Jeansson. 1Department of Immunology, Genetics and Pathology, Uppsala Univ, Uppsala, Sweden; 2Feinberg School of Medicine, Northwestern Univ, Chicago, IL.

Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in αSMA+ fibroblasts, myofibroblasts that produce collagen. Identification of factors that regulate the profibrotic response are excellent candidate targets for treatment of kidney diseases. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing and diabetic nephropathy. Angpt1 acts through the Tie2 tyrosine-kinase receptor expressed on endothelial cells and a subset of myeloid cells. Here, we test the hypothesis that loss of Angpt1-Tie2 signaling destabilizes endothelial cells and results in an increased fibrotic response.

Methods: To investigate the role of Angpt1 in renal fibrosis we utilized Angpt1 conditional knockout mice in experimental models of renal fibrosis, including unilateral ureter obstruction (UUO) and ischemia/reperfusion injury. Gene and protein regulation of fibrotic markers were investigated at different time points. We also performed lineage tagging experiments using Tie2-Cre and LysM-Cre to better understand the contribution of Tie2+ cells and macrophages to the myofibroblast population in UUO.

Results: Angpt1 deficient mice showed a significant (p<0.01) increase in fibrotic area 3days after UUO, 9.7±0.45%, compared to controls, 7.9±0.24%. At the same time point, there was a trend (n.s) towards an increased number of myofibroblasts per field from 15.4±1.8 in controls to 20.1±1.4 in Angpt1 deficient mice. Ischemia/reperfusion experiments are ongoing. In our lineage tagging experiment we found that 18.5±0.03% of myofibroblasts came from the Tie2-lineage whereas the LysM lineage contributed minimally, 2.4±1.00%.

Conclusions: Our results suggest that loss of Angpt1-Tie2 signaling increases tubulointerstitial fibrosis as seen by the increased expression of fibrosis markers in Angpt1 deficient mice. Ongoing work is designed to use other models of fibrosis and to elucidate the mechanisms(s).

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SA-PO485
Inter-Alpha-Inhibitor Heavy Chain5 Interactions Control Fibroblast: Myofibroblast Differentiation John Martin, Timothy Bowen, Soma Meran, Aled O. Phillips, Robert Steadman. Nephrology, Cardiff Univ, Cardiff, Wales, United Kingdom.

Background: Fibroblasts are central to CKD through their Transforming Growth Factor-β1 (TGF-β1)-triggered profibrotic transition into contractile, α-smooth muscle actin (α-sma)-positive myofibroblasts. Transition is dependent on an increase in the synthesis and accumulation of a pericellular matrix of hyaluronan (HA) and the HA-dependent α-sma-positive myofibroblasts. TSG-6, however, contributes to the mechanism(s).

Methods: Fibroblasts were incubated for 72 h with 10ng/ml TGF-β1 to become myofibroblasts. RT-PCR was used to assess mRNA, sIRNA was used to knockdown mRNA expression of TSG-6, HA, α-SMA and SDNPA4. Western Blotting assessed protein levels.

Results: Following TGF-β1 treatment, TSG-6 and α-sma, had different kinetics of induction. Using siCD44 or EGFR inhibitor AG1478 to interfere with the CD44/EGFR-dependent signal initiation prevented differentiation but had no effect on TGF-β1 expression. TSG-6, however, was essential for differentiation and using monoclonal antibody A3K, HA-oligosaccharides, Cobalt, or siBknkin to interfere with the activity of TSG6, all prevented phenotypic change. These results suggested that it was the TSG6/siAld heavy chain (HC) interaction that was necessary for the effect. HC5 was shown to be the principal HC expressed in these cells. HC5 was released by hyalurondase treatment of the fibroblast cell surface and siCD44, siTSG6 and siBknkin all inhibited the expression of HC5 protein. Finally, HC5 could be deleted on the cell by specific siRNA and this resulted in antagonism of phenotypic change, confirming its role in myofibroblast differentiation.

Conclusions: The mechanisms regulating TGF-6 and HA synthesis, during TGF-β1-dependent induction of myofibroblasts are distinct. TSG-6, however, contributes to the pro-fibrotic response through its catalytic transfer of IntⅤ HC5 to HA leading to the subsequent induction of phenotypic change.

Funding: Private Foundation Support

SA-PO486
Role of IL-4 Receptor α in Bone Marrow-Derived Fibroblast Activation and Renal Fibrosis Hua Liang, Yuanbo Wu, Yanlin Wang. Medicine, Baylor College of Medicine, Houston, TX.

Background: Renal fibrosis is a common pathway leading to progression of chronic kidney diseases. We and others have shown that bone marrow-derived fibroblasts contribute significantly to the pathogenesis of renal fibrosis. However, the signaling pathways underlying the activation of bone marrow-derived fibroblasts in the kidney are incompletely understood. We have found that IL-4 and its receptor α (IL4Rα) are induced in the kidney during the development of renal fibrosis. However, little is known about the role of IL-4Rα in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis.

Methods: We examined the role of IL-4Rα in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis using renal fibroblasts from IL-4Rα-deficient mice with a pericellular matrix of hyaluronan (α-sma)-positive myofibroblasts. Transition is dependent on an increase in the synthesis and accumulation of a pericellular matrix of hyaluronan (HA) and the HA-dependent α-sma-positive myofibroblasts. TSG-6, however, contributes to the mechanism(s).

Results: Compared with wild-type (WT) mice, IL-4Rα-deficient (KO) mice exhibited significant preservation of kidney function as measured by serum urea nitrogen and accumulated significantly fewer bone marrow-derived fibroblasts dual positive for CD45 and PDGFR-β in the kidney 2 weeks after fibrotic treatment. Furthermore, IL-4Rα-KO mice exhibited fewer α-smooth muscle actin (α-sma) positive myofibroblasts and expressed less α-sma protein in the kidney following fibrotic acid treatment. Consistent with these findings, we also observed significantly decreased collagen deposition and suppression of extracellular matrix proteins (collagen 1 and fibrocin). In cultured bone marrow monocytes, IL-4 activated STAT6 and induced expression of α-SMA and extracellular matrix proteins, which was abolished in the absence of IL-4Rα.

Conclusions: Our results strongly suggest that IL-4Rα plays an important role in the activation of bone marrow-derived fibroblasts and the development of renal fibrosis. These results indicate that IL4R signaling may represent a novel therapeutic target for chronic kidney disease.

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SA-PO487
Role of Scaffolding Protein JLP in Preventing Renal Fibrosis in Obstructive Nephropathy Qiang Fu, Qi Yan, Qin Zhang, Guohua Ding, Huiming Wang. Renmin Hospital of Wuhan Univ.

Background: Renal fibrosis is a common pathological lesion in the end stage of various progressive kidney diseases, and is characterized by interstitial inflammation, proliferation of fibroblasts, and accumulation of extracellular matrix (ECM). The ECM-associated leucine zipper protein (JLP) is a crucial scaffolding protein in signals transduction and molecular trafficking. JLP has been found expressed in mouse tissues of brain, lung, spleen, testis, and kidney. We reported here, for the first time, the effects of JLP deficiency on the progression of renal fibrosis in mice model of unilateral ureteral obstruction (UUO).

Methods: JLP Wild type (jlp+/+) and jlp deficient (jlp−/−) mice were divided into four groups: jlp−/− and jlp−/+ sham-operated groups, jlp−/− and jlp−/+ unilaterally ureteral obstruction (UUO)-operated groups (jlp−/− UUO group and jlp−/− UUO group). Mice were sacrificed at the days of 7 and 14 to evaluate the fibrosis by Masson and H&E staining. The expression of transforming growth factor-β1 (TGF-β1), α-smooth muscle actin (α-sma), collagen I (COL-I), and collagen III (COL-III) were assayed by immunohistochemistry staining.

Results: One week after the surgery, more collagen deposition was observed in the renal interstitial area in jlp−/− UUO group than in jlp−/+ UUO group. Similar to that, the expression of COL-I and COL-III were significantly increased in the kidney cortices in jlp−/− UUO-operated group than in jlp−/+ UUO-operated group. The expression of TGF-β1 and α-SMA was also significantly higher in jlp−/+ UUO-operated group than in jlp−/− UUO group.

Conclusions: Scaffolding protein JLP is critical in preventing renal fibrosis through the mechanism of inhibition TGF-β1 expression and myofibroblast induction.

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SA-PO488
HGF-Producing Cell Sheet Suppress Renal Fibrosis Induced by Unilateral Ureteric Obstruction in a Rat Masatoshi Oka,1 Sachiko Sekiya,2 Ryoichi Sakiyama,2 Kosaku Nitta,1 Tatsuya Shimizu.2 ‘Nephrology, Tokyo Women’s Medical Univ, Shinjuku, Tokyo, Japan; ‘Tokyo Women’s Medical Univ Inst of Advanced Biomedical Engineering and Sciences, Shinjuku, Tokyo, Japan.

Background: Tubulointerstitial fibrosis is a typical pathological finding in chronic kidney disease (CKD) and is associated with the progression of renal dysfunction. Recently several studies reported to suppress renal fibrosis by transplantation of cells expressing several growth factors, for example hepatocyte growth factor (HGF) with HGF-producing cell sheet (HGF sheet) transplantation. The expression of transforming growth factor-β1 (TGF-β1), α-smooth muscle actin (α-sma), collagen I (COL-I), and collagen III (COL-III) were assayed by immunohistochemistry staining.

Methods: Human mesothelial cells transplanted human HGF gene by lipofection were cultured on temperature-responsive dish for 4 days. When temperature reduced, these HGF-producing cells were detached from dishes as cell sheet without enzyme-treated. We performed unilateral ureteric obstruction (UUO) in nude rat and transplanted the HGF sheet immediately. To compare HGF sheet transplantation with intermittent administration of HGF protein, we also injected HGF protein from tail vein every 24 hours for UUO rat (HGF iv). The kidney volume after operation measured with CT every 7 days for 4 weeks. After the 1st week, the one week after operation, the biopsies were collected. The expression of α-sma and smooth muscle actin in kidney transplanted HGF sheet was significantly less compared to that in HGF iv kidney. Moreover, the kidney volume treated HGF sheet with UUO was significantly less compared to control 4 weeks after operation. And it maintained thick cortex features with a lot of glomeruli, tubule and microvessels in the kidney treated HGF sheet.

Conclusions: Local and sustained HGF administration with HGF sheet strongly suppressed renal fibrosis induced by UUO in a rat. Our results suggested that cell sheet therapy may be a promising strategy for renal disease.

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Extracellular Matrix Modulates Macrophage Phenotype Profile

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Background: It is known that macrophages play an important role in kidney damage and resolution. An increase in macrophages phenotype type 1 (M1) is known to promote scarring while an increase in macrophage phenotype type 2 (M2) leads to prophylactic kidney healing processes. However little is known on how the extracellular matrix (ECM) can direct macrophages toward a specific phenotype acquisition during development, tissue homeostasis and disease.

Methods: Using established protocols we decellularized human adult, healthy, diseased, and fetal kidneys; monocytes were seeded on the different ECMS and macrophage phenotype switch after 24hrs and 5 days was assessed. Macrophage maturation was tested by releasing culture of IL-10, IFN-γ, TNF-α and IL-4 in the culture media along with qRTPCR and immunochemistry to evaluate expression of M1 (CD80 and CD86) and M2 (CD16, CD163, CD14 and CD200R) phenotypes.

Results: We observed that monocytes cultured on ECMS were able to mature into macrophages and present an increase in M1 marker (CD80) on diseased ECM, an increase in M2 markers (CD163, CD200R) on healthy ECM, and an increase in anti-inflammatory M2 marker (CD16) on fetal ECM, after 24hrs. After 5 days of co-culture there was an overall decrease in gene expression for all markers followed by an increase in media secretion of IL-10 on diseased ECM vs healthy and fetal ECM. Additionally after 5 days higher number of seeded monocytes appear to adhere onto the adult ECM vs the fetal ECM. IFN-γ, IL-4, IL-10 or CD64 expression was not detected during 24hrs and 5 days. Monocytes capacity to mature into macrophages was confirmed in vitro by administration of phorbol myristate acetate (PMA) and 1,25-dihydroxy vitamin D3 with LPS.

Conclusions: Our work suggests that the ECM has the capacity to modulate macrophage phenotype and might contribute to disease progression. Additionally, this model may be used to investigate mechanisms of ECM-dependent macrophage activation during renal disease and regeneration.

High Salt Diet Induces Blood Pressure Independent Tubulointerstitial Remodeling and Lymphangiogenesis in Rat Kidney Ryanne S. Hijmans, Saleh Yazdani, Gerjan Navis, Jacob van den Born. Nephrology, Univ Medical Center Groningen, Groningen, Netherlands.

Background: In chronic kidney disease (CKD), proteinuria is an important cause of tubular activation and progressive tubulointerstitial damage. It has been shown that high salt (HS) intake can aggravate this renal damage. Although earlier studies mainly focused on the blood pressure dependent (BP) effects of sodium on the kidney, recent studies suggest there is a BP independent route as well. A HS diet has been shown to store Na+ in the skin and as a result of binding of Na+ to proteoglycans, the influx of macrophages stimulates the secretion of vascular endothelial growth factor C (VEGF-C). Macrophage-derived VEGF-C has been shown to induce lymphangiogenesis (LA) in the skin. As LA has a role in inflammatory remodeling, we hypothesize that HS diet exerts its BP independent effects on the kidney by inducing LA and renal tubulointerstitial (TI) remodeling. We tested this hypothesis in normal rats, to avoid interference with TI remodeling due to the primary renal disorder.

Methods: Male Wistar rats (n=15) were randomly assigned to one of three study groups. Two groups (both n=5) received a high salt diet of 8% salt, while the control group (n=5) had a normal salt diet. After 2 weeks, one of the two groups on a high salt diet was sacrificed, and the other group was sacrificed at 4 weeks. The kidneys were stained and quantified for lymphangiogenic, fibrotic and inflammatory markers.

Results: Rats with HS intake showed an increased number of lymph vessels compared to their controls at weeks 4 (p=0.06). ED1+ macrophages also increased in the HS group at week 4 (p=0.06). There was a significant increase of myofibroblasts (α-SMA) after 4 weeks in the HS group (p<0.02). Except for week 1 (p<0.05), the HS groups showed no significant BP differences with their controls at 2, 3 and 4 weeks.

Conclusions: We showed that high salt intake induces tubulointerstitial remodeling, inflammation and profibrotic changes in rat kidneys, even when the BP is not significantly different between the groups. This finding supports our hypothesis that the HS intake has BP independent effects next to it’s well known BP dependent effects in CKD.

Genetic and Epigenetic Analysis of the MicroRNA-200 Family for Association with End Stage Renal Disease Laura Jane Smyth, 1 Gareth J. McKay, 1 Alexander P. Maxwell, 1 A. J. McKnight. 1Centre for Public Health, Queen’s Univ of Belfast, Belfast, Northern Ireland, United Kingdom; 2Regional Nephrology Unit, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom.

Background: DNA methylation and miRNA profiles are associated with complex diseases including kidney diseases. We evaluated CpG sites, gene expression and SNPs of the miRNA-200 family and their target genes, including exploration of relevant methylation quantitative trait loci (meQTLs).

Methods: Quantitative DNA methylation was extracted from existing epigenome-wide association data (Illinima’s 450K Methylation array) for individuals with and without kidney disease (n=407). Following stringent quality control, a total of 14 significant CpG sites were identified within the miRNA-200 family, the p-value significance of which was cg23655182 (MI924, P=4.1x10^-16). The top 20 predicted target genes were determined using mirDB for each miRNA (MIR141, MIR200A, MIR200B, MIR200C and MIR429). Target genes had 308 CpG sites with methylation data; the most significant for MI924 were cg16682004 in EL2 and cg19038462 in ZFBI (P=4.2x10^-10). RNA-Se analysis was performed on renal transplant recipients and healthy controls using the Ion Proton™ RNA was selectively depleted for ribosomal RNA and up to 40 million reads were gained per sample. Differential methylation status was associated with expression of miRNA and their target genes. Additionally, using mirQTL data (rs9568773 and rs10200550) for miRNA-200, miRNA-200 family and their target genes for MI924. Genome-wide significant results (n=476 SNP) were obtained for 67 target genes (maximum P=9.98x10^-11). These genes may influence miRNA regulation.

Conclusions: CD36, the top-ranked gene, has previously been linked to kidney disease where it is suggested that it has a prominent role in the development of renal fibrosis. We have provided a genomic map of the miRNA-200 family using novel data in order to assist in determining its association with ESRD.

A MicroRNA Signature of Epithelial–Mesenchymal Transition in Progression of Chronic Renal Disease Ali Ramezani, 1 Joseph M. Devaney, 2 Akshay Roy-Chaudhury, 3 Richard Scott, 2 Sara Karandish, 2 Susan Knoblauch, 2 Jeffrey B. Kopp, 1 Dominick S. Raj. 1 ‘Div of Renal Diseases and Hypertension, George Washington Univ, Washington, DC; 2 Center for Genetic Medicine Research, CNMC, Washington, DC; 3 NIDDK, NIH, Bethesda, MD.

Background: Irrespective of the diverse initial causes, progression of CKD is characterized by increasing tubulointerstitial fibrosis. There is a great need for accurate, noninvasive biomarkers for early detection of fibrosis in the kidney and the progression of kidney disease. Recent evidence suggests that miRNAs participate in the fibrotic process in the kidney. The aim of this study was to examine the urinary and circulatory miRNA expression profiles regulating the EMT and whether they are reflected by parallel changes in the pro-fibrotic factors and the progression of kidney disease.

Methods: Blood and urine samples were obtained from 28 patients with CKD. Patients were divided into two groups according to their GFR: GFR<30 and GFR>30. Plasma and urinary levels of two biomarkers of fibrosis, collagens III (PIIINP) and IV, were measured. To determine involvement of miRNAs in kidney fibrosis, the plasma and urinary miRNA expression profiles of the patients were analyzed.

Results: Plasma and urine PIIINP and CIV levels were significantly increased in patients with GFR<30 compared with patients with GFR>30. Furthermore, miRNA expression profile of the patients showed 58 downregulated and 60 upregulated miRNAs in urine, and 51 downregulated and 61 upregulated miRNAs in the plasma of the patients with GFR<30 compared with GFR>30. A panel of 4 urine and 6 plasma miRNAs was identified which not only distinguished patients with GFR<30 from GFR>30, but their altered expression were also implicated in the phenotypic changes that occur during EMT and fibrosis. The altered expression levels of these miRNAs were validated in a tubular epithelial cell line, and studies are underway to validate their expression in vivo, in the Alt-TGFβ mouse model.

Conclusions: Plasma and urinary miRNAs are reliable, noninvasive, and inexpensive nephrofibrotic miRNAs. These studies may provide a basis for the development of large cohorts plasma- and urine-based assays could provide a more feasible and safer screening compared to biopsy.

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The PR3 Receptor CD177 Is Controlled by Epigenetic Mechanisms Claudia Eulenberg, 1 Sylvia Bähring, 2 Friedrich C. Luft, 1 Ralph Kettertz, 1 Charité-Buch, Experimental and Clinical Research Center, Berlin, Germany; 2Nephrology and Intensive Care Medicine, ECRC, Berlin, Germany.

Background: Proteinase 3 (PR3) is a major ANCA antigen in granulomatosis with polyangiitis (GPA). PR3-ANCA binding to membrane-PR3 (mPR3) is a key event for neutrophil activation and vascular damage. The neutrophil-specific CD177 gene expression pattern. We hypothesized that epigenetic mechanisms control CD177 gene expression.

Methods: Haplotype analysis, genome-wide methylation analysis, chromatin immunoprecipitation (ChIP) analysis and CD177 expression studies were performed in neutrophils and HeLa cells.

Results: Methylation analysis on CD177 in PR3 and mPR3 neutrophils revealed three CpGs in the potential CD177 promoter that were methylated in CD177 in GPA patients, but not in CD177 in controls. ChIP analysis revealed enrichment of the H3K4me3 mark (enhocromatin) in the predicted CD177 promoter region in CD177 in neutrophils (p<0.05; n=4). This putative promoter region contains a TATA box and binding sites for several transcription factors, including the AP1 family. We established a HeLa cell model that recapitulates the neutrophil specific expression of the observed CD177 in GPA and HeLa cells. HeLa cells also had euchromatic in the promoter region and CD177 mRNA followed a monomethlic expression pattern.
Application of Human Kidney RNA-seq Expression Quantitative Trait Loci in Chronic Kidney Disease Yi-An Ko, Frank S. Chinga, Nora Ledo, Katalin Susztak. Renal Electrolyte and Hypertension Div; Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA.

Background: There are more than 5 million sequence variants in humans. Somogeneous variations influence transcript levels and therefore have the ability to interfere with cell and organ function. Such genetic variants are called expression quantitative trait loci (eQTL). The goal of our study was identify such functionally important genetic variants at the genome-wide level.

Methods: This analysis requires the collection of large number of human tissue samples with genotype and transcript level data. Here we used 99 human kidney samples of Central European descents RNAseq and genotype data was normalized and genotype data was imputed using 1,000 Genome reference data. The association between genotype and transcript levels was performed using Matrix eQTL software and was limited to cis-eQTL where the genetic variant and transcript levels were within 2 megabases distance.

Results: We identified 164 significant target genes (we call these eGenes) and 7590 significant SNPs (eSNPs) that passed the threshold for statistical significance after multiple testing correction using adjusted p-values<10^-6. Next we compared variants that influence gene expression in the kidney to those that have been published for other organs using the publicly available Genotype-Tissue Expression project (GTEx). Of the 164 eGenes,103 were common between the kidney and other organs, indicating that there are cell type specific and cell type independent eGenes. Using kidney specific epigenome maps, we found that eSNPs were enriched on kidney specific regulatory elements, including promoters and enhancers. We also found a significantly greater overlap between kidney eGenes and polymorphisms that are associated with CKD development, compared to other tissues (digestive, nervous, immune system diseases, hematological measurement, cardiovascular, and metabolic disease).

Conclusions: We identified transcript level changes associated with genotypic variations. These results can highlight kidney specific regulatory elements and may also help to identify target genes for polymorphisms associated with kidney function related traits.

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SA-PO496

Gene Expression Based Dissection of Chronic Kidney Disease Traits Pazit Beckerman, Katalin Susztak. Renal, Electrolyte and Hypertension Dept, Univ of Pennsylvania, Philadelphia, PA.

Background: Chronic kidney disease (CKD) is a progressive decline in kidney function. There are several manifestations of CKD including glomerular function change, albuminuria, glomerulosclerosis, tubulointerstitial fibrosis and metabolic changes. These traits are strongly correlated but the question remains whether they are driven by identical mechanisms.

Methods: We conducted genome wide transcript level analysis of 95 microdissected human kidney tubule samples. We used transcript level changes as quantitative traits to dissect underlying mechanisms. These samples included subjects with normal eGFR with or without diabetes (DM) or hypertension (HTM) and diseased kidney samples with low eGFR, fibrosis and sclerosis, with or without DM or HTM.

Results: We identified 1430 transcripts with significant linear correlation with eGFR. Pathway analysis indicated significant enrichment for TGFβ and Wnt signaling and ECM receptor interactions only in earlier CKD stages. Our analysis identified 1606 transcripts that correlated with fibrosis and 1803 transcripts correlated with glomerulosclerosis. Similar to the clinical overlap between eGFR and fibrosis, we found that 78% of transcripts with identical. Transcripts that showed correlation with fibrosis but not with eGFR were enriched for inflammation related pathways. On the other hand, metabolism related genes correlated with eGFR but not with fibrosis. There were significant differences between male and female samples as well.

Conclusions: Our transcriptome-based dissection method highlights the relatedness of eGFR and kidney fibrosis, but also indicates potential differences in the underlying mechanisms of the two processes.

Funding: NIDDK Support

SA-PO497


Background: Apolipoprotein L1 (APOL1) susceptibility alleles have been associated with kidney disease progression and ESRD in hypertensive African Ancestry (AA) populations. We explored whether these APOL1 alleles are associated with blood pressure-related traits in AA enrolled in the electronic medical records and genomics (eMERGE) Network.

Methods: Study populations included the Mount Sinai BioMe biobank discovery (dis) cohort (<5,213) and three EMR-linked biobank replication (rep) cohorts, including Vanderbilt BioVU (<2,889), Northwestern NUgene (<6,163), and Mount Sinai BioMe (<5,165). APOL1 single nucleotide polymorphisms (SNPs) rs73885319, rs71785313 and rs60910145 were genotyped in BioMe samples and imputed in BioVU and NUgene samples to determine APOL1 G1 and G2 risk alleles. Longitudinal phenotypic data were extracted from EMRs. Linear regression models & meta-analyses (META) were performed with age, sex, mean BMI, and eGFR as covariates.

Results: Compared with carriers of [0/0] APOL1 G1/G2 risk alleles, carriers of [2] risk alleles were diagnosed with hypertension a mean of 2.5 years (95%CI 1.9-2.9 yrs) earlier in life (P<0.04, P<3x10^-6; Cox hazard); manifested 2.3 mmHg higher systolic BP (SBP) in younger AA (age 20-39) (P<0.007, P<0.04); and were exposed to more antihypertensive medication classes (P<0.01, P<3x10^-6). Carriers of [2] risk alleles were more likely to manifest concentric left ventricular hypertrophy by echocardiogram (OR(95%CI)=1.521[1.14-2.02], P<0.01) and hemorrhagic cerebrovascular accidents (OR in 16C=2.42[1.01-5.79], P<0.05).

Conclusions: APOL1 G1/G2 susceptibility alleles are associated with early-onset, more severe form(s) of hypertension & with hypertensive complications hemorrhagic stroke
and concentric LVH independent of kidney function & BMI. These results may warrant a shift from kidney-intrinsic to systemic vascular pathomechanisms attributable to APOL1 G1/G2 susceptibility alleles.

**Funding:** Other NIH Support - NHGRI

**SA-PO498**

**Apolipoprotein L1 (APOL1) Gene Variants and Incident Proteinuria: Results from the African American Study of Kidney Disease and Hypertension (AASK)**

**Teresa K. Chen,** Carmen A. Peralta, Lawrence J. Appel, Michael J. Choi, Michelle M. Estrella, *Nephrology, Johns Hopkins Univ; Nephrology, Univ of California San Francisco; Medicine, Johns Hopkins Univ.*

**Background:** APOL1 gene variants are associated with kidney function decline. Whether these same gene variants are associated with incident proteinuria in the context of pre-existing chronic kidney disease (CKD) is unknown.

**Methods:** Using the trial and cohort phases of AASK (median follow-up of 6.8 years, maximum follow-up of 12.2 years), we evaluated participants who had hypertension-attributed CKD and who did not have proteinuria at baseline. Cox proportional hazards models were used to estimate the relative hazard of incident proteinuria (defined as a doubling of urine protein-to-creatinine ratio and UP/Cr >0.22) comparing APOL1 high-risk genotype (2 risk alleles) vs. low-risk genotypes (0-1 risk alleles). We adjusted for age, gender, baseline GFR, percentage of European ancestry, randomized blood pressure goal (usual vs. low), and randomized blood pressure drug (ramipril vs. metoloprol vs. amlodipine). Effect modification by randomized trial interventions and dietary sodium intake (as estimated by 24-hour urine sodium) was assessed.

**Results:** Of the 480 participants included in our study, 17% (n=82) had the APOL1 high-risk genotype. Individuals with the APOL1 high-risk genotype were 83% more likely to develop incident proteinuria compared to those with the low-risk genotypes (adjusted HR: 1.83; 95% CI: 1.36 to 2.47; p=0.001). The association between APOL1 and incident proteinuria was not modified by randomized blood pressure goal, randomized blood pressure drug, or dietary sodium intake (p-interaction>0.05 for each).

Conclusions: Among African-Americans with CKD attributed to hypertension but without baseline proteinuria, high-risk variants of APOL1 are associated with a greater risk of incident proteinuria.

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**SA-PO500**

**Role of Klotho Genetic Polymorphisms in Salt-Sensitivity: A Link Between Salt and Aging?**

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**Background:** Previous data in transgenic mice showed that one-half klotho deficiency resulted in extensive premature aging, increased salt sensitivity and caused salt-sensitive hypertension. Recent gene expression study confirmed the expression of klotho in renal distal tubular cells. The aim of this study is to evaluate the role of Klotho polymorphisms in salt sensitivity hypertension.

**Methods:** Design: study of pressure-natriuresis relationship in essential hypertensive patients, never treated before, naive (NHP) by Acute salt load (Na load: 310 mmol in 2 h iv) and low salt diet (Low SD: <100 mg/die for 15 days).

**Results:** GWA analysis identified 32 SNPs in Klotho gene (restricted to 15 with tagging r²>0.80). Six of these resulted significantly associated to BP variation after Na load and Low SD. The effect of intron 2 and 3 SNPs genotype on SBP variation after Na load and Low SD are reported in the (figure 1) confirming the similar effect in the two manoeuvres.

Conclusions: These results are the first demonstration of the role of Klotho gene in salt homeostasis and hypertension development and suggest that Klotho polymorphisms affect sodium renal tubular excretion. If confirmed these results propose Klotho as key gene in salt sensitivity and aging.

**Funding:** Government Support - Non-U.S.

**SA-POS51**

**Associations Between the Reticulon 1 Gene (RTN1) and End-Stage Kidney Disease**

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**Background:** RTN1 encodes endoplasmic reticulum stress proteins that have recently been associated with chronic kidney disease. We sought to determine if genetic variants within RTN1 were associated with end-stage renal disease (ESRD) in African Americans (AAs) and European Americans (EAs) with diabetic (T2D-ESRD) and non-diabetic forms of ESRD.

**Methods:** We examined the RTN1 gene region using a published AA T2D-ESRD genome-wide association study (Discovery study; n=922 cases, n=861 controls). Seven single nucleotide polymorphisms (SNPs) with p<0.015 were identified and genotyped in replication samples of AAs with T2D-ESRD (n=1,312) and controls (n=774), as well as increased UACR. Analyses used generalized linear mixed models that accounted for the sampling strategy and family relatedness, age, sex, diabetes, systolic blood pressure and anti-hypertensive medications, and stratified by Hispanic background.

**Results:** There were 41% men, and mean age was 46 (SD =14). The prevalence of increased UACR was 14%, reduced eGFR was 4%, and combined CKD outcomes was 16%. Caribbean Hispanics (Cuban, Dominican, Puerto Rican, N=5380) had higher prevalence of 2 APOL1 risk alleles (1% vs 0.1%) and rs334 allele (2% vs. 0.7%) compared to Mainland Hispanics (Central American, Mexican, South American, N=6,539). APOL1 alleles were associated with increased UACR (p<0.01) and the composite CKD outcome (p<0.01), and rs334 was associated with same outcomes (UACR, p<0.01; CKD composite outcome, p<0.01) among Caribbeans only.

Conclusions: African-specific alleles are associated with CKD in Hispanics, but associations vary by Hispanic background. Medical care providers should be aware of the impact of these genetic variants for CKD risk in Hispanics.

**Funding:** Other NIH Support - R21HL123677, 1R01ES021367, 1R01HL118305-01A1

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

Underline represents presenting author.

738A
EAs with T2D-ESRD (n=602) and controls (n=1030). SNPs were also investigated in AAs considering pseudogenes, compared to two independent NGS exome sequencing strategies (1) Panel for glomerular disease (26 genes, 89 patients) and (4) Panel for tubule/interstitial disease (36 genes, 120 patients). Our results suggest that the significant SNPs identified in our study may be useful in the development of diabetic nephropathy.

Conclusions: The results of this study may provide new insights into the genetic basis of nephropathy.

SA-P050

An Efficient and Comprehensive Strategy for Genetic Diagnostics of All Hereditary Kidney Diseases

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Background: Sanger is a traditional and reliable method for sequencing, but next generation sequencing (NGS) has improved genetic diagnosis in a time and cost effective manner. We established and validated a NGS strategy for all hereditary kidney diseases, and compared it with traditional and NGS exome sequencing technologies.

Methods: Based in clinical classification and population prevalence, we generated four panels and test them in 318 patients with renal disease during 2 years of routine clinical practice: (1) Panel for common, rare and ultra-rare cysitic diseases (72 genes, 48 patients); (2) Panel for glomerular disease (26 genes, 89 patients) and (4) Panel for tubule/interstitial disease (36 genes, 52 patients).

Results: This strategy has shown greater gene coverage, sensitivity and specificity considering pseudogenes, compared to two independent NGS exome sequencing strategies (ampliseq n=2 and sureselect n=115). Moreover, we also used an in-house database containing a total of 6945 genomic variants (248 frameshift and 66 nonframeshift insertion/deletion/substitutions, 44 stopgain, 102 splicing, 807 nonsynonymous SNV, 592 synonymous SNV and 39326 non coding variants) that we have used to classify and re-classify considering every single genetic variant described into the literature. We have identified genetic interaction as the most common functional genetic diagnosis and the major mechanism of phenotypic inter- and intra-familial variability.

Conclusions: Here we describe a novel strategy to anticipate disease and provide complete genetic information for clinical decision-making, in a time- and cost-efficient manner.

SA-P050

The First Genome-Wide Association Study of Diabetic Nephropathy in Korean Type II Diabetes Patients

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Background: It has been suggested that genetic susceptibility plays an important role in the pathogenesis of diabetic nephropathy. Recently, several genome wide association studies (GWASs) suggested that specific polymorphisms of candidate genes were associated with susceptibility to diabetic nephropathy. However, there was weak point in contents of GWAS DNA chip for GWAS. In fact, previous contents of GWAS DNA chip were fixed and did not cover SNPs in exon region and promoter region. In present study, we used the Axiom® Genome-Wide Human Assay. The contents of assay are selected by researcher and useful to investigate association between several candidate SNPs in specific diseases.

Methods: To investigate whether specific polymorphisms are involved in the development of the diabetic nephropathy, 87 diabetic nephropathy patients and 104 diabetic controls in Korean with type II diabetes were studied. We firstly selected 47,777 genes of homo sapiens in NCBI gene database and searched the SNPs in dbSNP database. And the criteria for selection exonic SNPs, promoter SNPs, and intron SNPs in each gene were following: (1) SNPs with >10% minor allele frequency (MAF), (2)<0.1 heterozygosity, (3) known genotype frequencies of SNPs in Asian population, (4) SNP studies in previous study, (5) unknown SNPs. Finally we selected 378,707 SNPs. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value. The analysis was using Helixtree program.

Results: Among 378,707 SNPs, three SNPs (rs3214159 in ABC8 gene, rs3747636 in PIK3C2G gene, and rs3765156 in PIK3C2B gene) showed strongly significant association with diabetic nephropathy (p<0.00001).

Conclusions: These results suggest that these significant SNPs may be useful to investigate the development of diabetic nephropathy.

Funding: Clinical Revenue Support

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

Underline represents presenting author.

739A
Exome Sequencing as Diagnostic Tool in Daily Clinical Nephrology Practice
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Background: Next generation sequencing, e.g. exome sequencing (ES), is currently the state of the art technique to identify mutations in genetic diseases. We developed a workflow for implication of ES in daily clinical practice for patients with a suspected hereditary kidney disease. The aim of this study was to analyze the diagnostic yield of this approach in clinical practice.

Methods: We developed a two-tier analysis, in which the first step is a kidney disease gene panel to screen for pathogenic variants in 187 genes, minimizing the chance of coincident findings. If causative mutations are not identified (first step), the complete exome data set was analyzed after additional written informed consent. We analyzed the diagnostic yield of this approach.

Results: From Jan. 2013 till Jan. 2015 we included 74 unrelated patients with kidney disease, defined as glomerular disease (n=34), cystic renal disease (n=16), electrolyte disorders (n=11), renal insufficiency of unknown cause (n=4) and other (n=9). The kidney disease gene panel revealed pathogenic mutations in 11 (15%), and likely pathogenic variants in 12 other cases (16%), necessitating follow-up studies. Further analysis of the complete exome data set in 19 patients, revealed candidate genes in 6 patients that are under investigation. In addition, copy number variation analysis revealed a pathogenic deletion in 2 patients (in one patient another pathogenic mutation was also identified in step one). There was 1 coincidental finding necessitating follow up for colon carcinoma. In 23 patients open exome analysis is currently ongoing. Nine patients refused further analysis.

Conclusions: Currently, in 30 out of 74 patients (41%) (likely) causative mutations or new candidate genes were identified. We conclude that diagnostic exome sequencing is a powerful tool for detecting causative mutations in daily clinical practice without having the limitations of other gene testing approaches (single gene testing/targeted sequencing).

Atypical Hemolytic Uremic Syndrome Targeted Re-Sequencing Study in a South Italian Cohort of Patients
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Background: Atypical hemolytic uremic syndrome (aHUS) is a multifactorial disease due to autoimmune or genetic factors leading to deregulated alternative complement pathway activation. At present 12 genes are associated to aHUS, however 30-50% of patients lack mutations in these genes resulting in still partially obscure genotype-phenotype correlations.

Methods: We enrolled 20 aHUS patients and 2 relatives from Apulia Region, Italy. We performed targeted parallel re-sequencing of the 12 known genes plus ADAMTS13, in a split design for generic diagnostic routine screening. We analyzed the genotype investigating the overlapping with other alternative complement pathway disorders, such as C3 glomerulopathy, Age-related Macular Degeneration (AMD) and drusen. We selected patients for their history of sporadic aHUS. Target enrichment was performed using an Illumina TrueSeq Custom Amplicon panel. Sequencing was performed on Illumina MiSeq Desktop Sequencer. All variants were evaluated for their pathogenicity according to CADD, Sift and Polyphen algorithms.

Results: We identified 30 missense and one nonsense variants in known aHUS genes, plus seven missense variants in ADAMTS13. Several combined variants were identified which might explain the different phenotypic nuances of our patients, as well as, in some cases, their signs of other Complement-related diseases. We evidenced that different combination of variants together with different triggering factors result in a phenotypic spectrum encompassing all the Complement-related disease range. Additionally, in presence of some combinations, also other underlying pathologies can act as a triggering background for aHUS.

Conclusions: Our data suggest that (i) ADAMTS13 gene should be routinely sequenced for aHUS (ii) the overlapping with other complement-related diseases is considerable. Mutations should therefore be analyzed in combination, and the high-throughput strategy is the only feasible in this scenario.
Discovery of New Risk Gene Loci in IgA Nephropathy: Genome-Wide Human Assay

**Background:** IgA nephropathy (IgAN) is the most common form of glomerulonephritis in Korea. The etiology of IgAN is complex with high genetic heterogeneity. Several genome-wide association studies (GWAS) have suggested that specific polymorphisms of candidate genes are associated with susceptibility to IgAN. However, previous contents of GWAS image chip were fixed and did not cover SNPs in exonic region and promoter region.

**Methods:** We used the Affymetrix Genome-Wide Human Assay by Affymetrix. The contents of assay are useful to investigate association between several candidate SNPs and end-stage renal disease. We selected 47,777 genes of homo sapiens in NCBI gene database and searched the SNPs in dbSNP database. And the criteria for selection exon, promoter, and intron SNPs in each gene were following: SNPs with >10% minor allele frequency, >0.1 heterozygosity, known genotype frequencies of SNPs in Asians. SNPs were studied in previous study, and unknown SNPs. Logistic regression models were performed to determine odds ratio (OR), 95% confidence interval (CI), and P value. The analysis was using Helix tree program.

**Results:** To investigate whether specific polymorphisms are involved in the development of IgAN, 182 biopsy confirmed IgAN patients and 455 healthy controls were studied. We selected 378,707 SNPs. We carried out genome wide genotyping on customized Affymetrix Genome-Wide Human Assay Among 378,707 SNPs, 19SNPs showed strongly significant association with IgAN (p<0.00001). We identified at rs201580039, rs12219125 and rs57351989 that implicated the genes encoding KLIF14, Kruppel-like factor 14, ITGB3, OR 8.04, 1.7x10^{-3}, and 5.1x10^{-3} as susceptibility genes. To validate the previous reported susceptibility SNPs of IgAN, we selected and genotyped 19 SNPs, rs660895 of HLA-DRB1 and rs2856717 of HLA-DQB1 were significantly different between two groups.

**Conclusions:** These results suggest that these significant SNPs may be useful to investigate the development of IgAN.

**SA-PO511**

Mannan-Binding Lectin 2 Polymorphisms Were Associated with Progression of IgA Nephropathy

**Background:** Our aim is to evaluate whether MBL2 polymorphism associates with progression of IgA nephropathy (IgAN). Patients with Primary IgAN were retrospectively recruited from 2009 to 2013. Renal specimen was semi-quantitative scored according to the Oxford scoring system. Whole coding and promoter regions of MBL2 were sequenced in 101 patients. Then 3 SNPs (rs11003125, rs7096206 and rs7095991) in promoter and 1 SNP (rs1800845) in exom of MBL2 were genotyped in other 185 patients by Sanger sequencing. The associations of the 4 SNPs with patients' clinical, pathological and prognostic parameters were analyzed. Serum MBL level was measured by ELISA.

**Results:** A total Of 286 patients were enrolled, mean age at time of biopsy was 36.2 years, and 192 patients were male (67.1%). Previous study showed mean follow-up time was 34.80 months. Among the 4 SNPs, only rs1800845, coding the 54 amino acid of MBL, significantly increased the risk of ESRD. More patients with rs1800845-A allele (27.3%) progressed to ESRD compared to patients with GA genotype (15.5%) (P=0.326) or GG genotype (9.9%) (P=0.011). Then all patients were divided into GG group (n=91), GA group (n = 84) and AA group (n=11) based upon genotypes of rs1800450. There were no differences of demographic, clinical and pathological parameters at time of biopsy, except for proteinuria (P=0.028). Interestingly, serum MBL levels in patients with AA genotype (median 0.9ng/ml) were significant lower than GA genotype (median 243.29ng/ml) [P=0.001] and GG genotype (median 1033.03ng/ml) [P=0.001]. Kaplan-Meier survival analysis showed that survival time of AA group (38.90 months) [P<0.001] and GG genotype (median 1033.03ng/ml) [P<0.001] was significantly shorter than GA group (66.01±1.9 months) [P=0.173] and GA group (56.37±2.6 months) [P=0.001]. Finally, AA independently increased the risk of ESRD (AA vs GG-GA, HR=26.73, 95%CI 14.92-145.30, P<0.001) after adjusted by sex, age and clinical indicators by COX regression analysis.

**Conclusions:** IgAN patients with rs1800450-A allele have a higher risk of disease progression probably as a result of lower MBL levels in these patients, which may increase the risk of infection.

**SA-PO512**

ARHGAP32 as a Candidate Gene for Primary Focal Segmental Glomerulosclerosis

**Background:** Focal and segmental glomerulosclerosis (FSGS) is one of common causes of end-stage renal disease worldwide. Previous studies showed that genetic factors played an important role in the pathogenesis of FSGS. The purpose of this study was to identify the candidate genes of FSGS in Chinese familial FSGS.

**Methods:** Total 21 individuals of a FSGS pedigree were involved in this study. First, we detected the mutations of ACTN4, TRPC6, and NPHS2 in this pedigree. Then we conducted a genome wide scan for linkage study. And DNA of four members were assayed by whole exome sequencing. The data were filtered according to the 1000 Genomes Project, ESP5500 and dbSNP information, and database with 69 exome sequence (Exome Sequencing Project) (without kidney diseases). By PIR sequencing methods, we detected candidate causal mutation. And then, we tested the mutation in other 97 sporadic FSGS patients and 96 normal controls.

**Results:** No mutation was detected from these exons of INP2, ACTN4 and TRPC6 in the FSGS pedigrees. 8 loci suggested for linkage were identified, and the multipoint parametric LOD score of 1.69 was marked by DS21215. A mutation (c.1213G, p.L405V) of ARHGAP32 gene was identified by combination with exome sequencing, genome-wide scan, function prediction of coding proteins. A new mutation (c.A5539G, p.R1870H) of ARHGAP32 gene was detected in one sporadic FSGS patient from 97 cases and 96 controls. The ARHGAP32 expression was detected in the glomerul and tubule. Conclusions: We found a candidate mutation of ARHGAP32 gene for primary FSGS by combination with whole genome linkage analysis and whole exome sequencing.
SA-POS15

Premature Death in First Degree Relatives of End Stage Renal Disease Patients

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Background: Increased risk of end stage renal disease (ESRD) and death in Norwegian living kidney donors has been reported. The majority of donors were related to the recipients.

Methods: The present study investigates risk of death in first degree relatives of ESRD patients. A cohort-design was used, ESRD in a first degree relative was the main exposure variable. All citizens born in Norway with at least one registered first degree relative were included.

Results: Five thousand two hundred and sixty eight (5180) articles were identified. Fifty-three articles investigating 55 genetic variants were included, 31 of which remained associated with EAV in a meta-analysis. These genetic variants were in or near the following genes: SERPINA1, CD226, CTLA4, HLA-B, HLA-DR, HLA-DQ, HLA-DQ, HLA-DRD1, RF35, RF11, RENG1, RYX2, RFX, and TRAF2. Moreover, we identified genetic distinctions between granulomatosis with polyangiitis and Wegener granulomatosis and between proteinase 3 ANCA vasculitis and myeloperoxidase ANCA vasculitis. In 79% of the genetic variants, subdivision based on ANCA serotype resulted in higher odds ratios than subdivision based on clinical diagnosis.

Conclusions: This meta-analysis identified 31 genetic variants associated with AAV, supporting a role for alpha-1-antitrypsin, the major histocompatibility complex system, and several distinct inflammatory processes in AAV pathogenesis. Our results indicate that subdivision of AAV based on ANCA serotype has a stronger genetic basis than subdivision based on clinical diagnosis.

SA-POS18

SA-POS16

Identifying Genetic Predictors of Skin Cancer in Renal Transplant Populations

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Background: The majority of kidney transplant recipients have been reported. The majority of donors were related to the recipients. In the present study investigates risk of death in first degree relatives of ESRD patients.

Methods: A cohort-design was used, ESRD in a first degree relative was the main exposure variable. All citizens born in Norway with at least one registered first degree relative were included.

Results: Five thousand two hundred and sixty eight (5180) articles were identified. Fifty-three articles investigating 55 genetic variants were included, 31 of which remained associated with EAV in a meta-analysis. These genetic variants were in or near the following genes: SERPINA1, CD226, CTLA4, HLA-B, HLA-DR, HLA-DQ, HLA-DQ, HLA-DRD1, RF35, RF11, RENG1, RYX2, RFX, and TRAF2. Moreover, we identified genetic distinctions between granulomatosis with polyangiitis and Wegener granulomatosis and between proteinase 3 ANCA vasculitis and myeloperoxidase ANCA vasculitis. In 79% of the genetic variants, subdivision based on ANCA serotype resulted in higher odds ratios than subdivision based on clinical diagnosis.

Conclusions: This meta-analysis identified 31 genetic variants associated with AAV, supporting a role for alpha-1-antitrypsin, the major histocompatibility complex system, and several distinct inflammatory processes in AAV pathogenesis. Our results indicate that subdivision of AAV based on ANCA serotype has a stronger genetic basis than subdivision based on clinical diagnosis.

SA-POS15

Meta-Analyses of Genetic Associations in New Onset Diabetes After Kidney Transplantation

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Background: New-onset diabetes after transplantation (NODAT) is a serious complication following solid organ transplantation. Although a genetic contribution to this disease and we have previously identified genetic risk factors associated with NODAT following kidney transplantation. These meta-analyses examine the pooled effect of genetic variants associated with NODAT in kidney transplant populations.

Methods: Relevant articles investigating the association between genetic markers and NODAT were identified by means of a database search of PubMed, Web of Science and Google Scholar from 1945 to 2015. Variants replicated in a minimum of three studies were included for analysis. Data was analysed using a random effects model in Review Manager 5.3. The association between identified variants and NODAT was calculated at the per-study allele level, where original studies were concordant with Hardy-Weinberg Equilibrium, to generate overall significance values and effect sizes.

Results: Our literature search returned 4,147 citations. Of the 36 eligible articles identified, 21 genetic variants from 13 genes were included for analysis. Of these, three were significantly associated with NODAT by meta-analysis at the 5% level of significance: TCF7L2 rs7903146 p<0.01 OR=1.41, 95%CI=1.07-1.85 (n=2967 individuals), CDKL1 rs1046398 p<0.006 OR=1.43, 95% CI=1.11-1.85, (n=696 individuals), and KCNJ12 rs2237892 p<0.007 OR=0.70, 95% CI=0.54-0.91, (n=1270 individuals).

Conclusions: These meta-analyses identified three genetic variants statistically associated with NODAT. Ideally, these variants should be assessed in less heterogeneous studies with larger numbers of kidney transplant recipients with a carefully defined NODAT phenotype.

Funding: Private Foundation Support

SA-POS19

New Prioritization and Burden Analyses of Rare Variants in 208 Candidate Genes Are Questioning the Pathogenicity of Previously CAKUT-Associated Genetic Variants

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Background: The leading cause of end-stage renal disease in children is attributed to congenital anomalies of the kidney and urinary tract (CAKUT). Familial clustering and mouse models support the presence of monogenic causes. Genetic testing is insufficient as it mainly focuses on HNF1B and PAX2 mutations that are thought to explain CAKUT in 5–15% of patients.

Methods: To identify novel, potentially pathogenic variants in additional genes, we designed a panel of genes identified from studies on familial forms of isolated or syndromic CAKUT and genes suggested by in vitro and in vivo CAKUT models. The coding exons of 208 genes were analyzed in 453 patients with CAKUT using next-generation sequencing. Rare truncating, splice-site variants and non-synonymous variants, predicted to be deleterious and conserved, were prioritized as the most promising variants to have an effect on CAKUT.

Results: Previously reported disease-causing mutations were detected. Five variants were fully penetrant causal mutations that improved diagnosis. We prioritized 148 candidate genes. We found no significant excess of rare variants in any of the genes in our cohort compared to controls.

Conclusions: Thus, in a study that represents the largest set of genes analyzed in CAKUT patients to date, the contribution of previously implicated genes to CAKUT risk is significantly smaller than expected and the disease may be more complex than previously assumed.

Funding: Private Foundation Support

SA-POS17

Genetic Variants in ANCA-Associated Vasculitis: A Meta-Analysis

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Background: Genetic factors may influence the pathogenic pathways leading to anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV). We performed a meta-analysis to determine the genetic variants most likely associated with AAV and investigated whether diagnostic and serological subtypes within AAV have distinct genetic backgrounds.

Methods: Studies investigating the association between genetic variants and AAV in humans were searched in PubMed, Embase, and Web of Science. All variants significantly associated with AAV in at least one study and investigated in at least two studies were included. Additionally, data on these genetic variants from the largest GWAS in AAV were included to increase the validity of this meta-analysis.

Results: One thousand one hundred and eighty articles were identified. Fifty-three articles investigating 55 genetic variants were included, 31 of which remained associated with AAV in a meta-analysis. These genetic variants were in or near the following genes: SERPINA1, CD226, CTLA4, HLA-B, HLA-DR, HLA-DQ, HLA-DQ, HLA-DRD1, RF35, RF11, RENG1, RYX2, RFX, and TRAF2. Moreover, we identified genetic distinctions between granulomatosis with polyangiitis and Wegener granulomatosis and between proteinase 3 ANCA vasculitis and myeloperoxidase ANCA vasculitis. In 79% of the genetic variants, subdivision based on ANCA serotype resulted in higher odds ratios than subdivision based on clinical diagnosis.

Conclusions: This meta-analysis identified 31 genetic variants associated with AAV, supporting a role for alpha-1-antitrypsin, the major histocompatibility complex system, and several distinct inflammatory processes in AAV pathogenesis. Our results indicate that subdivision of AAV based on ANCA serotype has a stronger genetic basis than subdivision based on clinical diagnosis.
Background: The PediGFR Consortium aims to identify genetic factors associated with pediatric chronic kidney disease (CKD) progression. The optimal model for CKD progression for testing is unclear. To address this question, we performed genome-wide association studies (GWAS) of two different definitions of CKD progression, slope of the annual change in estimated GFR (eGFR) versus time-to-event (TTE).

Methods: There were >8 million genotyped and imputed markers from 1,122 patients. The calculation of slope was based on 2-41 eGFR values per patient. TTE was a combined endpoint of dialysis, transplant, 50% GFR loss or GFR <5 ml/min/1.73m2. Respectively, cox proportional hazards and linear regressions were used for the GWAS of TTE and slope. Baseline variables were adjusted for age, sex, principal components, and baseline eGFR. For each definition, data were meta-analyzed from five study-ancestry specific groups in PediGFR.

Results: For TTE, follow-up time was 1.66-5.0 years (IQR) and an event rate of 34%. For slope, mean slope was -4.2 ml/min/1.73m2. For comparison, we focused on SNPs present in all five groups with a minor allele frequency >0.05, and I2<50%. For TTE, 6 genomic regions contained one or more of such SNPs with p<1E-6, one of which reached genome-wide significance (p=3E-8). Hazard ratios per allele range from 1.58-1.97. For slope, there were 3 regions with p<1E-6, one of which reached genome-wide significance. All GWAS variants were nominally associated with TTE, of which 2 of the 3 slope variants were nominally associated with TTE. None of the loci with p<1E-6 overlapped between the two definitions.

Conclusions: Genetic variants associated with CKD progression differed based on the definition of the phenotype. GWAS of TTE identified more loci at p<1E-6 than slope, and these were biologically more plausible based on current knowledge of kidney disease. However, the number of genome-wide significant loci was the same.

Funding: NIDDK Support, Private Foundation Support

SA-PO521
New Candidate Genetic Loci Associated with Pediatric Proteinuria in the CKiD Cohort
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Background: Proteinuria is an early marker for chronic kidney disease in adults and children. Here, we sought to identify genetic variants associated with baseline proteinuria in African American children diagnosed with chronic kidney disease from the CKiD cohort.

Methods: We genotyped 149 CKD participants using the Illumina HumanMethylation450 BeadChip v2.1 comprising over 250,000 markers, including putative functional exonic variants that were implicated in common metabolic disorders. 81,460 SNPs passed quality control and were tested for association with baseline proteinuria in 129 children with chronic kidney disease. T-tests were adjusted for age, gender, and the first five eigenvectors from the population stratification analysis.

Results: We identified several genetic loci that were significantly associated with proteinuria (PE100), as well as new candidate loci (10-90-10). Among the top hits, we notably revealed gene-expressed genes that were previously associated with the TGFbeta pathway, renal homeostasis, IgA nephropathy, congenital kidney disease, and vascular integrity (e.g. V4P3, STRA4, and HDAC7).

Conclusions: Our study emphasizes the power of unbiased large genetic screenings to discover new factors associated with pediatric kidney conditions. These new results warrant independent replication and functional validation.

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SA-PO522
Genotype-Phenotype Analysis in Pediatric Patients with WT1 Glomerulopathy Eunjin Park,1 Yo Han Ahn,1 Hee Gyung Kang,1 Hye Won Park,1 IL-Soo Ha,1 Hae Il Cheong,1,2 Dept of Pediatrics, Seoul National University Children’s Hospital, Seoul, Korea; Research Coordination Center for Rare Diseases, Seoul National University Hospital, Seoul, Korea; Dept of Pediatrics, Seoul National Univ Bundang Hospital, Seongnam, Korea.

Background: The WT1 gene plays an essential role in urogenital and kidney development and its mutations manifest two different types of glomerulopathies, Denys-Drash syndrome (DDS) and Frasier syndrome (FS). In this multicenter retrospective cohort study, genotype-phenotype correlations in Korean pediatric patients with WT1 mutations were analyzed.

Methods: During the period from 2001 to 2015, WT1 mutations were detected in a total of 28 patients by gene screening.

Results: The patients were grouped into FS (n=10, having a mutation in intron 9) and DDS (n=13, having an exon mutation). Nine (69%) DDS patients presented as congenital nephrotic syndrome (CNS) or infantile nephritic syndrome (INS), while 7 (70%) FS patients presented as segmental focal segmental glomerulosclerosis. Interestingly, monoxynogotic twin patients with DDS presented as end-stage renal disease (ESRD) without any previous history of glomerulopathy. Progression to ESRD was noted in 11 (85%) DDS patients at the median age of 0.22 (interquartile range [IQR], 0.07-1.65) years and in 5 (50%) FS patients with a median age of 16.50 (IQR, 10.16-16.50) years. 10 (77%) DDS patients died at the median age of 0.22 (IQR, 0.07-1.65) years, whereas 2 (26%) FS patients presented as congenital nephrotic syndrome at the median age of 0.22 (IQR, 0.07-1.65) years. Disorder of sexual development (DSD) was accompanied in 8 (62%) DDS and 7 (70%) FS patients. Three (13%) patients (2 with DDS and 1 with FS) had diaphragmatic defect/ hernia. Five (22%) and six (26%) patients underwent prophylactic nephrectomy and gonadectomy, respectively. Among the rest of the patients, Wilms tumor and gonadal/blastoma developed in 3 DDS patients and 1 FS patient, respectively.

Conclusions: The clinical manifestations and disease course of the Korean patients with WT1 glomerulopathy were mostly same as those of previous reports. Of note, patients with DDS presented as congenital nephrotic syndrome manifested two different types of glomerulopathies, Denys-Drash disease by linear regressions adjusted for age, gender, and the first five eigenvectors of recombination in each generation for n generations from 6 to 48.

Methods: Inheritance of the V260E mutation from two parents with a common ancestor will result in a region of homozygosity surrounding the locus, indicating the overlap of extended haplotypes preserved around the locus. To test for this we genotyped 10 individuals homozygous for the mutation, and 74 individuals homozygous for the wild type variant, with the Illumina exome chip. After QC, this chip provided 1674 markers within 20 megabases (Mb) of V260E. To predict the distribution of lengths of homozygous regions around the locus as a function of the number of generations between parents and their common ancestor carrying the mutation, we performed 10,000 coalescence simulations of recombination in each generation for n generations from 6 to 48.

Results: Plotting heterozygous and homozygous loci in the region surrounding V260E clearly showed regions of homozygosity around the locus. 8 of the 10 individuals had segments of homozygosity from 1.9 to 3.6 Mb. This distribution of lengths is inconsistent with a common ancestor within the last 20 generations.

Conclusions: Cryptic consanguinity does not explain the presence of homozygosity for NPHS2 V260E among Durban children with SR-FSGS. The indicated age of the mutation is consistent with introduction by the Omanii Empire, which spread in East Africa beginning in the 1600s.

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Conclusions: We confirmed the association of selected genetic variants with decline in GFR in children with progressive CKD, with differential effects by ethnicity at specific loci. Clarification of the genes involved in susceptibility to anemia has the potential to identify new therapeutic targets.

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SA-PO525

Cell-Free Hemoglobin and HMox1 in Sickle Cell Nephropathy

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Background: Chronic kidney disease (CKD) is observed in over 50% of adults with sickle cell disease (SCD) and hemoglobinuria, a consequence of intravascular hemolysis, is independently associated with CKD stage and its progression. In this study we investigate the mechanistic role of hemoglobinuria and HMox1, the rate limiting enzyme for heme metabolism, in SCD nephropathy.

Methods: Urinary tubular (kidney injury molecule-1, KIM-1) and glomerular (neprhin) biomarkers of injury were measured in 32 SCD patients by ELISA from the University of Illinois at Chicago (UIC). We then cultured human-kidney (2HK) tubular cells with lyophilized hemoglobin (L-Hb) to determine biological responses and expression of candidate genes. We examined the association of KIM with 11 tag SNPs and the GT-repeat polymorphism in HMox1 in 247 UIC SCD patients and in a separate replication cohort (Walk-PhaSt) of 482 SCD patients.

Results: Urine KIM-1 correlated with increasing urine cell-free hemoglobin concentration (P=0.005), while urine nephrin levels did not. HK2 culture studies showed increasing KIM-1 concentrations in the culture medium (P=0.01), decreasing HK2 cell viability (P=0.01), increased HMox1 expression (P=0.0001) and protein concentration (P<0.0001) with incremental concentrations of L-Hb. We identified a SNP in HMox1 (rs7438111, MAF=0.14) that was significantly associated with KCD stage (OR 2.8, P=0.0093) and CKD stage 3 (OR 3.0, P=0.02) in the UIC cohort and with ESRD (OR 9.8, P=0.0004) and CKD stage 3 (OR 2.3, P=0.04) in our replication cohort. UIC SCD patients with E25 GT-repeat in the promoter region of HMox1, known to be associated with increased HMox1 inductability and activity, had higher estimated glomerular filtration rate (eGFR)(P=0.2, P=0.01).

Conclusions: Cell-free hemoglobin contributes to sickle cell nephropathy through renal tubular injury. A tag-SNP in HMox1, rs743811, was associated with kidney disease and the presence of shorter (GT)n repeats correlated with increasing eGFR, raising the possibility that altered HMox1 activity has a critical role in SCD-nephropathy.

SA-PO527

Differences in Susceptibility to Cisplatin Nephrotoxicity Among 8 Mouse Strains

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Background: Cisplatin is a widely used chemotherapeutic agent with remarkable efficacy, but its use is limited by significant nephrotoxicity. Significant differences in susceptibility to nephrotoxicity among individual mouse strains have been noted, but predicting those at risk remains a challenge. To begin to identify genes that play a role in susceptibility to cisplatin nephrotoxicity (CPN), we set out to determine differences in CPN among 8 genetically distinct founder mouse strains of the Collaborative Cross: A/J, C57BL/6J, 129S1/SvJ, NOD/ShiLtJ, NZO/HIL1CAST/EJ, PWK/Phl, and WSB/EJ.

Methods: 10-14 week old male mice received ip. injection of 25 mg/kg cisplatin and serum was collected 72 hours later to sacrifice. Serum urea nitrogen (BUN) was measured for the 8 strains using a nonenzymatic, colorimetric kit (Arbor Assays) and analyzed by one way ANOVA and two sided t-test. Serum creatinine was measured using an enzymatic, colorimetric kit (Crystal Chem) and analyzed by a two sided t-test for the 2 strains that showed the largest difference in BUN.

Results: The 8 strains differed significantly in their serum BUN values (p=0.042). The number of animals in each group, and the mean and SD of BUN (mg/dl) were as follows: C57BL/6J (n=14) 188.6±9.2, CAST/Eij (n=3) 207.9±32.7, NOD/ShiLtJ (n=5) 256.7±93.0, PWK/Phl (n=4) 240.9±57.2, WSB/EJ (n=5) 254±15.6, A/J (n=5) 267.6±62.3, NZO/HIL1 (n=5) 290.0±50.7, 129S1/SvJ (n=4) 319.5±28.3. The biggest differences were seen between the C57BL/6J and 129S1/SvJ strains, (p=0.0001). In direct comparison the serum creatinine was significantly different between C57BL/6J (n=10) and 129S1/SvJ (n=9) strains, (p=0.0084) (Figure 1).

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subjects. Among healthy Montreal newborns, this same PAX2 SNP (rs11190739) was associated with a 10.2% decrease in newborn combined kidney volume in 14.6% of babies who were heterozygous for this common variant (p=0.036).

**Conclusions:** Our study provides the first evidence that a common PAX2 variant associated with newborn renal hypoplasia is also associated with decreased eGFR among Caucasians with diabetes mellitus for 15-25 years.

**Funding:** Private Foundation Support, Government Support - Non-U.S.

**SA-PO529**

Cefepime Dosing in Modeled Critically Ill Patients Receiving SHIFT Hemofiltration or Hemodialysis Renal Replacement Therapies

Katherine N. Gharibian, Susan J. Lewis, Bruce A. Mueller. College of Pharmacy, Univ of Michigan, Ann Arbor, MI.

**Background:** Cefepime is an antibiotic commonly used in the ICU where acute kidney injury (AKI) is prevalent. SHIFT therapy, a 6-12 hour renal replacement therapy (RRT), also referred to as Prolonged Intermittent Renal Replacement Therapy (PIRRT) or Slow Low Efficiency Daily Dialysis (SLEDD), is increasingly utilized to help treat AKI. However, dosing information for cefepime in critically ill patients receiving SHIFT therapy is currently lacking.

**Methods:** Using previously-published pharmacokinetic (PK) data and a PK model developed for critically ill patients receiving SHIFT RRT, a series of 5000-subject Monte Carlo simulations were performed for 18 cefepime regimens in 8 scenarios with varying duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT relative to cefepime doses. Cefepime regimens were evaluated on the probability of attaining a free drug concentration equal to at least the minimum inhibitory concentration (MIC) for ≥60% of the dosing interval during the first 48 hours of therapy. Optimal regimens yielded a probability of target attainment (PTA) ≥90% for MIC values ≤8 mg/L using the smallest total daily dose.

**Results:** Cefepime 1 g q6h hours with a 2 g loading dose was the only regimen to yield a PTA ≥90% in all 8 SHIFT settings while limiting the total daily maintenance dose to 4 g. This dosing regimen resulted in 48-hour mean trough concentrations >32 mg/L in most subjects.

**Conclusions:** In PK models of critically-ill subjects receiving 8 or 10 hours of SHIFT RRT, a cefepime dose of 1 g q6h hours with a 2 g loading dose yielded pharmacodynamic target attainment for >90% of the population.

**Funding:** Pharmaceutical Company Support - NxStage Medical, Inc.

**SA-PO530**

Identification of Optimal Ceftazidime Dosing Regimens in Modeled Critically Ill Patients Receiving SHIFT Renal Replacement Therapy

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**Background:** Ceftazidime is an antibiotic commonly used in critically ill patients. Ceftazidime doses of 2 g every 12 hours have been recommended for continuous renal replacement therapies (CRRT), however, no studies have evaluated the optimal dose in patients receiving SHIFT Therapy (NxStage Medical), a 6-12 hr RRT commonly referred to as Prolonged Intermittent Renal Replacement Therapy (PIRRT) or SLEDD, according to the shifts in settings including duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT relative to cefazidime dose. Using a series of 5000-subject Monte Carlo simulations, 12 cefazidime regimens were applied to each model and evaluated for the probability of attaining free drug concentrations equal to or greater than the minimum inhibitory concentration (MIC) of Ceftazidime administered in 4 g total daily doses (2 g q12h; 1 g q6h) yielded a PTA ≥90% in all 8 RRT models. Continuous infusion of the drug (3 g continuous infusion with a 2 g loading dose) achieved similar PTA values.

**Conclusions:** Published ceftazidime CRRT doses (2 g every 12 hours) yielded 90% PTA in modeled critically ill patients receiving 8 or 10 hours of SHIFT RRT. Future studies should validate these findings in the clinical setting.

**Funding:** Pharmaceutical Company Support - NxStage Medical, Inc.

**SA-PO531**

Use of Monte Carlo Simulation to Determine Optimal Meropenem Regimens in Patients Receiving SHIFT Renal Replacement Therapy

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**Background:** Current antibiotic dosing regimens often result in subtherapeutic concentrations in critically ill patients, but scant pharmacokinetic (PK) data exist to support antibiotic dosing. This study applied Monte Carlo simulations (MCS) to determine the initial meropenem regimen to treat critically ill patients receiving SHIFT Renal Replacement Therapy (RRT), a daily prolonged intermittent RRT.

**Methods:** Body weight & PK parameter [non-renal clearance, free fraction, volume of distribution & extraction coefficients] estimates with variability were obtained from relevant published studies. Values were randomly selected from the log-Gaussian distribution within the assigned limits to vary individual free meropenem concentration profiles. MCS were performed for 13 meropenem regimens including weight-based and pre- & post-SHIFT dosing, in 4 different SHIFT settings (4L/hour x 10 hours or 5L/hour x 8 hours in hemodiagnosis or hemofiltration) occurring either at the beginning of or 14-16 hours after meropenem infusion. Probability of target attainment (PTA) was evaluated using a pharmacodynamic target of ≥40% free meropenem concentrations above 4 times the minimum inhibitor concentration (TI<4xMIC) for Pseudomonas aeruginosa (2 µg/mL) for the first 48 hours of therapy. A ≥90% of PTA with the smallest daily dose was defined as optimal.

**Results:** Meropenem regimens using 2g/day attained ≥90% PTA. Meropenem 1g q12h and 1g given pre- & post-SHIFT were optimal regimens for all SHIFT settings. Weight-based dosing did not yield better target attainment than fixed-dose regimens.

**Conclusions:** This simulation indicates that meropenem regimens using 2g/day should be used initially to treat critically ill patients receiving 8 or 10 hour SHIFT RRT. These results warrant clinical validation.

**Funding:** Pharmaceutical Company Support - NxStage Medical Inc.
SA-PO532
Evaluation of Piperacillin/Tazobactam Regimens in Patients with SHIFT Renal Replacement Therapy: Susan J. Lewis,1 Katherine N. Gharibian,1 Ashita J. Tolwani,2 William Henry Fissell,3 Bruce A. Mueller.1 1College of Pharmacy, Univ of Michigan, MI; 2Univ of Alabama, AL; 3Vanderbilt Univ, TN.

Background: SHIFT Renal Replacement Therapy (RRT) is a prolonged intermittent RRT to treat critically ill patients with acute kidney injury, but lack of antibiotic pharmacokinetic (PK) data in this RRT limits its utility. This study evaluated probability of target attainable (PTA) of piperacillin/tazobactam regimens recommended in critically ill patients receiving SHIFT RRT, using Monte Carlo Simulations (MCS).

Methods: Mathematical PK models were constructed using literature-derived demographic/PK data with known variability. Four daily-SHIFT settings (hemofiltration or hemodialysis with effluent rates of 5L/hour x 8 hours or 4L/hour x 10 hours) occurring at 2 different times relative to drug dose were modeled. PTA of 13 piperacillin regimens (2-4g q6h-8h and 3 tazobactam regimens (0.5g q6h) with intermittent or prolonged infusion (4-hour or continuous) were evaluated. MCS generated free drug concentration profiles for each regimen in the 5,000 virtual patients. Pharmacodynamic targets were >90% of time free piperacillin concentrations above 4x the minimum inhibitory concentration (MIC) of Pseudomonas aeruginosa (16 µg/mL) and ≥50% of time free tazobactam concentrations above corresponding threshold (4 µg/mL) for the initial 48-hour-therapy. The optimal regimen required ≥90% of PTA for both agents.

Results: The attainment of ≥90% of PTA required piperacillin 16g/day and tazobactam 2g/day in all SHIFT settings. Prolonged infusion was not superior to intermittent infusion to yield better PTA in patients receiving SHIFT RRT.

Conclusions: Piperacillin/tazobactam 4.5g q6h is recommended for critically ill patients receiving 8 or 10 hour SHIFT RRT. These PK simulation results need to be clinically validated.

Funding: Pharmaceutical Company Support - NxStage Medical Inc.

SA-PO533
Beta-Blocker Dialyzability in Chronic Hemodialysis Patients: Alvin Tieu,1 Thomas Velenosi,1 Andrew S. Kucey,1 Laura Elisabeth Mccuaig,1 Matthew A. Weir,1 Brad Urquhart.2 1Dept of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, London, ON, Canada; 2Dept of Medicine, Div of Nephrology, Western Univ, London, ON, Canada.

Background: There is a paucity of data available to describe beta-blocker dialyzability. Of the available information, most were obtained prior to implementation of high-flux dialysis membranes. This study aims to characterize the dialyzability of four of the most commonly prescribed beta-blockers in patients undergoing conventional high-flux hemodialysis (HD). Based on physicochemical properties, we hypothesize atenolol and metoprolol to be extensively removed by HD, while bisoprolol and carvedilol to be poorly dialyzed.

Methods: HD patients from the London Health Sciences Centre were recruited for a Dialyzer and Recovery Clearance study investigating the removal of piperacillin (1 g) and tazobactam (0.5 g) from plasma. A total of 10 patients were included and dialysis was performed until a minimum of 90% removal was obtained. The plasma samples were collected prior to and at various times during dialysis.

Results: Following dialysis, 6.78 mg of atenolol, 0.66 mg of bisoprolol, 0.02 mg of carvedilol, and 1.53 mg of metoprolol were recovered in spent dialysate. The amounts of diazylized beta-blockers were applied in the recovery clearance method to produce dialytic clearance values of 124.0, 91.5, 1.3, and 150.2 mL/min for atenolol, bisoprolol, carvedilol, and metoprolol, respectively.

Conclusions: Beta-blocker efficacy can be hindered if substantial dialytic clearance occurs. Accordingly, atenolol and metoprolol were extensively cleared by HD, while carvedilol displayed low dialyzability. Contrary to previous literature, our data suggests moderate dialyzability for bisoprolol. With recent studies indicating heightened recurrence risk in HD patients prescribed highly-dialyzable beta-blockers, drug dialyzability data is critically important to optimize pharmacotherapy in HD patients. Definitive characterization of beta-blocker dialyzability can allow for determination of post-dialysis supplemental drug dosing strategies. Patients.

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SA-PO534
Rituximab Exhibits Altered Pharmacokinetics in Patients with Membranous Nephropathy: Uma R. Foegi,1 Visit Cheungpasitporn,2 David Bourne,1 Fernando C. Fervenza,2 Melanie S. Joy.1 1Schools of Pharmacy and Medicine, Univ of Colorado, Aurora, CO; 2Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Rituximab (RTX) is an anti-CD20 antibody used in the treatment of glomerular diseases including membranous nephropathy (MN). There is little information about the pharmacokinetics of therapeutic proteins, including RTX in patients with glomerular diseases. The study evaluated rituximab pharmacokinetics in patients with MN from a pilot investigation(Fervenza et al, 2010).

Methods: Patients with MN (n=20) received 4 RTX weekly IV infusions (375mg/m²), with a repeat of the identical treatment at 6 months. Patient baseline characteristics were: gender (17M/3F), age (49±13.3 y), BSA (2.22±0.24 m²), urinary protein excretion (11.3±4.1 g/d), creatinine clearance (72.3±33 mL/min). Pharmacokinetic analysis was performed using rituximab-plasma concentrations. Comparisons of pharmacokinetic parameters were made between the MN patients and published data from other populations.

Results: The MN population had a favorable reduction in urinary protein excretion 3 months after each RTX treatment course (7393±4114 mg/day and 4131±3441 mg/day, respectively), while creatinine clearance values were similar to baseline (72±31 mL/min and 82±37 mL/min, respectively). Patients with MN exhibited a shortened half-life (T1/2), greater volume of distribution (Vd), and enhanced clearance of RTX vs. previous reports in other patient populations. These characteristics resulted in an exposure (AUC) that was significantly reduced in patients with MN.

Conclusions: The pharmacokinetics of RTX in patients with MN are significantly altered compared to published data from cancer and autoimmune populations. These results suggest shorter T1/2 and lower exposures to RTX in MN may necessitate higher doses and/or changes to dosing frequency in order to elicit an optimal therapeutic effect.

Funding: Pharmaceutical Company Support - NxStage Medical Inc.

SA-PO535
Eculizumab Treatment Efficiently Prevents C5 Cleavage without C5a Generation in Atypical Hemolytic Uremic Syndrome: Gretthe Bergseth,1 Nicole Van De Heuvel,2 Lambertus P.W.J. Van den Heuvel,1 Tom Eirk Mollnes.2 1Dept of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, London, ON, Canada; 2Radboud Univ Medical Center, Nijmegen, Netherlands; Nordland Hospital, Bodø, Norway.

Background: The C5 inhibitor eculizumab has been successfully used to treat atypical hemolytic uremic syndrome (aHUS), however, available data on pharmacodynamics of this medication are limited. Recently, increased generation of C5a in a single patient with HELLP syndrome treated with eculizumab has been reported. Since this observation was unexpected, we aimed to reproduce these data and search for possible explanations for the findings.

Methods: Levels of C5a were analyzed in EDTA plasma samples of aHUS (n=3) patients using three commercial ELISA kits, one of the kits was also used in the HELLP study and other two kits were included as controls. The samples were collected before the first eculizumab dose and then at various time points during treatment.

Results: In line with the report on HELLP patient, the C5a values, measured by one of the commercial ELISA kits, increased significantly in all aHUS patients after the first eculizumab dose as compared to the values obtained before treatment (p<0.016). C5a remained elevated throughout the treatment period. Such increase could not be reproduced by using another two commonly available commercial kits. When eculizumab was added in vitro to normal human serum prior to activation, no generation of C5a was measured by all used kits.

Conclusions: Our data indicate that existing commercial assays require validation for specificity before being used to monitor effect of eculizumab, especially in clinical laboratory practice. This example illustrates how false conclusions can be drawn when based on results from one single commercial assay not satisfactorily validated for the purpose it is used.

Funding: Government Support - Non-U.S.

SA-PO536
Sensitive, Reliable and Easy-Performed Laboratory Monitoring of Eculizumab Therapy in Atypical Hemolytic Uremic Syndrome: Elena Volokhina,1 Nicole Van De Kar,1 Gretthe Bergseth,2 Theo J. Van der Velden,3 Jack F. Wetzels,1 Lambertus P.W.J. Van den Heuvel,1 Tom Eirk Mollnes.2 1Radboud Univ Medical Center, Nijmegen, Netherlands; 2Radboud University, Nijmegen, Netherlands; 3Nordland Hospital, Bodø, Norway.

Background: Atypical hemolytic uremic syndrome is a severe renal illness caused by complement dysregulation. Treatment with the complement C5 inhibitor eculizumab is effective, but associated with high costs. Laboratory monitoring of these patients with eculizumab therapy is therefore of great importance, but laboratory assays are still not widely available.

Methods: We evaluated the performance of three commercially available C5a ELISA kits (Bender, MyBioSource, and Empower) on EDTA plasma samples from patients with atypical hemolytic uremic syndrome treated with eculizumab. The kits were compared to a recently published calibration curve. The performance characteristics of these kits were determined in a blinded, quality controlled study.

Results: The performances of all kits were within the limits of recommendation. The kits were used to monitor the therapy of 10 patients with atypical hemolytic uremic syndrome. The time to reach the initial C5a nadir, and the number of days until the C5a concentration reached the treatment threshold was significantly lower compared to historical controls. The results of this study are consistent with published data from other institutions.

Conclusions: Eculizumab treatment is well tolerated by patients with atypical hemolytic uremic syndrome. The monitoring of C5a levels using commercially available kits is feasible and reproducible. Further studies are needed to establish the optimal monitoring strategy.

Funding: Government Support - Non-U.S.
respect to complement function has not been standardized. The aim of this study was to evaluate level complement functional assays for their application in routine follow-up of eculizumab-treated patients.

Methods: Complement activity in serum samples was analyzed using Wieslab® complement screen assay. The presence of eculizumab-C5 complexes in serum, EDTA plasma samples and in urine was measured using ELISA. Levels of scf5b-9 in urine were measured using electroluminescent epitope assay.

Results: First, we documented that the Wieslab® complement screen assay showed a sensitivity of 1-2% of C5 activity by adding purified C5 or normal human serum to a C5 deficient serum. Second, we documented that all the patient samples obtained during the standard treatment course, were completely blocked for terminal complement pathway activity. Moreover, complement remained fully blocked when intervals between the eculizumab infusions were extended to four weeks. Levels of complexes between eculizumab and C5 were inversely correlated to the complement activity (p=0.01). Third, titrating serum from eculizumab-treated patients into normal serum, revealed that eculizumab was present in excess up to four weeks after infusion. Finally, we showed that increased urine scf5b-9 disappeared after eculizumab treatment.

Conclusions: We demonstrate sensitive, reliable and easy-performed assays to monitor eculizumab-treated patients, which can be used to design individual dosage regimens.

Funding: Government Support - Non-U.S.

SA-PO537

Background: AKB-6548 is a novel, once-daily, oral hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) in development for the treatment of anemia in non-dialysis dependent (NDD) and dialysis dependent (DD) chronic kidney disease (CKD). Studies in NDD-CKD patients have shown AKB-6548 produces physiologic increases in erythropoietin, enhances iron mobilization, and produces a dose dependent increase in hemoglobin levels.

Methods: The pharmacokinetics (PK) of AKB-6548 have been evaluated in single and multiple dose studies in healthy volunteers and CKD patients (NDD-CKD and DD-CKD) over a broad range of dose levels. An analysis of results across studies was conducted to assess the potential impact of renal function on selecting the dose levels and dosing regimen in CKD patients. The analyses evaluated dose-linearity in drug exposure, clearance routes of AKB-6548 and its metabolites, as well as the impact of CKD severity and the hemodialysis procedure on drug disposition.

Results: In healthy volunteers, AKB-6548 demonstrated dose linearity and proportionality over single doses of 80-1200 mg and multiple doses of 500-900 mg/day. The PK parameters of AKB-6548 in healthy volunteers, NDD-CKD and DD-CKD patient populations except for a slightly longer half-life with declining renal function (4.7 hr., 7.9 hr. and 9.1 hr., respectively). A mass balance study (using 13C-labeled drug) in healthy volunteers demonstrated both renal and fecal routes of parent drug and metabolite clearance, supporting use of AKB-6548 in CKD patients without significant differences in drug exposure. Moreover, AKB-6548 was minimally cleared by the hemodialysis procedure and the PK parameters were similar whether AKB-6548 was administered prior to or following dialysis.

Conclusions: The results demonstrate a linear dose-exposure relationship for AKB-6548 over a wide range of dose levels and support the utility of once-daily dosing and similar dose levels across the spectrum of CKD severity.

Funding: Pharmaceutical Company Support - Akebia Therapeutics

SA-PO538
Nonclinical Pharmacokinetics and Toxicokinetics of RG-012, an Inhibitor of MicroRNA-21 Being Investigated for Treatment of Alport Syndrome John Stewart Grundy,1 Kai Liu,2 Steven Neben,3 Cindy L. Berman,2 Deidre Mackenna,1 Neil W. Gibson,1 2Regulus Therapeutics, San Diego, CA;2Berman Consulting, Wayland, MA.

Background: RG-012 is a single-stranded chemically modified oligonucleotide being developed to treat patients with Alport syndrome, which is characterized by loss of renal function associated with defects in specific collagen genes expressed in the kidney glomerular basement membrane. RG-012 inhibits miR-21, a microRNA target known to have increased expression in context of kidney stress and associated with renal dysfunction.

Methods: In vitro pharmacokinetic (PK) evaluations of RG-012 conducted during preclinical development included: tissue protein binding, metabolic stability in whole blood and liver lysates, and CYP3A5 inhibition/induction potential in cryopreserved human hepatocytes. In vivo PK and toxicokinetic (TK) properties of RG-012, and its major active metabolite (G0005), were determined upon subcutaneous dosing of RG-012 in a set of nonclinical PK, pharmacology, and safety studies in CD-1, SV129, and COL4A3 mice (62.5 mg/kg weekly) and folicacid-dependent mice (3x225 mg/kg/wk).

Results: Both RG-012 and RG0005 were highly bound (≥98%) to proteins in plasma from mice, monkeys, and humans. RG0005 was the only major degradation product seen from mice, monkeys, and humans. RG0005 was the only major degradation product seen from mice, monkeys, and humans. RG-012 demonstrated dose dependent displacement of miR-21 from polysomes in both liver and kidney with a maximum effect reached at dose levels that are efficacious in the Col4A3 mouse models. Loss of miR-21 from the polysomes was specific as levels of Let-7a, a control microRNA to which RG-012 has no complementarity, were unaffected. In the liver, target engagement was also assessed using mRNA derepression of a set of confirmed miR-21 target genes. Here, target gene derepression strongly correlated with polysome displacement. This comparison was not possible in kidney, however, because target genes are not regulated in kidneys in the absence of stress.

Conclusions: RG-012 directly and specifically inhibits miR-21 resulting in its displacement from actively translating polysome complexes and subsequent derepression of messenger RNA targets.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

SA-PO540
Tacrolimus Pharmacokinetics in Nephrotic Stage Maria Medeiros,1 Saul Valverde,1 Luis Velasquez-Jones,1 Ana M. Hernandez,2 Gilberto Castaheda-Hernandez,2 Guido Filler.1 Hospital Infantil de México Federico Gomez, Mexico;2CINVESTAV, IPN, Mexico;1Children’s Hospital, Univ of Western Ontario, Canada.

Background: While tacrolimus (Tac) therapy is not first-line therapy for childhood nephrotic syndrome, it is often used instead of cyclosporine to ameliorate the side effects. The pharmacokinetics of Tac can be influenced by many conditions, and it has a high plasma protein binding. The Tac pharmacokinetics during relapse and remission of childhood nephrotic syndrome have not been well described.

Methods: We performed 14 pharmacokinetic (PK) profiles (with measurements before and 0.5, 1, 2, 4 and 12 hours post intake) in 7 children with steroid-resistant nephrotic syndrome (SRNS) during relapse and in remission. These data were compared with historical PK data of 161 PK profiles in 87 pediatric renal transplant recipients with measurements before, 0.5, 1, 2, 4, 6, 8 and 12 hours post intake. Tac levels were measured using the Abbott Tacro II assay. We used descriptive statistics to generate percentiles and compared these with the SRNS patients. We also compared the PK profiles during relapse and remission.

Results: Median age of SRNS patients was 3.2 years. Tacrolimus dose, biochemical values and pharmacokinetics parameters are shown in Table 1. Values as median and interquartile range.

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The PK profiles were well within the percentiles of the transplant children. **Conclusions:** Tac profiles are not different in children with nephrotic syndrome during relapse and remission. **Funding:** Government Support - Non-U.S.

**SA-PO541**

*Clinical and Genetic Determinants of Longitudinal Dose-Corrected CNI Exposure in Chilren Under Renal Transplantation*  
_Norrel Knox,1 Elena N. Lofts,2 Dirk R. Kuppers,2 Pediatric Nephrology, Univ Hospitals Leuven, Belgium; 2Nephrology, Univ Hospitals Leuven, Leuven, Belgium.*

**Background:** Calcineurin-inhibitors (CNI) have a narrow therapeutic index and dosing is difficult due to inter- and intra-individual variation in pharmacokinetics (PK). Polymorphisms in genes involved in drug metabolism can play a critical role in individual exposure. Data concerning long-term CNI exposure in relation to dose in children are scarce and in general based upon trough levels. We present the longitudinal follow up of 124 children in the period from the time of transplantation to 1-year post transplant in relation to dose, clinical and genetic factors in a cohort pediatric renal allograft recipients.

**Methods:** Retrospective single center study in subjects after renal transplantation (age 0-20 years) with annual PK assessments (6-point AUC0-12hr) for tacrolimus (Tac) or cyclosporine (CsA). Clinical and laboratory data were retrieved. Analysis of polymorphisms in CYPIA4, CYPIA5, CYPIA7, POR, CYP3A4, CYP3A5, CYP3A7, CYP2C9 was performed.

**Results:** We collected 180 “full” AUCs for Tac, 56 for CsA in 51 kids. Mean age at Tx: 9.9 yrs (1-19). FU after Tx: 4.6 yrs (0-16). Dose-corr exposure according to BS, in contrast to bodyweight, CL/LBW were noted with sex sub-analysis and summarized as Phenotypic Mean with Underline represents presenting author.

**Conclusions:** Sex-race differences in Tac PK contribute to differential dosing requirements in AA vs C. A more individualized approach to chronic Tac immunosuppression integrating sex-race with TDM and a standardized adverse effect assessment may benefit RTR. **Funding:** NIDDK Support, Pharmaceutical Company Support - Astellas Scientific and Medical Affairs, Inc.

**SA-PO543**

*Sex and ABCB1 Haploype Associations with Tacrolimus Pharmacokinetics in Renal Transplant Recipients*  
_Kathleen M. Tomatore,1 Daniel Brzezka,2 Calvin J. Meaney,3 Louise M. Cooper,1 Rocco C. Venuto.3 NTS Center of Excellence in Bioinformatics & Life Science; Pharmacy, School of Pharmacology & Pharmaceutical Sciences; 3GAP-Core Faculty; Schools of Pharmacy & Medicine, Univ of New England, Portland, ME; 3Medicine, ECMC, School of Medicine; 1Univ at Buffalo, Buffalo, NY.*

**Background:** Tacrolimus (TAC) is the mainstay calcineurin inhibitor for immunosuppression in renal transplant recipients (RTR). Tac exhibits interpatient variability in pharmacokinetics (PK) attributed primarily to CYP 3A5 isoenzymes and P-glycoprotein (Pgp). Pgp is encoded by the ABCB1 gene. The common single nucleotide polymorphisms (SNP): rs12367726 (T>C) and rs77752582 (C>T) have conflicting associations to TAC PK. This study objective evaluated these common SNPs as haplotypes in relation to TAC PK.

**Methods:** During a 12-hr PK study, trough (C0), apparent clearance (CL) and lean body weight (LBW) normalized CL were determined in 29 female and 36 male African American (AA) and Caucasian (C) stable RTR greater than 6 months post-transplant receiving Tac and mycophenolic acid. TAC dosage was adjusted to C0 range of 4-9 ng/ml. The ABCB1 SNPs: rs12367726 (T>C) and rs77752582 (C>T) were assessed. **Results:** TAC C0 range of 5-10 ng/ml with no difference between groups in spite of higher doses in AA (P<0.0001). Significant associations of TTT to TAC dose, CL and CL/LBW were noted with sex sub-analysis and summarized as Phenotypic Mean with Confidence Interval (CI) of WT compared to variant in table. These data suggest RTR with TTT variant received lower doses and had slower TAC CL relative to sex.

**Conclusions:** Sex-race differences in Tac PK contribute to differential dosing requirements in AA vs C. A more individualized approach to chronic Tac immunosuppression integrating sex-race with TDM and a standardized adverse effect assessment may benefit RTR. **Funding:** NIDDK Support, Pharmaceutical Company Support - Astellas Scientific and Medical Affairs, Inc.

**SA-PO544**

*Pharmacokinetics and Pharmacodynamics of Tacrolimus, and NFAT Regulated Gene Expression in Kidney Transplant Patients*  
_Friedler Keller, University Ulm, Germany.*

**Background:** Suppression of genes that are regulated by the nuclear factor of activated T-cells (NFAT) is an effect of calcineurin inhibitors. We correlated the pharmacodynamics to the pharmacokinetics of tacrolimus.

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

1 Underline represents presenting author.

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### Table 1: Tacrolimus (TAC) Pharmacokinetic Parameters in Renal Transplant Recipients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Value</th>
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<tbody>
<tr>
<td>TAC C0h (mg/dL)</td>
<td>7.9 (3.6, 11.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>TAC dose[mg]</td>
<td>5.0 (1.7)</td>
<td>0.8</td>
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<tr>
<td>TAC C (ug/ml)</td>
<td>7.2 (1.8)</td>
<td>6.7 (1.7)</td>
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<tr>
<td>AUC 0-12/hr (mg*hr/ml)</td>
<td>854 (mean) in &lt;5 yrs to 2702 &gt;15yrs); 817 to 1787 ng*hr/ml per mg/m2 body surface (BS)</td>
<td>40.0 (6.16)</td>
</tr>
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</table>

**Conclusions:** The ABCB1 haplotypes provide important insight into interpatient variability in TAC PK post renal transplant and the role of P-gp that is also influenced by sex. **Funding:** NIDDK Support, Pharmaceutical Company Support - Astellas Scientific and Medical Affairs, Inc.
Methods: This study was undertaken in the University Hospitals of Ulm (Frieder Keller) and Heidelberg (Claudia Sommerer, Thomas Giese, Martin Zeier). Tacrolimus trough concentrations (Trough) and 1.5 – 2 hours later the peak concentrations (Peak) were measured by LCMS. Simultaneously, the Nfat trough effect (Trough) and the nadir effect (Nadir) were determined. The pharmacokinetic half-life (T1/2) was estimated from peak (Peak) and trough concentrations (Trough) considering the time distance between steady-state peak and troughs (10.5 – 10 hours). The pharmacodynamic concentration producing the half-maximum effect (CE50) and the Hill coefficient (H) were estimated from trough effect (Trough) at trough concentrations and from nadir effect (Nadir) at peak concentrations. The two equations were solved by numerical iteration for an estimate of the two unknown parameters (CE50, H).

Results: A total of 10 stable kidney transplant patients were included. The median age was 58 years and the median serum creatinine was 306 μmol/L. The pharmacokinetics of tacrolimus were estimated with T1/2 = 11 hours, CL/F = 64 L/h and Vd/F = 480 L. The median value for Nfat was 89% (Trough) of normal gene expression, and the nadir effect was 43% (Nadir) representing the strongest immunosuppression of basal gene expression. The pharmacodynamics of tacrolimus were estimated with CE50 = 7.7 ng/ml and the Hill coefficient with H = 4.6, respectively.

Pharmacodynamic Hill equation

![Figure 1: Tacrolimus pharmacokinetics (blue) and pharmacodynamics (red).](image)

Conclusions: While on triple immunosuppression, the Nfat pharmacodynamics indicate a low concentration producing the half-maximum effect and a high Hill coefficient. These findings suggest a narrow trough-to-peak target concentration range of 4.0-to-9.5 ng/ml for tacrolimus.

**SA-POS456**

Renal Nitrates in Chronic Kidney Disease

**Background:** Endogenously synthesised nitric oxide (NO) is rapidly oxidised to nitrite and nitrate. These oxidation products can be recycled back into nitric oxide via a complex entero-salivary pathway, thus preserving NO activity. It has previously been shown that 66% of circulating nitrite is excreted in the urine in 48 hours with the fate of the remainder unknown. 24-hour urinary nitrate excretion is often used to estimate total body nitrite oxide synthesis rates. It is not known what effect declining GFR has on renal nitrate clearance.

**Methods:** 27 subjects, 14M,13F, median age 70 (range 27-74 years) with CKD-EPI eGFR between 9 and 89 were recruited. Following 24hrs low nitrate diet plasma nitrate concentration and 24 hour urinary nitrate excretion were measured to determine renal nitrate clearance using a microplate spectrophotometric method. 24-hour urinary nitrate excretion is often used to estimate total body nitrite oxide synthesis rates.

**Results:** There was a statistically significant correlation between renal nitrate clearance and eGFR. Pearson r = 0.748, p<0.0001. There was no relationship between plasma nitrate concentration and eGFR, p=0.239, or between plasma nitrate concentration and renal nitrate clearance, p=0.547.

**Conclusions:** As plasma nitrate concentration is unchanged despite diminished renal nitrate clearance at lower eGFRs, we suggest that non-renal clearance is responsible for a greater proportion of nitrate elimination as GFR falls. We conclude that 24 hour urinary nitrate excretion cannot be considered a reliable measure of total body nitric oxide synthesis in CKD. Elucidating the non-renal pathways of loss of the NO storage molecule, nitrate, may lead to novel therapeutic strategies in CKD and cardiovascular disease.

Reference

**SA-PO547**

The Pharmacodynamic Effect of Tenapanor Is Most Pronounced when Administered After Food in Healthy Volunteers

**Methods:** In this open-label, 3-way crossover study (NCT02226783), 18 healthy adults (mean age=SD, 35±11 years; 14 men) completed a randomized sequence of 4-day treatments with tenapanor hydrochloride 15 mg bid: before food (5–10 min before breakfast and dinner); after food (30 min after the start of breakfast and dinner); and at fasting (1 h before breakfast, and 3 h after dinner). As plasma nitrate concentration is unchanged despite diminished renal nitrate clearance at lower eGFRs, we suggest that non-renal clearance is responsible for a greater proportion of nitrate elimination as GFR falls. We conclude that 24 hour urinary nitrate excretion cannot be considered a reliable measure of total body nitric oxide synthesis in CKD. Elucidating the non-renal pathways of loss of the NO storage molecule, nitrate, may lead to novel therapeutic strategies in CKD and cardiovascular disease.

**Results:** Stool Na content was higher for tenapanor taken before food than for after food or at fasting, with least-squares mean differences significant in both cases (Table). Differences in urinary Na were not significant. The difference in stool phosphorus (P) content was significant for tenapanor taken before food versus at fasting. The difference in urinary P was significant for administration before food or after food versus at fasting. Stool frequency and consistency were similar across treatments, and there were slightly higher stool weights for administration before or after food, compared with at fasting. There were no serious AEs or discontinuations due to AEs.

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<tr>
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<td>Cre</td>
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</table>

**Reference**

1 Martin Kaufmann, 1Glenville Jones, 1Rachel M. Holden, 2Michael A. Adams, 1Biomedical and Molecular Sciences, Queen’s Univ, Kingston, ON, Canada; 1School of Medicine, Queen’s Univ, Kingston, ON, Canada.

**Background:** The lack of simple and sensitive tools for longitudinal kidney function assessment in rodent models has impeded analysis of CKD onset and progression and the impact of interventions. This study evaluates 2-sample plasma clearance (pCl) of iohexol, a radio-contrast agent, compared to previously validated inulin pCl in rats to estimate GFR.

**Methods:** Progressive CKD was induced with a 0.25% adriamycin diet in male Sprague-Dawley rats (N=8). Following serial tail vein injections of iohexol (51.92 mg/kg) and FITC-inulin (2.5 μL/kg of 5% solution), 12 saphenous blood samples were taken from conscious rats over 5 hours, weekly (control, 5 weeks of adenine). Plasma creatinine was measured via the Jaffrey method, FITC-inulin via fluorometry, and iohexol via UPLC-MS.

Two reference methods for pCl calculation were used: a 2-compartment model (2 COM) and trapezoidal approximation (TRA) of area under the curve.

**Results:** Reference methods of inulin pCl agreed well with iohexol pCl.

pCl of iohexol and inulin was significantly decreased, compared to baseline, after one week (p<0.005), whereas plasma creatinine concentration was not significantly elevated until the third week (p=0.02). Characterisation of a 1-compartment model using 2-samples was employed: samples at 30 and 90 min post injection yielded high agreement (R²=0.98) and no significant bias.

**Conclusions:** Iohexol pCl sensitively and accurately measures an early decline in kidney function, especially compared to creatinine. The 2-sample method for assessing kidney function is straightforward and is therefore suitable for large rat cohorts. This approach will both enable detection of early kidney disease and facilitate concise interpretation of results derived from pre-clinical studies.

**Funding:** Government Support - Non-U.S.

**SA-POS547**

Renal Nitrates in Chronic Kidney Disease

**Background:** Endogenously synthesised nitric oxide (NO) is rapidly oxidised to nitrite and nitrate. These oxidation products can be recycled back into nitric oxide via a complex entero-salivary pathway, thus preserving NO activity. It has previously been shown that 66% of circulating nitrite is excreted in the urine in 48 hours with the fate of the remainder unknown. 24-hour urinary nitrate excretion is often used to estimate total body nitric oxide synthesis rates. It is not known what effect declining GFR has on renal nitrate clearance.

**Methods:** 27 subjects, 14M,13F, median age 70 (range 27-74 years) with CKD-EPI eGFR between 9 and 89 were recruited. Following 24hrs low nitrate diet plasma nitrate concentration and 24 hour urinary nitrate excretion were measured to determine renal nitrate clearance using a microplate spectrophotometric method.

**Results:** There was a statistically significant correlation between renal nitrate clearance and eGFR. Pearson r = 0.748, p<0.0001. There was no relationship between plasma nitrate concentration and eGFR, p=0.239, or between plasma nitrate concentration and renal nitrate clearance, p=0.547.

**Conclusions:** As plasma nitrate concentration is unchanged despite diminished renal nitrate clearance at lower eGFRs, we suggest that non-renal clearance is responsible for a greater proportion of nitrate elimination as GFR falls. We conclude that 24 hour urinary nitrate excretion cannot be considered a reliable measure of total body nitric oxide synthesis in CKD. Elucidating the non-renal pathways of loss of the NO storage molecule, nitrate, may lead to novel therapeutic strategies in CKD and cardiovascular disease.
Conclusions: The pharmacodynamic effect of tenapen, as judged by stool Na content, was greatest when tenapen was taken before food. This supports taking tenapen before meals in future trials.

Funding: Pharmaceutical Company Support - AstraZeneca

SA-PO548

Triferic Does Not Induce Non-Transferrin Bound Iron or Labile Plasma Iron: In-Vivo/In-Vitro Correlation Raymond D. Pratt,1 Dorine W. Swinkels,2 Carrie D. Guss,1 Ajjay Gupta.1 1R&D, Rockwell Medical Inc., Wixom, MI; 2Radioud Univ Medical Center, Nijmegen, Netherlands.

Background: Triferic is a complex iron salt approved for administration via hemodialysis to maintain hemoglobin in patients with CKD SHD. Triferic crosses the dialyzer membrane and binds to transferrin during hemodialysis replacing the obligate iron losses in HD patients. Serum iron and transferrin saturation (TSAT) values rise after HD and return to the baseline by the end of the next dialysis session.

Methods: A pharmacokinetic (PK) study in healthy volunteers administered up to 10 mg of Triferic iron over 4 hours and up to 20 mg Triferic iron over 12 hours assessed the PK of serum total iron (sFe-total) and transferrin bound iron (TBI). An in-vitro study assessed labile plasma iron (LPl). Triferic iron was added to plasma like medium (40 mg/ml human serum albumin) at a concentration range of 0 to 112 mg/dL. In addition, Triferic was added to 5 different human plasma’s (TSAT, range 10 - 46%; total iron binding capacity (TIBC), mean 374 mg/dL, range: 342-446 mg/dL) across a concentration span up to and exceeding 100% TSAT. LPl was measured in the presence of 40 mM ascorbate used dihydorodihamine (DHR)-123 in the presence of 50 mM deferiprone (DFO) to detect iron-catalyzed radical generation.

Results: In the human PK study, sFe-total and TBI showed an identical PK profile. Non-transferrin bound iron (NTBI), calculated as the difference between sFe-total and TBI, showed no dose dependent increase up to a TSAT of 100%. In plasma like medium, LPl increased with increasing concentrations of Triferic iron. When Triferic was added to human plasma, there was a small increase in LPl observed when iron concentrations were less than 100% TSAT. The mean magnitude of LPl (expressed in concentration units) at approximately 100% TSAT was 5.35 mg/dL (mean 1.4% of the total iron concentration). Once 100% TSAT was exceeded, the LPl increased rapidly.

Conclusions: Triferic rapidly donates iron to transferrin in vivo and in vitro. In vivo, at TSAT less than 100%, NTBI was minimal. In vitro, the LPl results confirm the lack of redox active iron in plasma until the plasma TIBC is exceeded.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO549

Impact of Tubular Luminal H+/Organic Cation Antipporter, MATE, on Imatinib-Induced Fluid Retention Moto Kaiwara,1 Satohito Masuda.1 1Dept of Pharmacy, Kyushu Univ Hospital, Fukuoka, Japan; 2Dept of Research and Development of Next Generation Medicine, Kyushu Univ, Fukuoka, Japan.

Background: A tyrosine kinase inhibitor, imatinib (IMA) is the first class agent against chronic myeloid leukemia. Although little is known about mechanism involved, more than 50% of imatinib-treated patients suffering from edema. In vitro study reported that clinical blood level of IMA inhibits multidrug and toxin extrusion (MATE, SLC47A)-mediated transport of metformin, a hypoglycemic drug. MATE is highly expressed in the brush border membrane of proximal tubular cells mediating the efflux of organic cations, such as metformin, monoamines. The renal dopaminergic system is likely responsible for regulating >50% of net renal salt and water excretion when salt intake increases. In this study, we test a hypothesized that IMA prevents natriuresis by inhibiting MATE-mediated dopamine (DA) secretion into tubule lumen and consequently causes edema.

Methods: C57BL/6 wild type mice (WT) and Mate1 knockout mice (KO) were used. By RT-qPCR. CYP3A4 and CYP3A5 protein expression was examined by Western blotting. Serums were collected from critically ill adults with varying AKI severity. Hepatic drug metabolism by cytochrome P450 3A (CYP) is reduced in end stage kidney disease (ESKD) and acute kidney injury (AKI). The underlying mechanisms are uncertain. Previously we reported suppression of CYP3A4 mRNA transcription when human hepatocytes ( HepG2) were exposed to serum from ESKD patients compared to healthy adults. CYP3A4 and 5 protein concentrations were unchanged. We now investigate whether serum from patients with AKI elicits similar results.

Methods: Serum was collected from critically ill adults with varying AKI severity. Sera from KDIGO 0 (n=15) and KDIGO 3 (n=16) AKI patients were applied individually to HepG2s for 24 h, when cells were lysed. CYP3A4 and 5 gene expression was examined by RT-qPCR. CYP3A4 and CYP3A5 protein expression was examined by Western blotting. The sera were also applied to HepG2 in a pooled fashion, alongside pooled sera from adults with ESKD prior to hemodialysis (n=10) and healthy adults (n=6), to allow comparison with previous data.

Results: AKI serum exposure doubled CYP3A4 gene expression compared to No AKI serum (p=0.0055 individual and p=0.003 pooled). AKI serum CYP3A5 mRNA increased approx. 25% compared to No AKI serum (p=0.11 individual and p=0.0098 pooled).

Conclusion: The correlations observed in this study indicate that patients poorly responding to one dose or mode of albuminuria lowering intervention also respond poorly to other doses or modes of intervention in the RAS. Whether other drugs targeting pathways beyond the RAS improve individual response variability requires further study.

SA-PO550

Optimizing Between-Patient Variability in Response to Renoprotective Drugs: Meta-Analysis of Rotation Trials Sergei Petrykiv,1 Dick de Zeeuw,2 Frederik I. Persson,2 Peter Rossing,2,3 Hans-Henrik Parving,2 Gozewijn Dirk Laverman,2 Hiddo Jan Lambers Heerspink,1 1Univ Medical Center; Groningen, Netherlands; 2Steno Diabetes Center; Gentofte, Denmark; 3Univ Copenhagen, Denmark.

Background: Individual response to albuminuria lowering intervention is highly variable among patients. To investigate whether up-titrating the dose of drug, changing the mode of intervention (with similar or different drug classes), or lowering dietary sodium intake improves individual response variability, we meta-analyzed individual responses to different modes of anti-albuminuric intervention in non-diabetic and diabetic patients.

Methods: Randomized rotation trials were analyzed to assess correlation of patient-specific responses (n=216 patients) to anti-albuminuric interventions. Included studies (N=20) compared the anti-albuminuric effect of up titrating the dose of intervention in the RAS (RAS) (N=10 comparisons) and NSAIDs (N=1), rotation within the same class of RAS (e.g. ACE1 to ARB; N=5) or NSAIDs (N=3), rotation between RAS and NSAIDs (N=2), and rotation from high to low sodium intake during RAS (N=1). A two stage meta-analysis was performed. First, deeming regression was conducted in each study to assess correlation in response. Individual study results were then meta-analyzed. Albuminuria was measured in 24-hr urine samples.

Results: The albuminuria response to one dose of RAS or NSAID positively correlated with the response to a higher dose of RAS or NSAID, rotation within the same class of RAS or NSAIDs, rotation between RAS and NSAIDs, and rotation from high to low salt intake. Correlations were consistent in diabetic and non-diabetic patients.

Conclusions: The correlations observed in this study indicate that patients poorly responding to one dose or mode of albuminuria lowering intervention also respond poorly to other doses or modes of intervention in the RAS. Whether other drugs targeting pathways beyond the RAS improve individual response variability requires further study.

SA-PO551

Acute Kidney Injury Serum Upregulates Hepatic Transcription of Cytochrome P450 3A4 and 3A5 Katie Lane,1 John Dixon,1 Ekram Nabi,2 Barbara J. Philips,1 Iain Macphee,1 Mark E. Dockrell,2 1Critical Care, St. George’s Univ of London, United Kingdom; 2South West Thames Inst for Renal Research, United Kingdom.

Background: Hepatic drug metabolism by cytochrome P450 3A (CYP) is reduced in end stage kidney disease (ESKD) and acute kidney injury (AKI). The underlying mechanisms are uncertain. Previously we reported suppression of CYP3A4 mRNA transcription when human hepatocytes ( HepG2) were exposed to serum from ESKD patients compared to healthy adults. CYP3A4 and 5 protein concentrations were unchanged. We now investigate whether serum from patients with AKI elicits similar results.

Methods: Serum was collected from critically ill adults with varying AKI severity. Sera from KDIGO 0 (n=15) and KDIGO 3 (n=16) AKI patients were applied individually to HepG2s for 24 h, when cells were lysed. CYP3A4 and 5 gene expression was examined by RT-qPCR. CYP3A4 and CYP3A5 protein expression was examined by Western blotting. The sera were also applied to HepG2 in a pooled fashion, alongside pooled sera from adults with ESKD prior to hemodialysis (n=10) and healthy adults (n=6), to allow comparison with previous data.

Results: AKI serum exposure doubled CYP3A4 gene expression compared to No AKI serum (p=0.0055 individual and p=0.003 pooled). AKI serum CYP3A5 mRNA increased approx. 25% compared to No AKI serum (p=0.11 individual and p=0.0098 pooled).

Comparison of Pooled Serum (10%) Effects on HepG2 CYP3A4 and CYP3A5
gene expression

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

Underline represents presenting author.
CYP3A4 and 3AS protein concentrations did not differ after exposure to AKI or No AKI sera (p=0.35, p=0.43).

Conclusions: In contrast to ESKD, hepatoocyte exposure to AKI serum upregulates CYP3A4 and CYP3A5 transcription compared to No AKI serum. CYP3A4 and 3AS protein concentrations were unchanged. Further serum analysis will determine whether differences in inflammatory profiles may be responsible. The results underscores the need to view drug metabolism in AKI as distinct from that in ESKD.

Funding: Private Foundation Support

SA-PO552

The Effect of Gut-Derived Uremic Toxins on the Expression of Hepatic Drug Metabolizing Enzymes in Chronic Kidney Disease  
Thomaz Velosenoi, Alvin Tieu, Andrew S. Kucey, David A. Feere, Brad Urquhart.  
Pharmacology, Univ of Western Ontario, London, ON, Canada.

Background: Hepatic drug metabolism is altered in patients with chronic kidney disease (CKD). Previous studies suggest that uremic toxins affect drug metabolizing enzymes in CKD. We hypothesize that gut-derived uremic toxins are involved in the downregulation of hepatic drug metabolizing enzymes and that removal of gut-derived uremic toxins by AST-120 will recover hepatic CYP3A4 and CYP2C enzyme function and expression in rats with CKD.

Methods: Huh7 human hepatoma cells were treated with various uremic toxins as well as a cocktail of all uremic toxins. Chronic kidney disease was induced in male Wistar rats using 0.5% adenine supplemented into rat chow. Control rats were pair-fed to CKD animals. After 5 weeks, control and CKD animals were further divided and received 8% AST-120 or a control diet. Rats were sacrificed 8 weeks after initiation of the study and plasma and liver tissue were obtained.

Results: Indoxyl sulfate caused a concentration-dependent decrease in Huh7 CYP3A4 expression with an IC50 value of 179.8 nM. AST-120 had indoxyl sulfate, p-cresyl sulfate and hippuric acid levels significantly lower than CKD animals and similar to control animals. Hepatic CYP3A2 mRNA expression was significantly decreased by 90% in rats with CKD (P<0.05); however, rats with CKD given AST-120 had a 25% recovery in CYP3A2 mRNA expression. Rats with CKD had decreased hepatic CYP2C11 mRNA expression that was not recovered by AST-120.

Conclusions: Uremic concentrations of indoxyl sulfate decreased CYP3A4 mRNA expression in Huh7 cells. AST-120 given to rats with CKD reduced indoxyl sulfate, p-cresyl sulfate and hippuric acid levels significantly lower than CKD animals and similar to control animals. Hepatic CYP3A2 mRNA expression was significantly decreased by 90% in rats with CKD (P<0.05); however, rats with CKD given AST-120 had a 25% recovery in CYP3A2 mRNA expression. Rats with CKD had decreased hepatic CYP2C11 mRNA expression that was not recovered by AST-120.

SA-PO553

The Effect of AST-120 on Hepatic and Intestinal Drug Transporter Expression in Chronic Kidney Disease  
Andrew S. Kucey, 1 Thomas Velosenoi, 1 Alvin Tieu, 1 Stephanie E. Nevison, 1 Brad Urquhart.  
Dept of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, London, ON, Canada;  
Lawson Health Research Inst, London, ON, Canada.

Background: Chronic kidney disease (CKD) is the progressive decline in renal function over time. There is a marked reduction in both renal and non-renal drug clearance in CKD. AST-120 is an oral adsorbent that promotes the elimination of gut-derived toxins that accumulate in CKD due to impaired clearance. It is hypothesized that there will be a reduction in the expression of drug transporters in CKD conditions. AST-120 will help recover drug transporter expression in CKD by decreasing uremic toxins that accumulate in CKD.

Methods: In vivo: CKD was induced in Wistar rats by treatment with adenine (0.7%) in standard rodent chow for 7 weeks. Treatment groups received AST-120 in the final 3 weeks to decrease the concentration of uremic toxins. Expression of hepatic and intestinal transporters were determined by real-time PCR. In vitro: Using the human hepatic hepatoma cell line Huh7, specific uremic toxins (e.g. indoxyl sulfate, p-cresyl sulfate, CMP3) will be tested to see if they directly impair rosuvastatin transport. Rosuvastatin uptake will be measured with ultra-performance liquid chromatography coupled to mass spectrometry.

Results: Preliminary results have shown that OATP2 expression is decreased by 25% in CKD rat livers compared to control. Treatment with AST-120 causes a significant reduction in the plasma concentration of the uremic toxins indoxyl sulfate and p-cresyl sulfate. AST-120 treatment restores OATP2 expression to control levels.

Conclusions: Decreased hepatic OATP2 expression in CKD will result in reduced clearance of substrate drugs. This could lead to toxicity if a lowered dose is not administered. On average a CKD patient will be co-prescribed 10 different drugs. Clarifying the impact of CKD on drug transporter expression and activity will help guide dosing in this patient population.

SA-PO554

Patient Characteristics and Genes Contribute to Kidney Function After Cisplatin Therapy  
Cara A. Chang, 1 Nickie L. Johnston, 1 Madeleine Gomez, 1 Lucas Ellison, 1 Lauren Alekssunes, 2 Steven R. Kleeberger, 1 Cindy L. O’Bryant, 1 Melanie S. Joy. 1  
Skaggs Schools of Pharmacy and Medicine, Univ of Colorado, Aurora, CO;  
Ernest Mario School of Pharmacy, Rutgers Univ, NJ;  
NIEHS.

Background: It is known that kidney function can decline after a single dose of cisplatin necessitating alternate chemotherapy regimens. The current study explored the contribution of patient characteristics and polymorphisms in drug metabolism and transport genes relevant to cisplatin kidney disposition on changes to renal function.

Methods: Blood (5mL) was obtained from patients (n=206) who received cisplatin. Genetic assessments included candidate SNPs in kidney uptake and efflux transporters (SLC22A2, ABCB2, SLC22A4) and metabolism pathways (GSTA1, GSTP1, GGT1). Genotyping was performed using QuantStudio multiplex assays and coded [0(0 wt/ wt), 1(0 wt/ var), 2(0 var/ var)]. Glomerular filtration rate (GFR, mL/min/1.73m2) and changes from baseline to cisplatin at the time just prior to the second dose were calculated. Univariate and multivariate analyses were performed using patient characteristics and genotyping results.

Results: Patient demographics (mean±sd) included: age 53±14 y, weight 80±20 kg, BSA 1.9±0.3, Caucasian 90%, gender (50%/50%), and cisplatin dose (65±23 mg/m2).

Specific patient characteristics that significantly (p<0.05) contributed to a beneficial effect on GFR were non-Caucasian race, baseline GFR, and non-fractionated cisplatin dosing. Genetic variant in GSTP1/GST pi-1 variant (rs1695) and wildtypes in SLC22A2/OCT2 (rs2279463 and rs1327573) significantly (p<0.05) contributed to a beneficial effect on GFR. Variables retained in the final model (R2: 25.2%, P<0.0001) were: Change in GFR, T OF: 38.0±6.8, CO: 0.17±4.0 (weight) −0.3685 (baseline GFR) + 5.953 (GFR; rs1695).

Conclusions: The results from this study demonstrate the combined role of patient characteristics and genetic variants in drug disposition genes on changes to GFR secondary to cisplatin. Appropriate risk stratification based on patient characteristics and genetics may be used to select precision medicine to reduce the risk of kidney injury from cisplatin and potentially other nephrotoxins.

Funding: NIDDK Support

SA-PO555

Influence of Genetic Variations in Fev Receptors (FcγR) and Cytochrome P450 (CYP) Enzymes on Treatment Outcomes in ANCA-Associated Vasculitis (AAV)  
Divya Indrakanti, 1 Rodrigo Cattin-ceba, 1 Gary S. Hoffman, 1 Cees Kallenberg, 2 Carol Langford, 1 Peter A. Merkel, 1 Paul Monach, 2 Robert Spiera, 1 E. William St. Clair, 1 Ulrich Specks, 1 John H. Stone, 1 Daniel J. Bourque, 1 Brad H. Roux. 1  
The Ohio State University Research Foundation, Columbus, OH;  
Mayo Clinic and Foundation;  
Cleveland Clinic Foundation;  
Univ of Groningen, Netherlands;  
Univ of Pennsylvania;  
Boston Univ School of Medicine;  
Hospital for Special Surgery;  
Duke Univ Medical Center;  
Massachusetts General Hospital.

Background: The Rituximab in AA V (RA VE) trial compared rituximab (RTX) to CYC for treatment of AAV. Using the RAVE cohort we investigated whether known single nucleotide polymorphisms (SNPs) in FcgR or CYP450 enzyme genes were associated with the response to RTX and CYC treatment, respectively. Methods: SNPs for FcgR (FcgRIIA 491G>A, FcgRIIB 695T>C, FcgRIIA 559T>G) and CYP450 (CYP2B6 1459 C>T, CYP2C19 681 G>A) were analyzed by direct sequencing of PCR-amplified genomic DNA. Each SNP was tested as a predictor of the primary outcome, complete remission at 6 months, using logistic regression including the covariates baseline BV AS/WG, ANCA type, and new versus relapsing disease. The association of these SNPs with the trial’s secondary outcomes, including time to complete remission, time to relapse, and time to B-cell reconstitution, were analyzed by Kaplan-Meier and Cox proportional hazard ratios.

Results: No significant associations were identified between FcgRIIA, FcgRIIB, CYP2B6 or CYP2C19 SNPs and the primary outcome. However, the 491AA genotype of FcgRIIA was associated with a shorter time (183: 47 versus 241: 114 days) to complete remission (p=0.001) in the entire cohort.

Conclusions: None of the SNPs tested influenced response to treatment with RTX or CYC in AAV. The finding that FcgRIIA 491G>A was associated with a shorter time to complete with both RTX and CYC implies FcgRIIA may be involved in disease pathogenesis and response to therapy.

Funding: Pharmaceutical Company Support - Genentech

SA-PO556

The GSTA1 Polymorphism and Cyclophosphamide Therapy Outcomes in Lupus Nephritis Patients  
Na Hong Wang, Jin Xue.  
Nephrology, Nephrology, Shanghai, China.

Background: Pulsed low-dose cyclophosphamide (CTX) therapy has become the most effective approach in improving the clinical outcomes of lupus nephritis (LN) patients. However, variations in CTX therapeutic outcomes in LN patients are incompletely understood.

Methods: We investigated the contributions of known allelic variants in CYP2B6, CYP2C19, CYP3A5, GSTA1, GSTP1, ABC17 and ABC4 genes to CTX therapy outcomes.
in LN patients. Pharmacokinetics of CTX and 4-hydroxycyclophosphamide (4OHCTX) were obtained from 22 patients randomly enrolled from 77 LN patients and applied to explore the mechanism.

**Results:** GSTA1, one of detoxification enzymes to CTX, gene polymorphism could greatly influence the therapeutic outcome to CTX treatment in these 77 LN patients. LN patients with a GSTA1*4 mutation (CT heterozygous) had a risk of non-response (P = 0.005).

Pharmacokinetics data indicated that patients with a GSTA1*4 heterozygous variant had a lower exposure to 4OHCTX compared to wild-type patients (12.8 (9.8, 19.5) h*mg/L vs. 27.5 (18.1, 32.8) h*mg/L, P = 0.023), but not CTX. And clinical efficacy was significantly related to higher exposure to 4OHCTX (P = 0.038).

Conclusions: LN patients with GSTA1*4 heterozygous genotypes had poor CTX treatment response due to less exposure to activated 4OHCTX. A pharmacogenomic approach using the GSTA1 SNP may be useful for predicting clinical efficacy to CTX therapy in LN patients, and facilitating individualized therapy.

**SA-PO558**

**CKD Induces Intrinsic Alterations in Osteoblast Response to 1,25D**

Renata C. Pereira,1 Nadine Khouzam,1 Richard E. Bowen,1 Isidro B. Salusky,1 Katherine Wesseling-Perry,1 Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; Orthopedics, David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Background:** Skeletal mineralization defects are common in pediatric CKD patients. In vivo 1,25(OH)2D3 (1,25D), the only currently approved therapy for the treatment of 2HPT in children, fails to normalize skeletal mineralization in these patients. We have recently demonstrated that primary osteoblasts obtained from patients with CKD have altered proliferation, differentiation and mineralization characteristics, suggesting that CKD results in intrinsic changes to osteoblast biology, independent of circulating mineral ion and hormone concentrations.

**Methods:** To evaluate the interaction between CKD and 1,25D therapy on osteoblast maturation and mineralization, primary human osteoblasts from 3 healthy controls, 3 pediatric dialysis patients with low bone turnover (adynamic bone) and 3 pediatric patients with high bone turnover (2HPT) were cultured under pro-mineralizing conditions consisting of 10μM β-glycerolphosphate and 100 μg/ml ascorbic acid in the presence of 1,25D at 1, 10, and 100 nM. After 2, 3, and 4 weeks of growth under mineralizing conditions, cells were washed with PBS, fixed with 10% formalin, and stained with 2% Alizarin Red S. The amount of mineral was assessed by measuring absorption of acetic acid-extracted Alizarin Red S dye (at 405 nm) normalized by live cell concentration (as assessed by absorption at 570 nm) of methanol-extracted Crystal Violet staining obtained from parallel cultures.

Results: 1,25D treatment decreased proliferation and increased mineralization; however, high concentrations were required in cells from CKD patients (Figure).

Conclusions: Diminished mineralization is present in CKD; as previously demonstrated in pediatric patients. Further studies are required to assess whether PTH, IGF1 and FGF23 have an effect on mineralization of human osteoblasts.

**SA-PO557**

**Effect of Growth Factors on Bone Mineralization in Health and CKD**

Nadine Khouzam,1 Renata C. Pereira,1 Isidro B. Salusky,1 Richard E. Bowen,2 Katherine Wesseling-Perry,1 1Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; 2Orthopedics, David Geffen School of Medicine at UCLA, Los Angeles, CA, United Kingdom.

**Background:** Children with chronic kidney disease (CKD) develop unexplained resistance to PTH and GH. Moreover, bone expression of FGF23 is very high in CKD. Data suggest that FGF23 may directly suppress osteoblast maturation and mineralization in mice (Weng JBM 2009); however, it is not known whether excess expression of this hormone has direct effects on bone cells in CKD. We have previously demonstrated that primary osteoblasts isolated from patients with CKD have defects in maturation and mineralization, even when removed from the uremic milieu. We thus hypothesized that CKD-mediated alterations in osteoblast maturation may contribute to a blunted response to growth factors in pediatric CKD.

**Methods:** Human osteoblasts isolated from 3 patients with CKD and 3 normal controls were grown to confluence and induced to mineralize. Cells were treated twice weekly with fresh media and 100 nm of PTH, 200ng/ml of IGFl or 10ng/ml of FGF23 for 0, 2, 3, and 4 weeks. Cell density and mineralization were assessed by staining parallel wells with crystal violet and alizarin red respectively and quantified using spectrophotometry.

Results were expressed as the mean (+ SE) in optic density. A mixed model was used to test differences in proliferation between CKD cells and healthy controls and between hormone dosages over time.

Conclusions: Cells from CKD patients mineralized at a slower rate than cells from normal controls (p<0.05). The addition of growth factors did not have a significant effect on the rate of mineralization for the same size used.

<table>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Funding: NIDDK Support, Private Foundation Support
Fourier Transform Infrared Spectroscopy Crystallinity Indices in Bone from Patients with ADPKD Renata C. Pereira,1  Berenice Y. Gitomer,1 Iisidro B. Salusky,1 Diana George,2 Jason W. Stoneback,2 Karen B. King,3 Myles S. Wolf,2 Michel Chonchol,2 1Pediatrics, UCLA, Los Angeles, CA; 2Medicine, Univ of Colorado, Aurora, CO; 3Orthopaedics, Univ of Colorado, Aurora, CO; 4Nephrology, Northwestern Univ, Chicago, IL.

Background: We have previously shown that patients with autosomal dominant polycystic kidney disease (ADPKD) and normal kidney function have a low bone turnover state. This is coupled with increased expression of fibroblast growth factor 23, dentin matrix protein 1 and osteopontin in bone compared to healthy controls. To further characterize the bone defect in ADPKD we have increased ADPKD and normal bone samples. The differences were more pronounced in the cortices (1.22 vs. 1.19; p = 0.03) than in the trabeculae (1.19 vs. 1.17; p = 0.08). There were no significant differences in heterogeneity of crystallinity, mineral matrix, carbonate/matrix, collagen maturity (cross links) or acid phosphatase substitution between ADPKD and historical control samples.

Conclusions: We describe for the first time a significant difference in the chemical composition of cortical bone measured by FTIR in patients with ADPKD when compared to historical control bone samples. Bone crystallinity has been associated with bone strength and stiffness, it is thus intriguing to hypothesize that the observed changes may impact bone quality and expression of bone proteins in ADPKD. Future studies that also assess bone strength and stiffness should be required to more fully investigate bone quality in ADPKD.

Funding: NIDDK Support

Late Onset Avascular Osteonecrosis in Renal Transplant Recipients Spyridon Arampatzis, Anita Maurer, Vasileios Devetzis, Uyen Huynh-do, Nephrology, Hypertension and Clinical Pharmacology, Uni. Hospital Bern, Inselpital, Bern, Switzerland.

Background: Avascular osteonecrosis (AO) after renal transplantation (RT) is a debilitating skeletal complication. In most studies patients with AO presented with the first 24 months after RT. In order to determine the prevalence and therapeutic outcome of late onset of AO (24 months after RT) we conducted a single-center retrospective study based on radiological/historical confirmed cases.

Methods: We conducted a single-center retrospective study about our RTR with a clinical diagnosis of AO over the past two decades. We evaluated 70 cases with a AO. In 46 patients AO was radiological/historical confirmed and all relevant clinical, radiological and laboratory data were extracted and analyzed.

Results: The average follow-up time was 14 (8-18) years after the first RT. The prevalence of AO was 5.4%. Overall, 41 patients showed AO of the femoral head, 23 bilateral AO of the femoral head, 5 of the knee and 5 of other locations, while 43 patients were symptomatic at diagnosis. At the first presentation, 72% presented AO osteonecrosis (2/3 months) AO after RT. On average, AO was diagnosed 90 months after RT (SD=78). Furthermore, RTR with late onset were younger at the first RT (39±15 years; p<0.01) than the ones with early on (53±14). A considerably higher cumulative dose of prednisone was administered to patients with late onset of AO prior to their first RT (21±11 g; early onset 8±1 g; p-value <0.001) and a higher percentage of late onset RTR received corticosteroids even prior to their first RT (48%) compared to the group of early onset (15%; p=0.038). Overall, 34% of the patients presented with an advanced stage of AO Ficat III or IV at first diagnosis of AO and 57% needed total hip arthroplasty.

Conclusions: Late onset avascular necrosis represent a corticosteroid related complication, with a particularly high prevalence among young RTR and is associated with a significantly higher percentage of late onset RTR received corticosteroids even prior to their first RT (48%) compared to the group of early onset (15%). AO of the femoral head is one of the most relevant complications in patients with CKD or on dialysis who receive corticosteroids.

Funding: Private Foundation Support

Indoxyl Sulfate Exacerbates Low Bone Turnover Induced by Parathyroidectomy in Rats Junya Hirata,1 Kazuya Hirai,2 Naoko Jisumura,1 Yosuke Tsukui,1 Hironobu Asai,1 Hidetomi Nishiya,2 Shuichi Kato,1 Hironobu Yokoyama,1 Shota Kato,1 Takehiro Inamoto,2 Takeshi Takagi,1 1Kureha Corporation, Tokyo, Japan; 2Tokyo Univ of Agriculture and Technology, Tokyo, Japan.

Background: Low-turnover bone disease is one of the bone abnormalities observed in chronic kidney disease (CKD) patients and recognized to be associated with low serum parathyroid hormone (PTH) level and skeletal resistance to PTH. Indoxyl sulfate (IS) is a representative uremic toxin that accumulates in the blood as renal dysfunction progresses in CKD patients. In order to examine whether IS exacerbates low bone turnover, we produced IS by feeding rats with low-protein diet and then added IS to the low-protein diet, we fed these rats a diet containing indole, a precursor of IS, to elevate bone IS level from indole metabolism.

Methods: Male SD rats were maintained on the low-protein diet for 2 weeks. Then, the rats were fed a diet containing 0.5% indole (w/w) for 4 weeks. Serum IS levels and bone metabolism related markers were examined periodically. After the end of indole treatment, histomorphometric analyses in the secondary spongosia of the femur and measurement of bone mineral density of the tibia were performed.

Results: Histomorphometric analyses revealed significant decreases in both bone formation-related parameters (mineralized surface/bone surface, bone formation rate/bone surface) and bone resorption-related parameters (eroded surface/bone surface, bone resorption surface/bone surface) in PTH rats. In indole-treated PTX rats, further decreases in bone formation-related parameters were observed. On the other hand, there were no decreases in bone resorption-related parameters in indole-treated PTH rats compared to the PTH rats. Serum IS levels in indole-treated PTX rats were elevated during the indole treatment period and the levels were similar to those in CKD and dialysis patients.

Conclusions: IS exacerbates low bone turnover through inhibition of bone formation by mechanisms unrelated to skeletal resistance to PTH in rats. Our data suggest that IS might directly act as one of the uremic toxins that contribute to progression of low-turnover bone disease in patients with CKD or on dialysis whose serum IS levels are elevated because of renal dysfunction.

Funding: Private Foundation Support

Changes of Marrow Adipocyte Away from Bone Surface After Parathyroidectomy in Patients with Secondary Hyperparathyroidism Aiji Yajima, Ken Tsujiuchi, Kosaku Nitta. Medicine, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: We’ve already reported that marrow adipocytes proliferated around bone surface after parathyroidectomy for secondary hyperparathyroidism. However, fibrous volume was reduced near bone surface where adipocytes proliferated after the surgery. It is suggested that adipocytes may be added with bone formation, because osteoblasts suppress the function of osteoblasts. Therefore, the parameters of marrow adipocyte, which are away from bone surface were histomorphometrically measured before and after parathyroidectomy for secondary hyperparathyroidism.

Methods: Sixteen hemodialysis (HD) patients suffering from secondary hyperparathyroidism (Age; 67 ± 14 years; HD duration; 14.3 ± 6.8 years) were treated by total parathyroidectomy with immediate autotransplantation (parathyroidectomy) and received iliac bone biopsies before and at 1 week (n=4) and at 4 weeks (n=10) after parathyroidectomy. Adipocyte volume per marrow volume (Fa/Vm/V), adipocyte number per marrow volume (N.Fa/Ma.V/mm²), and mean adipocyte volume (Fa/V:N.Fa/V=10^3 mm²/N) were obtained in the area away from bone surface. If there are so many artifacts in bone marrow, the bone samples were excluded from this research.

Results: Serum intact parathyroid hormone (i-PTH) level was decreased from 1268.8 ± 485.9 to 7.9 pg/mL. Fa/Vm/V was significantly increased from 22.4 ± 6.3 to 30.9 ± 8.1 % (P<0.001). N.Fa/Vm/V was also increased from 183.3 ± 48.1 to 217.7 ± 4.7 %/mm² (P<0.001), and Fa/V:N.Fa/V was not changed (146.9 ± 48.5 to 166.8 ± 54.8 %/10^-3 mm²/N) after parathyroidectomy.

Conclusions: The facts substantiate that an acute reduction of PTH induced an increase of adipogenesis. As reported previously, osteoblast surface transiently increased at 1 week after parathyroidectomy, but it acutely decreased at 4 weeks after the surgery. These findings mean that undifferentiated stem cells went to the adipogenesis after the acute reduction of PTH in patients receiving HD.

Funding: Private Foundation Support

Evaluation of Marrow Adiposity in Patients Pre and Post-Kidney Transplantation: Comparison Between Bone Histomorphometry Mariel Jose Hernandez,1 Luciende dos Reis,1 Igor Marques,2 Feltypes C. Barreto,2 Elias David-Neto,3 Rosa M.A. Moyses,2 Ezequiel R. Bellorin-Font,1 Vanda Jorgetti,2 1Nephrology Div, Univ Central de Venezuela, Caracas, Venezuela; 2Nephrology Div, Univ de Sao Paulo, Sao Paulo, Brazil; 3Medical School, Pontificia Univ Católica, Curitiba, Brazil; 4Urology Div, Univ de Sao Paulo, Sao Paulo, Brazil; 5UNINOVE.

Background: The osteoblasts (Ob) and adipocytes (Ad) derive from the mesenchymal stem cells (MSCs). An imbalance in the differentiation of Obs and Ad could be decisive to preserve the integrity of bone. We analyzed bone histomorphometry and marrow adiposity in bone biopsies from patients before and after kidney transplantation (KT).

Methods: We compared biochemical parameters and bone histomorphometry data from KT patients before and after KT, under standard immunosuppressive therapy including glucocorticoids. Adipocytes area (Ad.Ar/T.Ar,%), number (N.Ad/B.Ma.V/mm²), and the ratio adipocytes/active osteoblasts (N.Ad/N.AcOb), and adipocytes/total osteoblasts (N.Ad/N.TOb) indexes were measured.

Results: Our patients were young (42.3 ± 11.6 vs. 30.6 ± 11.5), N.Ad/N.TOb (240.4 ± 65.7 vs. 674.6 ± 1192.4) and N.Ad/N.TOb (128.2 ± 362.3 vs. 230.5 ± 642.4) and a decreased osteoblast number/ tissue surface (22.8 ± 21.9 to 5.3 ± 2.8) was observed. In the post-transplant biopsies significant correlation was found between N.Ad/N.TOb and PTH (r=-0.48), trabecular number - Tb.N (r=0.29) and mineral apposition rate (r=-0.23), as well as between Ad.Ar/T.Ar and bone volume (r=0.36) and between N.Ad/B.Ma.V and mineral apposition rate (r=72).

Conclusions: KT improved biochemical findings related to bone mineral disease, however, this condition is also clearly associated with an inverse relationship of the bone
mass and osteogenic cellularity with marrow adiposity, compromising dynamic parameters. MSCs differentiation is competitively balanced; mechanisms that promote one cell fate actively suppress mechanisms that incline the alternative.

SA-PO564

High Marrow Adiposity Is Associated with Low Turnover Bone Disease in Peritoneal Dialysis Patients

Feliype C. Barreto,1 Rodrigo Axezedo de Oliveira,1 Mariel Jose Hernandez,2 Ana Clara Simões Flórido Almeida,1 Luciene dos Reis,1 Aluizio B. Carvalho,1 Vanda Jorgetti,2 Rosa M.A. Moyses,2,4 Pontificia Univ Católica do Paraná; 1Univ de São Paulo; 2Univ Federal de São Paulo; 3Univ Novo de Julho, UNINOVE; 4Univ Federal do Rio Grande do Norte; 5Univ de Caracas.

Background: Marrow adiposity has been implicated in the pathogenesis of bone disorders, such as osteoporosis and bone fragility. We sought to investigate the relationship between marrow adiposity and renal osteodystrophy in peritoneal dialysis patients.

Methods: We analyzed transiliac bone biopsy specimens from 41 peritoneal dialysis patients (age:50±10.2 yrs) by quantitative histomorphometry to assess bone and marrow adipocyte parameters. Selected biochemical parameters, such as serum markers of bone turnover and sclerostin, were measured.

Results: Adipocyte area (Ad.Ar), perimeter (Ad.Pm) and percentage of adipocyte volume per marrow volume (Ad.V/Ma.V) correlated positively with age. Diabetic patients had higher marrow adiposity than non diabetic patients (Ad.V/Ma.V= 50±14 vs 39±12%; P=0.009; Ad.Ar=619±0.06 vs 610±0.05 mm²; P=0.02). Ad.V/Ma.V demonstrated inverse association with bone specific alkaline phosphatase (r=−0.32;P=0.04) and direct relationship with sclerostin (r=0.38;P=0.01). No association was found between marrow adiposity and dynamic bone hystomorphometric parameters. Interestingly, patients with Ad.V/Ma.V > 41% (median) presented higher percentage of low turnover bone disease (P=0.04) as well as significantly lower bone specific alkaline phosphate (39.5±27.3 vs 65.3±28.9 U/L; P=0.006) and higher sclerostin (2.3±0.97 vs 1.6±0.97 ng/ml; P=0.02) levels than patients below the median.

Conclusions: Increased marrow adiposity seems to be associated to lower osteoblast activity and to low turnover bone disease in peritoneal dialysis patients. The higher marrow fat in diabetic and aged patients might expose them to an increased risk for fracture. Further studies are required to understand the possible contribution of marrow adiposity to the pathogenesis of renal osteodystrophy.

Funding: Government Support - Non-U.S.

SA-PO565

Role of Wnt10b Signaling in Cinacalcet-Induced Bone Anabolic Effects Cai-Mei Zheng,1 Yung-Ho Hsu,1 Yuh-feng Lin,2 Jia-Pwu Shyu,1 Kuo-cheng Lu,1,4 1Graduate Inst of Clinical Medicine, Taipei Medical Univ, Taipei City, Taiwan; 2Dept of Nephrology, Shuang Ho Hospital, New Taipei City, Taiwan; 3Biologue and Anatomy, National Defense Medical Center, Taipei City, Taiwan; 4Dept of Medicine, Cardinal-Tien Hospital, New Taipei City, Taiwan.

Background: Chronic kidney disease-mineral bone disorders (CKD-MBD) is important for osteoporosis and bone fractures in CKD patients. Since calcium receptor plays an important role in osteoblast differentiation, we assume that calcimetric agents (cinacalcet) might have a role in bone remodeling.

Methods: Bone marrow mononuclear cells isolated from rat femur and tibia were induced into osteocytes by M-CSF and RANKL treatments. Osteocytes were treated with different doses of cinacalcet. Untreated osteocytes used as control. The release of Tracing C LASTONE Wnt10b was measured by ELISA and Western blot. Alizarin red staining was used to evaluate mineralization of osteoblasts co-cultured with osteocytes. Flow-AFM staining was used to determine intracellular calcium changes. Cinacalcet treated and untreated CKD animal models (5/6 nephrectomy) were used to analyse the changes in calcitones and bone mineral density.

Results: In osteoclasts, cinacalcet decrease the TRAP stain reaction. However, ELISA analysis showed increases of Wnt10b expression in supernatant collected from the cinacalcet-treated osteoclasts. Pretreatment of Wnt10b secretion inhibitor, C-59, blocked the increase of Wnt10b induced by cinacalcet. Western blot analysis showed an increase intracellular Wnt10b in the cinacalcet-treated osteoclasts. Culture of osteoblasts with the cinacalcet-treated osteoclasts supernatant showed an increase of mineralization as induced by alizarin red staining. Intracellular calcium staining is increased in cinacalcet-treated osteoclasts, which demonstrated its effect on osteoclast Wnt10b release is through intracellular calcium oscillation. Calcitones and bone mineral density (BMD) changes are also noted in CKD rats before and after cinacalcet treatment.

Conclusions: Cinacalcet decrease osteoclastic activity, but increase the secretion of Wnt10b through intracellular calcium oscillation. Cinacalcet also related with certain calcitones and BMD changes in CKD animals.

SA-PO566

Changes of Osteocyte Number in Micropetrosis Area After Treatment of Secondary Hyperparathyroidism Aiji Yajima, Ken Tsuchiya, Kosaku Nitta. Medicine, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Osteocyte number decreased after total parathyroidectomy with immediate autotransplantation (parathyroidectomy) for secondary hyperparathyroidism in hemodialysis (HD) patients (JBMR 2010). Osteocyte number in micropetrosis area around the middle area was measured before and after parathyroidectomy and treatment with cinacalcet hydrochloride (HCL).

Methods: Thirteen HD patients received parathyroidectomy and transiliac bone biopsies before and at 3-9 weeks after parathyroidectomy (Group I). And eight HD patients with secondary hyperparathyroidism were treated by cinacalcet HCL and received bone biopsies before and at 1 year after the treatment (Group II). Osteocyte number in micropetrosis area (N.Ot/Mp.V;N/mm²) and in the other area (N.Ot/(BV-Mp.V);N/mm²) were measured before and after the treatment.

Results: Serum intact Parathyroid Hormone (i-PTH) levels decrease from 1186.5 ± 768.3 to 24.8 ± 8.1 pg/ml after parathyroidectomy. No/OTi/Mp.V was decreased from 58.9 ± 7.1 to 110.1 ± 87.3 N/mm² (P<0.001) and No/OTi/(BV-Mp.V) was not changed (from 236.1 ± 69.3 to 262.2 ± 79.3 N/mm²) after parathyroidectomy (Group I). Serum i-PTH levels decrease from 903.6 ± 503.0 to 212.7 ± 98.1 pg/ml after the treatment with cinacalcet HCL. NO/OTi/Mp.V was not changed in both micropetrosia area (100.1 ± 68.2 to 99.6 ± 76.1 N/mm²) and in the other area (from 240.1 ± 56.3 to 279.6 ± 88.6 N/mm²) after treatment (Group II).

Conclusions: Cinacalcet HCL did not reduce osteocyte number in both micropetrosia area and in the other area, suggesting that this agent improves bone quality by maintaining osteocytic perilacunar/canalicular system. Parathyroidectomy reduces osteocyte number in only the micropetrosia area.

Funding: Private Foundation Support

SA-PO567

Trabecular Bone Score in Kidney Transplant Recipients Ylva Lynn Naylor,1 Lisa M. Liu,1 Didier Hans,2 Amir X. Garg,3,4 David N. Rush,2 William Leslie,31 Western Univ; 1Univ of Manitoba; 2Lassanne Univ Hospital; 3London Health Sciences Centre; 4Inst for Clinical Evaluative Sciences.

Background: Kidney transplant recipients have altered bone mineral metabolism and are at a higher risk of fracture compared to the general population. There is conflicting evidence regarding the ability of bone mineral density (BMD) to accurately predict fracture. Trabecular bone score (TBS) is a texture measure derived from dual energy x-ray absorptiometry (DXA) lumbar spine images which provides information independent of BMD. We assessed TBS in kidney transplant recipients.

Methods: We included 327 kidney transplant recipients from Manitoba, Canada, who received a post-transplant DXA (median 106 days post-transplant). We matched each kidney transplant recipient (mean age 45 years, 39% men) to three controls from the general population (matched on age, sex, and date of DXA). Lumbar spine (L1-L4) DXA images were used to derive TBS. Non-traumatic incident fracture (excluding hand, foot, and craniofacial) (n=31) were assessed during a mean follow-up of 6.6 years. We used logistic regression to determine predictors of TBS and hazard ratios per standard deviation decrease in TBS to express the gradient of risk for fracture prediction using Cox proportional hazards regression.

Results: Compared to the general population, kidney transplant recipients had a significantly lower lumbar spine TBS (1.41 ± 0.13 versus 1.37 ± 0.13, p<0.001). Multiple logistic regression revealed reduced TBS (lowest versus highest tertile) in kidney transplant recipients compared to the general population (adjusted odds ratio, 2.13 [95% confidence interval [1.47-3.07]). TBS predicted fractures in kidney transplant recipients independent of the Fracture Risk Assessment (FRAX) score and spine BMD (adjusted hazard ratio per standard deviation decrease in TBS 1.57, 95% CI 1.67-2.29).

Conclusions: Kidney transplant recipients had abnormal bone texture as assessed by TBS. Lumbar spine TBS was able to predict incident fractures in kidney transplant recipients and may provide novel insights into skeletal fragility in this unique population.

SA-PO568

Low Bone Turnover Disease Is Prevalent 1 Year After Successful Renal Transplantation: A Cross-Sectional Bone Biopsy Study Pieter Evenepoel,1 Patrick C. D’Haese,2 Liesbeth Vlaene,1 Geert J. Behets.1 1Nephrology, Univ Hospitals Leuven, Leuven, Belgium; 2Pathophysiology, Univ of Antwerp, Antwerp, Belgium.

Background: Studies evaluating bone histomorphometry in renal transplant recipients are scanty and so far hampered by small sample size and heterogeneity. Methods: We evaluated bone histomorphometry (according to TMV classification), laboratory parameters of mineral metabolism (including iPTH, FGF23, sclerostin, OPG, sRANKL), biomarkers of bone formation (bsAP) and bone resorption (TRAP5b, NTX), and inflammation (IL6) in an unselected cohort of 60 renal transplant recipients (64 males, age 56±12 yrs) 1 year after transplantation. Standard immunosuppressive regimen consisted of steroids, a calcineurin inhibitor and mycophenolate mofetil. Mean cumulative mycophenolate dose at 1 year was 1.7 g/d.

Results: Sixty-five % of the patients presented with disturbances in at least one of the bone turnover parameters.ハイリスクlow bone turnover disease were identified in 1.7, 45.0, and 53.3 % of renal transplant recipients, respectively. Mineralization was delayed in 17.0 % and bone volume was low in 15.0 %. Patients with persistent

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
hypercalcermic hyperparathyroidism (n=4, 7%) showed either low or normal bone turnover. Hypophosphatemia was present in 11%. Vitamin D stores were sufficient in 52% (median HydroxyvitaminD3 32 ng/ml). Spearman correlation revealed significant correlations between bone formation rate and biomarkers of bone formation & resorption (direct: b-AP: r=0.36, p=0.01; TRAP5b: r=0.40, p=0.01; NTX/r0.38, p=0.01) and inflammation (inverse: IL6: r=0.51, p=0.001), but not with mineral metabolism hormones (PTH, FGF23, sclerostin).

Conclusions: Low bone turnover disease is the most prevalent bone disease in renal transplant recipients 1 year after successful renal transplantation. Additional studies are required to clarify underlying pathophysiological mechanisms. PTH, FGF23 and sclerostin do not correlate with histomorphometric parameters and circulating biomarkers of bone turnover.

SA-PO569
Sclerostin Bone Expression and Blood Levels in Patients with Chronic Kidney Disease Stages 2-5
Florence Lima, Marie-claude M. Fugere, Hanna W. Mawad, Hartmut H. Malluche. Div of Nephrology, Bone & Mineral Metabolism, Univ of Lexington, KY, USA.

Background: Sclerostin (Scl) produced by osteocytes (ocy) was found to be increased in bone in early stages of CKD patients (pts) with renal osteodystrophy (ROD). The aim of this study was to establish when blood scl levels and bone expression are increased and how they progress with worsening CKD.

Methods: Fifty pts underwent anterior iliac crest biopsies and blood was drawn at time of biopsy. Kidney function was determined by creatinine clearance using MDRD calculation. There were: 11 CKD-2, 16 CKD-3, 9 CKD-4.5 pts, and 14 healthy age-matched controls. Scl concentrations in blood were determined by ELISA and scl expression in bone was determined in undecalcified bone sections by measuring number of ocy exhibiting positive Scl immunostaining. Measurements were done separately in cortical and cancellous bone. Bone sections were also evaluated by histomorphometry for turnover, mineralization and volume.

Results: Blood scl levels were significantly greater in CKD compared to controls with no differences between stages (P=0.01).

Bone scl expression was significantly higher in cortical CKD 2-5 pts compared to controls (P<0.01). Scl expression was significantly greater in cortical than in cancellous bone in CKD. In cancellous bone scl expression was higher in CKD; this reached significance in CKD-3 (Figure 1).

Scl expression in cortical and cancellous bone correlated with serum scl (rho=0.30, 0.40, r=0.05; P<0.05). Serum scl correlated negatively with bone formation, activation frequency and osteoblast number (rho=-0.33, -0.38, -0.43, P<0.05). Scl in bone correlated negatively with trabecular thickness (rho=-0.51; P<0.05), osteoblast and osteoclast surface, and erosion depth (rho=-0.50, -0.52, -0.05, P=0.01).

Conclusions: These findings ascribe a potential role to scl in the pathogenesis and management of ROD.

Funding: NIDDK Support, Private Foundation Support

SA-PO570
Single Timepoint and Longitudinal Serum Sclerostin Levels as Mortality Predictors in Prevalent Dialysis Patients
Lotte Lips,1 Camiel L.M. de Roij van Zuidewijn,1 Marc G. Vervoelt,2 Peter J. Blankestein,2 Denis Fouque,4 Solenne Pelletier, Peter M. Ter Wee,4 Menso Jan NBue,4 Muriel P. Grooteman.1,2,3

1Nephrology, 2PU Medical Center, Amsterdam, Netherlands; 3Nephrology, Univ Medical Center Utrecht, Utrecht, Netherlands; 4Internal Medicine, Maastricht Hospital, Rotterdam, Netherlands; 5Nephrology, Centre Hospitalier Univ de Lyon, Pierre Benite, France.

Background: Currently, data are conflicting whether high serum Sclerostin (sScl) levels, a 22kDa-sized glycoprotein inhibiting bone formation, are positively or negatively associated with mortality. Its concentration may change over time. Therefore, we investigated whether longitudinal sScl levels predict mortality better than a single measurement.

Methods: A post-hoc analysis on data from the CONTRAST study was performed, a RCT comparing online postdilution hemodiafiltration to hemodialysis in prevalent dialysis patients. sScl was measured in a subset of patients. Patients were eligible for analysis if a baseline (T0) and a 6 months (T6) sScl value were available. Hazard ratios (HRs) were calculated within quartiles for sScl level at T0, T6 and ΔsScl. All-cause mortality was used as end point. As the interaction between dialysis modality and ΔsScl was non-significant (p>0.1), pooled estimates are reported. To correct for multiple testing, a two-sided p-value <0.01 was considered statistically significant.

Results: Out of 714 patients, 341 were available for analysis. Baseline characteristics between the subgroups did not differ. Median sScl at T0, T6 and ΔsScl was 136.3 pmol/L (interquartile range [IQR] 98.7-186.1), 134.0 pmol/L (IQR 100.4-183.0) and 0 pmol/L (IQR -25 to 15), respectively. sScl values at baseline and T6 were negatively associated with mortality (adjusted HRs highest versus lowest quartile 0.49 [95% CI 0.30-0.81] and 0.48 [95% CI 0.29-0.82], respectively). However, we found no association between ΔsScl and mortality.

Conclusions: A single timepoint sScl is inversely associated with mortality in our cohort of dialysis patients. sScl change over a six month period does not predict mortality.

SA-PO571
Intereukin-1 Inhibition, Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), and Physical Function
Kristen L. Nowak,1,2 Adriana Hunj,3,4 Talat Alp Ikizler,3 Heather Farmer,1 Natjalie Salas,3 Rafa I. Chaudhry,2 Andrew N. Hoofnagle,4 Gerald John Smits,3 Michel Chonchol,1,4 Univ of Colorado Denver; 2Vanderbilt Univ; 3VA Tennessee Valley Healthcare System; 4Univ of Washington.

Background: Epidemiologic studies have suggested a possible link of chronic systemic inflammation with vitamin D deficiency, intact parathyroid hormone (iPTH), and fibroblast growth factor 23 (FGF23) excess, which are a central features of CKD-MBD. Declining renal function is also associated with worsening physical function, which may be explained by systemic inflammation, CKD-MBD, or both. We hypothesized that inhibiting inflammation with an interleukin-1 (IL-1) trap would improve vitamin D deficiency, iPTH and FGF23 excess, as well as physical function in patients with moderate-to-severe CKD.

Methods: In a two-site, double-blind trial, 42 patients with stage 3-4 CKD were randomized to receive either the IL-1 trap rilonacept (160 mg/week) or placebo for 12 weeks. The following CKD-MBD markers were assessed in serum before and after the intervention: calcium, phosphorus, 25-hydroxyvitamin D (25(OH)D), iPTH, FGF23, and parathormone (b-ALP). Also underlined by the KDIGO, clinical decision should be based on variations (or slopes) (∆, in%) of these biomarkers, more than on isolated concentrations. In this work, we studied the correlation between DPTH and ∆ of different bone biomarkers: PINP, CTX, TRAP-5b, osteocalcin and sclerostin. ∆ were studied at different timings, namely 6 weeks (T6W), 6 months (T6M) and 1 year (T1Y).

Results: We have prospectively followed the variations of these biomarkers over one year in patients from 3 independent dialysis centers at T6W (n=123), T6M (n=108) and T1Y (n=93). We analyzed DPTH with ∆ of bone biomarkers by univariate linear regression. We also categorized patients according to variations reaching the critical difference of the biomarkers at one year. Their results were analyzed by Mantel-Haenszel c² test.

Results: At T6W, a significant correlation was only found between DPTH and ∆CTX (r=0.38, p=0.0001). At 6M, a significant correlation was found between DPTH and ∆CTX (r=0.38, p=0.0001) and Dosteocalcin (r=0.27, p=0.0049). At T1Y, a significant correlation was found between DPTH and ∆CTX (r=0.47, p=0.0001), ∆PINP (r=0.4, p=0.0001), ∆b-ALP (r=0.29, p=0.0054) and Dosteocalcin (r=0.36, p=0.0004). No correlation was found at T1Y neither between DPTH and DTRAP-5b nor Dsclerostin. The same conclusions were reached when variations reaching the critical differences were considered. Correlations between DPTH and Dbone biomarkers were particularly poor in patients with low PTH levels (as defined by the KDIGO) at baseline. Conclusions remained the same if analysis was restricted to the 93 patients who completed the study.

Conclusions: A concordance between variations of PTH on one hand and variations of CTX, b-ALP, osteocalcin and PINP on the other hand can be observed in dialysis patients, but only after a long follow-up (at least one year). Variation of bone biomarkers need repeated measures and must not be analyzed on a too short period.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: 12 weeks of IL-1 inhibition did not improve circulating markers of CKD-MBD or physical function (although it tended to improve endurance). These results support that inflammation does not directly mediate CKD-MBD or select domains of physical function.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Regeneron Pharmaceuticals, Inc., Private Foundation Support

SA-PO573

Serum Metabolomic Profiling and CKD-MBD: A New Tool for Bone Turnover Evaluation Aline Lourenco Baptista,1 Kallyんだ Padilha,2 Pamela Arauo Malagrino,3 Gabriela Venturini,4 Ana Carolina de Mattos Zeri,5 Janaina Silva Martins,6 Rodrigo Azevedo de Oliveira,7 Geusa Dutra,8 Luciene dos Reis,9 Vanda Jorgetti,10 Alexandre Costa Pereira,11 Rosa M.A. Moyaes,1,9b,19b Nephrology, USP; 12 Molecular Cardiology, INCOR, USP; 13 Cardiology, INIC, USP; 14 UFMG; 15 Master Degree Program, UNIOINIZE, Brazil.

Background: Bone biopsy still is the gold standard to assess bone turnover in CKD patients and serum biomarkers are not able to replace histomorphometry. Recently, metabolomics has emerged as a new technique that could potentially improve disease diagnosis and the understanding of pathophysiology. However, as this approach has never been tested in the CKD-MBD scenario we investigated whether a serum metabolomic profile could help us to better predict bone turnover in CKD patients.

Methods: Serum and bone histomorphometry data from hemodialysis (HD, n=51) and peritoneal dialysis patients (PD, n=40) were analyzed. They were classified as high (HT, 49.4%) or low turnover (LT). Metabolomic analysis was done through MRI spectroscopy, followed by identification and quantification of metabolites and PLS-DA. As HD had a completely different metabolome of PD group, we analyzed them separately. In addition, we selected the main metabolites found in each group and searched for the metabolic pathways involved.

Results: The difference between LT and HT was explained by 12 metabolites in HD and 8 in PD (p = 0.03 and 0.01, respectively). ROC curve analysis showed that parathormone (PTH) could help us to better predict bone turnover in CKD patients.

Conclusions: In this preliminary analysis, we identified new metabolites that might be used as biomarkers of bone turnover. Moreover, the differences in metabolome between the two dialysis modalities and the different metabolic pathways suggest that the pathophysiological mechanisms involved in the modulation of bone turnover in these patients might be different.

Funding: Government Support - Non-U.S.

SA-PO574

Deletion of the Gene Encoding the Receptor Potential Canonical Type 1 (TRPC1) Channel Produces Hyperparathyroidism, Low Calcitonin (CaT), Hypercalcemia, but Hypocalciuria and Enhanced Bone Mass: Evidence for the Role of TRPC1 in Regulating Intracellular Ca ([Ca^{2+}]i) in Target Cells Bonnie Eby,1 Alexander Lau,2 Lindsay J. Barron,1 Marybeth Humphrey,1 Leonidas Tsiokas,2 Kai Lau,1,3,4 Medicine, Univ of Oklahoma, Oklahoma City, OK; 2Cell Biology, Univ of Oklahoma, Oklahoma City, OK; 3Medicine, VA Medical Center, Oklahoma City, OK.

Background: We recently showed that TRPC1 deficiency impairs store-operated calcium entry (SOCE), reduces [Ca\textsuperscript{2+}]i in HD and creatine-phosphate biosynthesis, pyruvate fermentation to lactate and AMPK and alkaline phosphatase were the best predictors for HT, whereas glycerol and glucose 8 in PD (p = 0.03 and 0.01, respectively). ROC curve analysis showed that parathormone we selected the main metabolites found in each group and searched for the metabolic

Conclusions: In this preliminary analysis, we identified new metabolites that might be used as biomarkers of bone turnover. Moreover, the differences in metabolome between the two dialysis modalities and the different metabolic pathways suggest that the pathophysiological mechanisms involved in the modulation of bone turnover in these patients might be different.

Funding: Government Support - Non-U.S.

SA-PO575

Role of the Sodium/Calcium Exchanger NCX1 in Osteoclasts Giuseppe Alibano,1,2,3 Candice Stoudmann,2,4 Willy Hofstetter,5 Olivier Bonny,5 Daniel G. Fuster,1,5a,6,7 Div of Nephrology, Hypertension and Clinical Pharmacology, Univ of Bern, Bern, Switzerland; 2Inst of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; 3Dept of Clinical Research, Univ of Bern, Bern, Switzerland; 4NCCR Kidney.CH, Univ of Zürich, Zürich, Switzerland.

Background: Previous studies demonstrated that inhibition or siRNA-mediated knock-down of sodium/calcium exchanger 1 (NCX1) in osteoclasts decreases bone resorption in vitro, indicating a critical role of NCX1 in osteoclast-mediated bone resorption.

Methods: To test the role of NCX1 in osteoclasts in vivo, we generated mice with osteoclast-specific deletion of NCX1 (NCX1\textsuperscript{Cre/loxP}). For this purpose, mice with a floxed exon 11 of NCX1 were crossed with mice expressing Cre-recombinase under the influence of the osteoclast specific calspHEN K promoter.

Results: Osteoclasts differentiated from NCX1\textsuperscript{Cre/loxP} mice displayed an 80-90 % reduction of NCX1 protein compared to wild-type mice. NCX1 expression was unaltered in extraosseous tissues in NCX1\textsuperscript{Cre/loxP} mice. NCX2 and NCX3 were present at low levels in wild-type osteoclasts and not upregulated in NCX1\textsuperscript{Cre/loxP} osteoclasts. In vitro RANKL stimulation of bone marrow cells isolated from wild-type and NCX1\textsuperscript{Cre/loxP} mice yielded no differences in osteoclast development and resorptive activity. In addition, at 3 months of age, structural parameters of bone, quantified by high-resolution microcomputed tomography, were not different in NCX1\textsuperscript{Cre/loxP} mice compared to wild-type littermates. To stimulate osteoclast-mediated bone resorption, we performed surgical ovarectomy (OVX) in 12 week old female mice, but OVX-induced bone loss over 12 weeks was similar in WT and NCX1\textsuperscript{Cre/loxP} mice.

Interestingly, however, at 6 months of age, female NCX1\textsuperscript{Cre/loxP} mice had significantly higher bone volume whereas male NCX1\textsuperscript{Cre/loxP} mice displayed reduced bone volume compared to wild-type mice.

Conclusions: Our data indicate that genetically induced deficiency of NCX1 in osteoclast-precursors and mature osteoclasts does not affect osteoclast differentiation and bone resorption in vivo. However, NCX1\textsuperscript{Cre/loxP} mice display an age- and sex-specific phenotype. Additional studies are needed to unveil the underlying mechanisms.

Funding: Government Support - Non-U.S.

SA-PO576

The Impact of a Previously Created AV-Fistula on Radial Bone Mineral Density Measurements in Renal Transplant Recipients Spyridon Arampatzis,1 Vasileios Devetzis,1 Uyen Huynh-do,2 Nephrology, Hypertension and Clinical Pharmacology, Uni, Hospital of Bern, Inselspital, Bern, Switzerland.

Background: The arteriovenous-fistula (AVF) of the distal radius often remain patent after transplantation. Distal radius is the typical site for peripheral DXA measurements in renal transplant recipients (RTR). Since no data exist concerning the impact of a previously created AVF on peripheral bone characteristics in RTR we evaluated the effect of AVF on bone mineral density (BMD) as mirrored by collateral differences between forearms and explored the densitometric correlation of distal radius with the tibia as an alternative peripheral measurement site.

Methods: This cross sectional study included 40 renal transplant recipients (RTR) and 40 chronic kidney disease (CKD) patients matched for age, gender and BMI. In addition to relevant demographic, biochemical and clinical aspects we assessed bone characteristics of both forearms, femoral neck and tibia by DXA.

Results: The CKD patients without any AVF, displayed no significant discrepancies concerning BMD in both forearms. In RTR BMD was significantly lower in the AVF fistulated forearm in comparison to the contralateral non AVF forearm. This observation was evident at all measured subregions of the AVF radius sides, i.e. at the 1/3 radius (0.710±0.103 vs. 0.727±0.104, p=0.003), ultradistal radius (0.424±0.085 vs. 0.444±0.080, p=0.007) and total radius (0.571±0.090 vs. 0.589±0.090, p=0.001) as well. This significant side-to-side difference was 7.5% at the 1/3 radius, 7.2% at the total radius, and 7.0% at the ultradistal radius, respectively. The BMDT interclass analysis between radius and distal tibia showed a strong and highly significant correlation (r= 0.736±0.857) between corresponding peripheral sites.

Conclusions: In conclusion, a previously placed AVF in RTR exerts a negative impact on the ipsilateral radius resulting in side-to-side BMD differences. A strong densitometric association exist between peripheral sites and thus DXA measurements at corresponding peripheral measurement site.

Funding: 

SA-PO577

Cortical Bone Analysis in Pre-Dialysis Patients: A Comparison with a Dialysis Population Catarina Carvalho,1 Juliana Magalhães,3 Ricardo Neto,1 Luciano Pereira,2 Teresa Adriagão,2 João M. Frazao,1 Nephrology and Infectology Research and Development Group, INEB, Porto, Portugal; 2Nephrology, Hospital Santa Cruz, Lisboa, Portugal.

Background: ROD presents early in CKD pts. Bone biopsy is the gold-standard diagnostic tool. Cortical bone represents 80% of human bone and is the major determinant of bone strength.

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

Underline represents presenting author.

756A
**Methods:** We evaluated cortical bone histomorphometry in 13 CKD stage 3 and 4 pts, (9 male, age 65±10.4, eGFR 23±8.3 mL/min/m²) who underwent trans-iliac bone biopsy and compared them to 13 dialysis pts (9 male, 11 on HD, age 52.15±10.2, 55.3±17.6 mo in RRT).

**Results:** Biochemical values and external cortical bone parameters of both groups shown in table

<table>
<thead>
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<th>Pre-dialysis</th>
<th>Dialysis</th>
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<tr>
<td>PTH (pg/ml)</td>
<td>157.8±85.9</td>
<td>283.2±187.5</td>
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<tr>
<td>Ca (mg/dL)</td>
<td>9.6±0.4</td>
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<tr>
<td>Pi (mg/dL)</td>
<td>3.6±0.8</td>
<td>4.8±2.2</td>
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</table>

**External Cortical**

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Ps (%)</td>
<td>12.5±7.9</td>
<td>12.6±6.6</td>
<td>0.973</td>
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<tr>
<td>CTh (μm)</td>
<td>635.6±323.2</td>
<td>384.6±170.5</td>
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<tr>
<td>OnMS/BS (%)</td>
<td>3.0±5.6</td>
<td>4.1±4.3</td>
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<td>OnBFRBS (μm³/3μm²)</td>
<td>1.8±2.4</td>
<td>15.0±15.4</td>
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<tr>
<td>OnOBS (%)</td>
<td>23.5±9.4</td>
<td>26.2±10.0</td>
<td>0.506</td>
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<tr>
<td>OnES/BS (%)</td>
<td>9.2±4.5</td>
<td>7.0±8.8</td>
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<tr>
<td>OnOTH (μm)</td>
<td>6.8±2.3</td>
<td>9.9±5.0</td>
<td>0.067</td>
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<tr>
<td>OnAjAR (μm³/μm²/day)</td>
<td>0.02±0.03</td>
<td>0.15±0.15</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Dialysis pts compared to the pre-dialysis population showed more denuded cortical bone, with decreased cortical thickness, increased osteobone formation rate and adjusted apposition rate. In this pre-dialysis population, external cortical porosity positively correlated with both trabecular bone volume and osteoid volume (respectively, r=0.70 and 0.76, p=0.016 and p=0.006). External cortical osteobone BFR correlated negatively with S-calcium (r=0.88, p=0.021) and positively with trabecular thickness (r=0.88, p=0.021). These findings were not observed in internal cortical suggesting that this is more stable to PTH effects.

**Conclusions:** In pre-dialysis pts, our findings support that PTH has a modulating effect on both trabecular and cortical bone. As renal disease progresses cortical thining is more pronounced, eventually contributing to the higher fracture rate. Understanding cortical abnormalities may have implications in the treatment of CKD-MBD.

SA-PO579

**Chronic Hyponatremia Is a Novel Risk Factor for Hip Fracture in Chronic Kidney Disease-Mineral Bone Disease**

**Sagar U. Nipwekar, 1 Andrew S. Allegretti, 1 Julia Beth Wenger, 1 Juan Carlos Ayus, 1 Ravi I. Thadhani, 1 Ishir Bhan, 1 Massachusetts General Hospital; 1 Renal Consultants of Houston.**

**Background:** Risk factors that make skeleton more fragile in chronic kidney disease (CKD) are uncertain. Considering recently reported direct effects of sodium depletion on bone health, we investigated chronic persistent hyponatremia (CPH) as a novel risk factor for hip fractures caused by CKD-mineral bone disease (CKD-MBD).

**Methods:** Cases for this multi-center case-control study were elderly (≥65 years) patients with CKD (eGFR <60 mL/min) with a new hip fracture. Controls (CKD patients with no hip fracture) were matched to cases on age, sex, race and comparative health. Primary exposure was serum sodium <135 mEq/L on at least 2 occasions ≥ 90 days apart within one year preceding hip fracture for cases and within the first year of study entry for controls (CH190). Secondary exposure definitions were hyponatremia on at least 1 occasion (H1) and hyponatremia on at least 2 occasions ≥ 180 days apart (CH180). Variables for multivariable logistic regression analyses were identified using stepwise selection.

**Results:** We analyzed 1,236 cases and 4,515 controls. Mean age of all patients was 84±9 years, 87% were whites, and 39% were females. Serum calcium, phosphate, parathyroid hormone and 25-hydroxy vitamin D levels were similar between cases and controls. Prevalence of CH180 (21.2 vs. 9.9%, P<0.001), CH180 (15.5 vs. 6.5%, P<0.001) and H1 (52.7 vs. 41.1%, P<0.001) were higher in cases compared to controls. In analyses adjusted for falls, tobacco-use, osteoporosis, eGFR, body mass index, heart failure and medications, CH190 and CH180 were associated with increased risk of hip fracture but H1 was not.

**Conclusions:** CPH is a risk factor for hip fractures caused by CKD-MBD. Mechanistic studies are needed to investigate the effects of CPH on bone turnover, mineralization and volume in CKD.

**Funding:** Private Foundation Support

SA-PO580

**Follicle Stimulating Hormone Is Associated with Low Bone Mineral Density in Women in Hemodialysis**

**Priscilla Ponce, 1 Enrique Rojas-Campos, Alfonso M. Cueto-Manzano, Benjamin Gonzalez-Navarro. 1 Unidad Investigación Médica en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico.**

**Background:** Prevalence of bone mineral density (BMD) in women during hemodialysis (HD) has been little explored. In the literature, FSH and estradiol were divided between female (FSH and estradiol) and estradiol (BMD) in women in hemodialysis (HD).

**Methods:** We performed a cross-sectional study of 46 women (20-60 years), at least 3 months in HD in a tertiary care setting between Jan-Jul 2014. Pregnant patients or those with steroid medication were excluded. Physical examination and blood markers of sexual hormonal and mineral-bone status were done. A bone densitometry of lumbar spine and non-dominant femur of the hip was performed; the results were classified as normal, osteopenia and osteoporosis.

**Results:** 5 had osteoporosis and 5 had osteopenia in the lumbar spine. In the femur, 2 had osteoporosis and 18 had osteopenia. Comparisons are shown in Table. BMI in lumbar spine was associated to FSH (R² 0.27, P<0.001), FSH (OR 0.52 [-0.02 - 0.008], P=0.001), on the other hand BMI in femur (R² 0.30, p<0.001), FSH (OR 0.34 [-0.01 -0.001], p=0.02), and CRP were significantly associated (OR 0.32 [-0.02 -0.001], P=0.03).
SA-PO581

Time Averaged Intact Parathyroid Hormone Concentration as a Risk Factor for Hip Fractures in Patients on Dialysis
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Background: Recent studies found the incidence of hip fractures has increased greatly in patients on dialysis. Most of the increase occurred in patients with characteristics typical of bone frailty, where over suppression of intact parathyroid hormone (iPTH) could be harmful. Since recent studies have not addressed clinical risk factors, we studied time-averaged iPTH as a risk factor for hip fractures.

Methods: 142,407 prevalent patients of Fresenius Medical Care had hip fractures identified by ICD-9 codes. Four cohorts were constructed: observation periods 2001-2003, 2004-2006, 2007-2009, 2010-2012. For each, the prior year was used to measure exposure. Risks for fractures were analyzed for each cohort and for the combined cohorts. Three models for risk adjustment were created: Case Mix CM-adjusted: age, gender, race, dialysis vintage, and diabetic status, CM+Lab adjusted and CM+Lab+Med adjusted.

Results: For the combined cohorts, unadjusted analyses indicated higher hip fracture risk with lower iPTH (p<0.0001), lower calcium (p=0.003), lower phosphate (p=0.0001) and lower IV vitamin D (p=0.0001). In the fully adjusted model the two lowest iPTH quartiles were significantly associated with greater risk of fractures (HR 1.2, 95% CI 1.01-1.44, p=0.03 for lowest quartile, iPTH < 181 pg/ml). Similarly the lowest quartile iPTH quartiles were significantly associated with greater risk of fractures (HR 1.2, 95% CI 1.01-1.37, p=0.04). Serum phosphate and IV vitamin D were no longer associated with risk in the fully adjusted model.

Conclusions: In women, in the higher levels of FSH predicts lower BMD in the lumbar spine, while in the femoral region higher FSH and CRP predicts lower BMD.

SA-PO582

The Discriminative Ability of Three Fracture Risk Assessment Tools in Hemodialysis Patients
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Background: The present study aimed to explore factors associated with fractures among hemodialysis patients, and assess the ability of the World Health Organization’s fracture risk assessment tool (FRAX) compared with bone mineral density (BMD) and OSTA to discriminate fracture status.

Methods: We enrolled 118 hemodialysis patients in this cross-sectional study. Parameters including serum calcium, phosphate, intact parathyroid hormone, 25 hydroxy vitamin D, alkaline phosphatase were analyzed. Clinical characteristics were also collected. BMD values were at the lumbar spine and hip region. OSTA and FRAX scores were calculated using formula or through the FRAX website. Factors associated with fractures were examined. Discriminative ability of BMD, OSTA and FRAX (non-BMD model and BMD model) in fracture status was assessed with receiver operator characteristic (ROC) analysis.

Results: There were 16 (13.5%) fractures in 118 hemodialysis patients. Patients with fractures were significantly older and more osteoporosis. All BMD parameters at hip region (including femoral neck, femoral shaft, and total hip) were notably lower in fracture group than in non-fracture group (p<0.05). But FRAX2 performed no better than FRAX1 (P>0.05). The best cutoff values were 0.91, -3, 7.2%, 3.4%.

Conclusions: Among hemodialysis patients, age and BMD at hip are associated with fracture. FRAX performs better than BMD and OSTA in discriminating fracture status, suggesting its usefulness of fracture risk prediction in hemodialysis patients.

Funding: Government Support - Non-U.S.

SA-PO583

Teriparatide for Low Bone Mass in Hemodialysis Patients
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Background: Fracture rates in dialysis patients are extremely higher than general population. Recently the prevalence of low turnover has greatly increased in dialysis population. Teriparatide would be also beneficial for low turnover dialysis patients with low bone mass. However, there have been only a few reports describing the use of teriparatide in dialysis patients.

Methods: Design This was a prospective, single-center, observational study. Hemodialysis patients with low iPTH (iPTH<60 µg/ml) coexisting low bone mass determined by lumbar spine (LS) or/and femoral neck (FN) T-score<-2.5 with DXA were eligible and subcutaneous recombinant human PTH(1-34) (Forteo) was injected 3 times per week at the end of each hemodialysis sessions. We analyzed the following parameters, including serum Ca, P, albumin, ALP, iPTH and bone metabolism makers including iPTH, BAP, and TRACP-5b at baseline and following teriparatide. BMD at LS and FN were measured at baseline, 6, 18 months after treatment.

Pharmacokinetics After the 24th administration of teriparatide, we measured the serum teriparatide acetate concentrations.

Results: Five patients (median age: 72 years old,median hemodialysis periods; 24 months) were included. After teriparatide injection, BMD of LS as well as FN at 6 months significantly increased from 0.67±0.18 to 0.86±0.19 g/cm² and from 0.44±0.08 to 0.48±0.07 g/cm², respectively. Corrected Ca levels significantly decreased at 3 and 6 months with increases in endogenous iPTH in response to lowering of serum Ca. As for bone metabolic markers, percent changes of serum BAP and serum iPTH significantly increased at 3 and 6 months. Conversely, serum TRACP-5b decreased after injection. Throughout this study, there were no fractures. Pharmacokinetics result is shown in Figure 1. There was a peak at 30 minutes at 157.2 µg/ml, and then it rapidly decreased to undetectable level at 240 minutes.

Conclusions: In conclusion, treatment with teriparatide, the dose was 20 µg 3 times/week, which is smaller than the suggested dose for non-dialysis patients, led to increase of BMD at LS and FN. Our data on pharmacokinetic of teriparatide suggested that we can use this agent in normal dose in dialysis patients.

Funding: Clinical Revenue Support

SA-PO584

Restless Leg Syndrome in Hemodialysis Patients: Possible Relationship with Mineral and Bone Metabolism
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Background: Restless legs syndrome (RLS) is a movement sleep disorder that is common among patients on hemodialysis (HD) and is associated with cardiovascular morbidity and mortality. The pathophysiology of this syndrome is not completely understood, and CKD-MBD may be implicated. We aimed to evaluate the prevalence of RLS in patients on hemodialysis, testing the relationship with CKD-MBD markers.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

758A
Methods: Prevalence and severity of RLS were assessed using the International RLS Study (ILRS) case definition.

Results: Of the 101 patients (53.5% women) included, RLS was observed in 29 patients (28.7%), with mild, moderate, severe and very severe presentation in 1, 12, 3 and 3 patients, respectively. RLS was more frequent among women (62% vs 38%, p=0.04), and was more severe in younger age group (P=0.047). Moreover, the expression of Runx2 and HO-1 was induced in calcium medium. At 5 weeks: The expression of Nrf2, HO-1, Runx2 could be induced by H2O2, but the expression of Runx2-induced calcification medium decreased gradually within incubation time after H2O2, or SFN + H2O2, pretreated.

Conclusions: The calcification in RASMCs is associated with the overexpression of endogenous ROS. Overexpression of Runx2 induced by endogenous ROS, but not exogenous ROS, may be inhibited or attenuated by the activated Nrf2/HO-1 pathway.

SA-PO587

Matrix Vesicles from Calcifying Vascular Smooth Muscle Cells (VSMC) Have Different MicroRNA (miRNA) Expression from Non-Calcifying VSMC

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Background: Matrix vesicles (MVs) are the matrix vesicles from calcifying VSMC that initiate mineralization within the extracellular matrix of VSMC. MV are similar to exosomes which are known to contain miRNA important in cell-cell communication. We hypothesized that the miRNA expression profile in calcifying MV (CaMV) would differ from non-calcifying MV (CTLMV) isolated from CKD rats.

Methods: CaMV were suspended in the culture media (DMEM) of hVSMC with normal fasting or high glucose (HG) (100 or 450 mg/dl), although hVSMC are usually cultured with normal fasting glucose at Day 7 and 14. At Day 7, the mRNA expression of Sox9, a chondro-osteogenic differentiation marker, was upregulated in hVSMC cultured with HG. The degree of calcification, the content of calcium P nanoparticle (CPP) at Day 1 and the correlation was −0.37, also consistent with higher observed basal iCa levels. There was no difference in SOCE at 10 weeks but by 35 weeks was 22.8% of patients were already admitted to parathyroidectomy, we further categorized PTH as ≥ or <500pg/ml. We analyzed the miRNA on array that changed at least 2 fold in the comparison groups with a p value of < 0.01 and false discovery rate of < 20%. Bioinformatic target gene prediction was performed using Targetscan and Miranda. CTLMV or calcifying MV were also co-cultured with VSMC to assess the change in calcification.

Results: At Day 14, CaMV increase calcification when added to VSMC compared to CTLMV. The arrays demonstrated 33 increased miRNAs and 17 decreased miRNAs in CaMV vs CTLMV. Real time PCR confirmed the mir-30c expression, known to regulate vascular calcification, is increased in CaMV vs CTLMV. Additional regulatory miRNA identified via target prediction analysis followed by functional enrichment yielded multiple mRNA-miRNA networks. Narrowing the analyses to only those RNA controlled by at least 3 miRNAs identified important miRNAs, including cell signaling pathways known to be involved in vascular calcification: Decreased expression of miRNAs (Ca vs. CTL) that would upregulate the target genes involved in P21 kinase signaling. In contrast, increased miRNA expression in CaMV vs. CTLMV would lead to downregulation of several signaling pathways including MAPK, RAS, mTOR and FOXO.

Conclusions: Calcifying MV contain different miRNAs compared to CTLMV. MiRNAs contained in calcifying MV may be transferred to other VSMC and regulate signaling pathways involved in vascular calcification.

Funding: Other NIH Support - NIH R01AR085805, Veterans Administration Support

SA-PO585

The Precedence of the Reduced Osteopontin Expression and the Increased Calcium Phosphate Calcification by the Calcification by Phosphate Load with Normal Fasting Glucose in Human Vascular Smooth Muscle Cells

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Background: It is well-known that vascular calcification (VC) develops in diabetes mellitus patients. On the other hand, malnutrition is also reported to induce VC. Thus, we examined how glucose load affects phosphate (P)-induced calcification in human vascular smooth muscle cells (hVSMC).

Methods: We added P of 1, 1.5, or 2.0 mM in the culture media (DMEM) of hVSMC with normal fasting or high glucose (HG) (100 or 450 mg/dl), although hVSMC are usually cultured with HG. The degree of calcification, the content of calcium P nanoparticle (CPP) in the media, and the expression of both the intrinsic calcification inhibitors and the chondro-osteogenic differentiation markers were examined at Day 1, 7, and 14. Moreover, it negatively correlated with the content of CPP at Day 1 and the correlation was −0.37, also consistent with higher observed basal iCa levels. There was no difference in SOCE at 10 weeks but by 35 weeks was increased in the CKD+Ca cohort (p=0.05) with a trend toward significance in the CKD cohort (p=0.08), also consistent with higher observed basal iCa levels.

Results: Basal iCa levels were lower in 10 week CKD VSMC compared to NL (0.76±0.02 vs. 0.66±0.02, p=0.05) however increased 1.5-fold by 35 weeks to be greater than NL (0.98±0.01 CKD, 0.81±0.02 NL, 0.90±0.04 CKD+Ca, p=0.05). SR store release was greater in CaMV at both 10 weeks (0.45±0.02 vs. 0.37±0.02, p=0.05) and 35 weeks (0.62±0.02 CKD, 0.44±0.03 NL, 0.50±0.03 CKD+Ca, p=0.05). At 10 weeks: SERCA2a expression was greater in CaMV in part explaining the lower basal iCa levels, however, at 35 weeks SERCA2a and NCX1 were both decreased in CaMV, consistent with higher iCa levels. There was no difference in SOCE at 10 weeks but by 35 weeks was increased in the CKD+Ca cohort (p=0.05) with a trend toward significance in the CKD cohort (p=0.08), also consistent with higher observed basal iCa levels.

Conclusions: Basal iCa, SR store release, and SOCE increases with progressive CKD at least in part due to changes in the expression of the common calcium regulatory proteins SERCA2a, NCX1, and NCX2. The increase in iCa is likely a key mechanism in our previous observations that CKD VSMC display an osteogenic phenotype, which is known to worsen cardiovascular outcomes.

Funding: Other NIH Support - NIAMS, NHLBI, Veterans Administration Support, Pharmaceutical Company Support - 2013-2014 Sanofi Nephrology Fellowship Award

SA-PO586

The Role and Mechanism of Nrf2/HO-1 Pathway in Oxidative Stress-Induced Vascular Calcification in End-Stage Renal Disease In Vitro

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Background: To investigate the mechanism of Nrf2/HO-1 pathway in oxidative stress-induced vascular calcification in ESRD (in vitro), and to explore a new target for the intervention of vascular calcification in ESRD.

Methods: 1. Rat aortic vascular smooth muscle cells(RASMCs) were cultured and divided into 4 groups: the complete medium cultured group, the calcification medium cultured group, the group of complete medium cultured for 42h and then sulforaphane (SFN) cultured for 6h, the group of complete cultured medium for 46h and then H2O2 cultured for 2h. Detect nuclear Nrf2 expression in each group by western blot. 2. 4 groups of RASMCs were cultured: the calcification medium cultured group, the group of H2O2 pretreated for 2h and then calcification medium cultured, the group of SFN pretreated for 6h and then calcification medium cultured, the group of SFN pretreated for 6h and H2O2 pretreated for another 2h, and then calcification medium cultured. Detect the expression of intracellular reactive oxygen species (ROS) by using DCFH-DA probe, and the expression of Nrf2, Heme Oxygenase (HO-1), Protein-related trypsin inhibitor (PI), Runx2 were measured.

Results: 1. Nrf2 expression in nucleus was enhanced after SFN and H2O2 stimulation. 2. The expression of Nrf2,Runx2 and ROS, but not HO-1, were induced by calcification medium in a time-dependent manner. 3. ROS was significantly reduced after H2O2, SFN, SFN + H2O2 pretreated, and decreased gradually with incubation time (P<0.05). 4. The expression of Nrf2 and HO-1 were induced by SFN, and the expression of Runx2 was inhibited in calcification medium. 5. The expression of Nrf2, HO-1, Runx2 could be induced by H2O2, but the expression of Runx2-induced calcification medium decreased gradually within incubation time after H2O2, or SFN + H2O2, pretreated.

Conclusions: The calcification in RASMCs is associated with the overexpression of endogenous ROS. Overexpression of Runx2 induced by endogenous ROS, but not exogenous ROS, may be inhibited or attenuated by the activated Nrf2/HO-1 pathway.
VCAM - 1 and TNF Alpha Induce Vascular Calcification In Vitro
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Background: VCAM, TNF alpha and soluble TNF alpha receptor 1 (sTNFR1) are elevated in patients with chronic kidney disease (CKD). In previous clinical trials with high cut-off dialysis plasma levels of these molecules and in vitro vascular calcification were lowered. Here we assessed the role of sTNFR 1 and VCAM on in vitro calcification.

Methods: In human vascular smooth muscle cells (VSMCs) vascular calcification was induced by osteogenic medium (OM). VCAM, TNF-α and sTNFR1 were added. Calcification was quantified by alkaline phosphatase staining and alizarin red staining. Calcification was then normalized to WST – 8.

Results: VCAM enhances vascular calcification in vitro in a dose-dependent manner (p<0,0001). TNF-α -induced calcification was effectively inhibited by sTNFR1 (50% reduction of the initial level; p=0,0001). sTNFR1 alone does not promote vascular calcification.

Conclusions: VCAM and TNF alpha promote vascular calcification in vitro. Their elimination with high cut-off dialysis or their pharmacological blockade may be advantageous in regard to vascular calcification in CKD.


SA-PO590
The Tripehelical Collagen Analog (GPO)α Acts Cofactors of Vascular Smooth Muscle Cells in a Concentration Dependent Manner
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Background: Extensive remodeling of the extracellular matrix and the transdifferentiation of vascular smooth muscle cells (VSMC) contribute to the pathogenesis of vascular calcifications in patients with chronic kidney disease (CKD). Matrix metalloproteinasises (MMPs) are proteolytic enzymes that impact on both of these processes and, thus, represent potential therapeutic targets. We have previously shown that the synthetic collagen analog (Gly-Pro-Hyp)3-α(GPO)α, a small peptide, could inhibit the enzymatic activity/stability of the gelatinases MMP-2 and -9 in a concentration dependent manner [1]. Aim of this study was therefore to investigate potential regulatory functions of GPO in an in vitro model of arteriolesclerotic VSMC calcification.

Methods: Cultures of murine VSMC were induced by a calcification medium (CM) containing elevated concentrations of calcium and phosphorus with or without the presence of different GPOα-concentrations (0.01; 0.1; 1 µM). VSMC calcifications were quantified by measuring calcium depositions and ALP-release.

Results: CM-induced VSMC calcification was enhanced in a concentration dependent manner (0.01; 0.1; 1 µM) while GPOα concentrations (0.01; 0.1; 1 µM) inhibited calcification in a concentration dependent manner. GPOα significantly reduced ALP release in VSMC cultures. These results suggest that GPOα inhibits the development of calcification in vitro.

Conclusions: GPOα acts as a cofactor of VSMC calcification. These results suggest that GPOα could be used as a potential therapeutic agent for the prevention of vascular calcification.

Funding: Private Foundation Support, Clinical Research Support

SA-PO591
Protective Effects of Epigallocatechin Gallate (EGCG) on Vascular Calcification In Vitro and In Vivo
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Background: Vascular calcifications are common in patients with chronic kidney disease (CKD). Our preliminary studies indicate that inhibition of matrix metalloproteinases (MMP)-2 and -9 suppresses the development of arterial calcification in uremic rats. Epigallocatechin gallate (EGCG), a polyphenol ingredient of green tea, has strong anti-inflammatory properties and inhibitory effects on MMPs. We therefore investigated potential protective effects of EGCG on vascular calcifications of smooth muscle cells (VSMC) in vitro and in an animal model of uremia-associated arteriosclerosis in vivo.

Methods: In vitro, calcifications of murine VSMCs were induced by a high phosphate (HP)-medium and cells were treated with different EGCG-concentrations (20–100µg/ml). VSMC calcifications were quantified using the orthro-cresolphthalein-method and proteolytic activities of MMP-2 and -9 in VSMC supernatants were determined by gelatin zymographies. In vivo, animals were treated with EGCG in drinking water. Animals were sacrificed after 2 weeks of treatment and aortic calcifications were quantified after von Kossa-staining.

Results: In vitro, EGCG provoked a dose-dependent increase of HP-induced calcification (up to 50%) of VSMCs and of proteolytic MMP-2 and -9 activities. In vivo, all EGCG-treated mice had severe arterial calcifications, involving 50% of the arterial wall wall after only 2 weeks of treatment. EGCG had no significant inhibitory effect on the development of vascular calcifications.

Conclusions: In this “negative experimental trial”, EGCG had no beneficial effect in the chosen animal model, which (considering the rapid development of calcifications) may have been too aggressive, thus overlooking potential protective effects of EGCG. Encouraged by the positive in vitro results, the effects of EGCG and other polyphenols should nonetheless be further investigated in other animal models of uremia-associated arteriosclerosis.

Funding: Private Foundation Support, Clinical Research Support

SA-PO592
Mechanism of Calcification by Iron Stimulation in Vascular Smooth Muscle Cells
Savuri Kawada, Yasuyuki Nagasawa, Mutsumi Kawaibe, Aritoshi Kida, Mana Yahiru, Tomoko Kimura, Kiyoko Yamamoto, Masayoshi Nanami, Yukiko Hasuike, Takahiro Kuragano, Keiji Nakasho, Hidemi Ohyama, Takeshi Nakamichi. Dept of Internal Medicine, Div of Nephrology and Dialysis, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; Dept of Pathology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.

Background: In CKD patients, atherosclerosis is one of important key factors which determine their prognosis. It was reported the calcification induced by TNF-α was related with iron in HUVeCs by our group. To reveal the relationship between calcification in vascular media and iron stimulation using vascular smooth muscle cells.

Methods: The aorta smooth muscle cells were cultured for three weeks. At day 0, we changed the usual culture medium to calcification medium, and TNF-α and iron were added to the calcification medium. Calcification in each condition was confirmed by Alizarin Staining. And to reveal early mechanism to enhance the calcification by iron and TNF-α-stimulation, we compared the gene expression profile between each condition in day 1 and day 3 using microarray analysis. We confirmed gene expression of cytokine which had increased in microarray analysis by real-time PCR.

Results: We confirmed both iron and TNF-α-stimulation enhanced calcium deposition in Alizarin Staining. Moreover, both iron and TNF-α-stimulation at the same time enhanced calcification more strongly than single stimulation. We picked up a cytokine which had increased with both iron and TNF-α-stimulation in the microarray analysis as similar as the Alizarin Staining result had shown. We confirmed gene expression of this cytokine by real-time PCR. Gene expression was increased at day 1 by stimulation of iron 5.8±3.0 fold change vs control), TNF-α (7.8±1.9 fold change vs control), and both stimulation (53.1±27.16 fold change vs control), synergistically.

Conclusions: Iron stimulation enhanced calcification in vascular smooth muscle cells along with TNF-α-stimulation. The possibility was suggested that this gene change from the early stage participated in the mechanism that iron promoted blood vessel media calcification.

Funding: Clinical Research Support, Government Support - Non-U.S.

SA-PO593
Kidney Injury/Repair Stimulates Vascular Disease Through Activin and Systemic Wnt Inhibition
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Background: We show that the vascular effects of CKD are an interplay of Wnt inhibition and activin induction mediated modulation of Activin receptor (ActRIIA) function resulting in a stimulation of atherasclerosis and vascular calcification.

Methods: CKD with elevated activin and Wnt inhibitors, especially Dkk1, was induced in the mouse models for vascular calcification, lineage tracing, and Alport’s. Activin, Dkk1, ActRIIA, psmad 2/3, aklotho and collagen levels were measured by Elisa, RT-PCR and westerns. Vascular smooth muscle cell (VSMC) function was measured by pressure

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
induced arterial dilatation in situ. Cell lineage tracing was performed in Rosa-tdT mice bred to CAG-CreERT mice. Mice harboring Rosa-tdT express tomato red cells in rearing Cre recombinein.

**Results:** Circulating activin and Dkk1 levels were increased while aklotho levels were decreased by CKD. In diseased kidneys, activin was expressed in myofibroblasts, and activin signaling was increased. Activin signaling correlated with Dkk1 expression, indicating a decrease in VSMC differentiation and inhibited osteoblastic transition and atherosclerotic calcification. In the circulation, the ActRIIA ligand trap decreased Dkk1 levels. CKD induced expression of tomato red cells in the adventitia after two weeks of femoral artery injury in Tek-Cre/ Rosalcre TKO mice compared to Tek-Cre/Rosa-tdT mice with normal kidney function.

**Conclusions:** CKD increased circulating free activin levels, decreased VSMC function, stimulated aortic osteoblastic transition and atherosclerotic calcification. Decreasing effects of elevated activin in CKD with an activin receptor type IIa (ActRIIA) ligand trap increased VSMC differentiation and decreased vascular calcification.

**Funding:** NIDDK Support, Pharmaceutical Company Support - Celgene

**SA-PO594**

*Translant Azotemia Episode Exacerbates Vascular Calcification in Adenine-Induced Uremic Rats* Daisuke Mori,1 Issai Matsui,2 Akihiro Shimomura,2 Yasuo Kusunoki,1 Sayoko Yonemoto,3 Masamitsu Senda,4 Yusuke Sakaguchi,5 Takayuki Hamano,5 Tetsuo Nakahara,5 Yoshikata Iiaka,3 Hiromi Kakuji,5 1Geriatric Medicine and Nephrology, Osaka Univ Graduate School of Medicine, Suita, Japan; 2Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Japan.

**Background:** Urea, the final metabolite of amino acids in the body, can carbanilate proteins at lysine residues, and thereby modifies characteristics of proteins reversibly. Several studies have revealed that functions of proteins are impaired by carbanylation. Acute kidney injury (AKI) is a representative pathological condition that elevates urea temporarily. Although AKI is not a perpetual condition, it is well-known that AKI increases subsequent risk of cardiovascular diseases through yet-unknown mechanisms. We evaluated the effects of transiently elevated serum urea on vascular calcification (VC).

**Methods:** Male Sprague-Dawley rats at age 9 weeks were divided randomly into two groups: cellulose-preload + adenine diet (group C+A) and urea-preload + adenine diet (group U+A). Urea-preload group received 10% urea diet from 9 to 13 weeks of age. Cellulose served as a control for urea. After one week of urea-washout period, all rats were euthanized for blood and tissue samples.

**Results:** Serum urea levels were 15.87 ± 2.96 mg/dL in cellulose-preload group and 39.20 ± 3.74 mg/dL in urea-preload group at the end of the preload period. Serum urea levels in urea-preload group were normalized to 14.73 ± 1.28 mg/dL during the washout period. At age 9 weeks, rats in group U+A developed severe VC in comparison with the rats in group C+A. Serum creatinine, urea nitrogen, calcium, phosphate, magnesium, albumin, and body weight were not different between the two groups at age 19 weeks. Western blot analysis of the aorta revealed that dietary preload of urea increased carbanilated proteins.

**Conclusions:** Preload of urea exacerbated VC in adenine-induced uremic rats. Protein carbanylation might link urea-preload to VC.

**SA-PO595**

*SNF472 Inhibits Cardiovascular Calcification in Uremic Rats* Joan Perello1,2 Carolina Salcedo,1 Ellen Neven,1 Geert J. Behets,1 Pieter H. Joubert,1 Patrick C. D’Haese,1,2 Miquel Ferrer,1 1R&D Dept, Laboratory Sanifit, Palma, Illes Balears, Spain; 2Laboratory of Renal Lithiasis Research, Univ of Balearic Islands, Palma, Illes Balears, Spain; 3Laboratory of Pathophysiology, Univ of Antwerp, Antwerp, Belgium.

**Background:** SNF472, an intravenous (i.v.) formulation of phytate, has been shown to inhibit cardiovascular calcification (CVC) in non-uremic conditions. We investigated the pharmacodynamics (PK) and efficacy (inhibition of CVC) of i.v. SNF472 in control and uremic rats.

**Methods:** The exposure to SNF472 in uremic animals was distinctly lower (5-fold for Cmax). SNF472 treatment resulted in a significant reduction in CVC of 80 and 88% in aorta and heart, respectively.

**Conclusions:** Daily SNF472 4 hour infusions of 50 mg/kg inhibit the development of CVC up to 88% in a rat, adenine model of uremia. These results support further investigation of SNF472 in the treatment of CVC in patients with calcification-related disorders such as calciphylaxis and ESRD patients.

**Funding:** Pharmaceutical Company Support - Laboratoris Sanifit S.L.

**SA-PO596**

*Enzyme Therapy for Vascular Calcification* W. Charles O’Neill,1 Kelly E. Manning,1 Koba A. Lomashvili,2 Nelson Haia,3 Peychi Lee,4 Francis T. Daney,5 Kim L. Askew,6 Anthony G. Quinn,7 1Renal Div; Emory Univ School of Medicine, Atlanta, GA; 2Synageva Biopharma, Lexington, MA.

**Background:** Pyrophosphate (PiPi) is a key endogenous inhibitor of hydroxyapatite formation that circulates at levels sufficient to prevent vascular calcification. PiPi is produced from extracellular ATP by the ectoenzyme, nucleotide pyrophosphatase pyrophosphorylase (NPP1) and deficiency of this enzyme produces severe fatal arterial medial arterial calcification in humans. Mice lacking NPP1 have undetectable plasma PiPi and also develop arterial calcification. We examined whether exogenous NPP1 can increase plasma PiPi and prevent vascular calcification in these mice.

**Methods:** Recombinant proteins containing the extracellular portion of human NPP1 fused to human IgG1 Fe (ENPP1-Fc) were created and injected into two mouse models of NPP1 deficiency (ENPP1−/− and ENPP1−/−/−). NPP1 activity was measured by conversion of [32P]ATP to [32P]Pi with separation by thin-layer chromatography. Plasma PiPi was measured by a radiometric enzyme assay using UDP-[14C]glucose and UDP-glucose pyrophosphorylase.

**Results:** Intravenous injection of NPP1-Fc (6 mg/kg) into ENPP1−/− mice increased plasma PiPi activity to a peak of +/− 18% of normal at 4 hours with a decline to 70 +/− 5% of normal by 72 hours. There was no increase in aortic NPP1. Plasma PiPi followed a similar pattern, with a peak of 2.2 +/− 0.6 µM at 4 hours declining to 0.21 +/− 0.04 µM at 72 hours (normal: 2.18 +/− 0.33 µM). With subcutaneous injection, plasma NPP1 was 110 +/− 13% of normal and plasma [PiPi] was 0.38 +/− 0.14 µM after 48 hours. Subcutaneous administration of NPP1-Fc 48 h reduced aortic calcium content 86 +/− 5% (p=0.001) after 18 days in ENPP1−/− mice fed a high phosphorus diet, and improved survival at 10 weeks from 15% to 50% (p=0.001) in ENPP1−/− mice fed a high phosphorus, low magnesium diet.

**Conclusions:** Administration of NPP1 in NPP1-deficient mice produces an increase in circulating PiPi that is sufficient to prevent vascular calcification and increase survival. The ability of ENPP1 fusion proteins to raise PiPi levels and inhibit tissue calcification supports the potential to reduce vascular calcification in other calcification-prone states.

**Funding:** Pharmaceutical Company Support - Synageva Biopharma

**SA-PO597**

*The Risk of Medial Arterial Calcification in Early Chronic Kidney Disease* W. Charles O’Neill,1 Kum Hyan Hun,2 Arshad Ali,1 Ansley O’Neill,1 Kelly E. Manning,1 1Renal Div; Emory Univ, Atlanta, GA; 2Internal Medicine, Dept of Internal Medicine, Inje Univ College of Medicine, Ilsan Paik Hospital, Goyang, Korea.

**Background:** Medial arterial calcification is common in advanced chronic kidney disease (CKD) but whether this risk begins in early CKD is unknown. There is also concern that possible benefits of vitamin D and calcium in this group may be offset by potential induction of vascular calcification. We have previously shown that breast arterial calcification is a readily available and specific marker of medial arterial calcification and that its prevalence is increased in advanced CKD.

**Methods:** From a computerized search of medical records, 446 women with CKD and mammograms were randomly selected. After exclusion of women with renal transplants or other stages of CKD, history of warfarin use, or non-screening mammograms, 333 women with CKD (MDRD formula) were identified and individually matched by age and diabetes status to women with an estimated GFR >90 ml/min/1.73 m². Digital mammograms were visually inspected for arterial calcification.

**Results:** Mean age was 69.5 +/− 0.6 (range: 44-91), mean eGFR was 49.5 +/− 0.4 ml/min/1.73 m², 20.1% had diabetes, 31.5% were receiving calcium supplements, 31.3% were receiving vitamin D (> 1000 units/d), and 1.8% were receiving an active form of vitamin D. Controls had a mean eGFR of 104.1 +/− 0.7 ml/min/1.73 m². The prevalence of arterial calcification was the same in CKD 3 patients (33.1%) and controls (33.3%). Dividing the CKD 3 patient group by different thresholds of serum creatinine yielded similar results. There was no difference in calcification between patients taking or not taking calcium supplements (36.2% vs. 34.1%), vitamin D (36.2% vs. 34.6%), or both (30% vs. 32.5% with neither). In a logistic regression, only age was a significant determinant of arterial calcification (p=0.0001).

**Conclusions:** The prevalence of medial arterial calcification is not increased in women with stage 3 CKD, indicating that the risk begins at stage 4 CKD. Supplementation of calcium or vitamin D does not increase the risk of medial arterial calcification in these patients.

**Funding:** Clinical Research Support.

Vascular Calcification: From Bench to Bedside

SA-PO598
Deoxycholic Acid (DCA), a Metabolite of Circulating Bile Acids, and
Coronary Vascular Calcifications in Chronic Kidney Disease (CKD)
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Nowak,1 Jessica B. Kendrick,1 Geoffrey A. Block,2 Michel Chonchol.1 1Univ
of Colorado Denver; 2Denver Nephrology.
Background: Our group has previously shown that DCA, a metabolite of circulating
cholic acid, induces vascular mineralization and osteogenic differentiation in animal models
and that circulating levels of DCA are elevated in patients with CKD. We investigated
whether increased DCA serum levels are associated with an increase risk for higher
coronary artery calcification (CAC) volumes and lower lumbar bone mineral density
(BMD) in CKD patients.
Methods: We used stored baseline serum samples in 112 patients with moderate to
advanced CKD (eGFR= 20-45 mL/min/1.73m2) who participated in a randomized-controlled
study to examine the effects of phosphate binders on vascular calcification. Circulating
DCA levels were assayed using liquid-chromatography-tandem mass spectrometry (LCMS/MS). CAC volume was obtained using GE-Imatron C150 scanner and lumbar BMD
was determined using abdominal computed tomography scans with a calibrated phantom
of known density. Linear regression models were used to examine the cross-sectional
association between DCA with CAC volume and lumbar BMD.
Results: Participant characteristics were as follows: mean age, 68±11 years; 50%
women; 10% black; mean eGFR, 32±8 mL/min/1.73m2; and median DCA 58.4 (IQR 29112) ng/mL. After adjusting for demographics, co-existing illness, body mass index, eGFR
and circulating markers of CKD-MBD including serum calcium, phosphorus, vitamin D,
parathyroid hormone and fibroblast growth factor 23, an increase serum DCA level > 58
ng/mL positively associate with CAC volume (ß: 494.84 ± 238.82; p=0.03) and negatively
associated with BMD (ß: - 20.35± 9.56; p=0.03).
Conclusions: Higher serum levels of DCA in patients with stage III and IV CKD is
independently associated with higher CAC volume and lower lumbar BMD. Larger cohort
studies are needed to confirm these findings.
Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO599
Fibroblast Growth Factor 23 and Fetuin A Levels in Pre-Dialysis Stage 4-5
Chronic Kidney Disease Patients with Aortic Calcification: A Case Control
Study Vijayakumar Theophilus-Sunder, Anna T. Valson, Vinoi George David,
Santosh Varughese, Tamilarasi Veerasamy. Dept of Nephrology, Christian
Medical College, Vellore, Tamil Nadu, India.
Background: Vascular calcification (VC) contributes to the increased cardiovascular
mortality seen in CKD. However, not everyone with advanced CKD develops VC, indicating
that circulating levels of factors that modulate VC may play a role in determining individual
susceptibility towards VC. We aimed to examine this hypothesis by measuring the levels
of FGF-23 and Fetuin-A in a group of pre-dialysis CKD Stage 4-5 patients who had
documented abdominal aortic calcification (AAC) and an age, gender and eGFR matched
group of patients who did not have AAC.
Methods: Out of a pre-existing cohort of 710 patients with CKD Stage 4-5, 28 patients
with AAC (Group 1, cases) were compared with an equal number of age, gender and eGFR
matched patients without AAC (Group 2, controls) with respect to their demographic and
biochemical parameters, including FGF-23 and Fetuin-A. AAC was assessed by lateral
abdominal X ray, while Fetuin-A and intact FGF-23 were estimated by ELISA in serum.
Results: Groups 1 and 2 were matched for age (mean age 57.7 and 57.8 years
respectively, p = 0.938), gender (84.6% males in both groups) and eGFR (median eGFR
14.5 and 13.1 respectively, p = 0.826), and were not significantly different with respect
to risk factors for AAC such as presence and duration of diabetes, hypertension, smoking
and obesity. Levels of calcium, phosphorus, PTH, 25 (OH) vitamin D, serum cholesterol,
triglycerides, HDL and LDL were also comparable between the two groups. However,
median FGF23 levels were significantly higher in Group 1 [25.2, (Q1= 14, Q3=34.2)]
compared to Group 2 [12.1 (Q1 = 6.6, Q3 = 14.1), n = < 0.001]. Median Fetuin-A levels
were also significantly higher in Group 1 [5.5 (Q1=4.4, Q3=6.5)] compared to Group 2
[4.1 (Q1 = 3.6, Q3 = 5.7, n = 0.034).
Conclusions: Pre-dialysis patients with Stage 4-5 CKD with AAC, had higher FGF23 and Fetuin-A levels compared to age, gender and eGFR matched patients who did not
have AAC. The nature and mechanism of this association between elevated FGF23 and
Fetuin-A levels and AAC requires further exploration.

SA-PO600
Lack of Association Between Serum Osteoprotegerin, Osteopontin and
Fetuin-A Levels and the Longitudinal Changes in Arterial Stiffness in CKD
Patients Undergoing Renin-Angiotensin System Blockade Cecilie Lyngsø,1
Marie Frimodt-Moller,2 Marianne Rix,2 Anne-Lise Kamper,2 Svend Strandgaard,1
Arne Høj Nielsen,1 Allan Flyvbjerg,3 Mette Bjerre.3 1Dept of Nephrology, Herlev
Hospital, Herlev, Copenhagen, Denmark; 2Dept of Nephrology, Rigshospitalet,
Copenhagen, Denmark; 3The Medical Research Laboratory, Dept of Clinical
Medicine, Aarhus Univ, Aarhus, Denmark.
Background: Osteoprotegerin (OPG), osteopontin (OPN) and fetuin-A, have been
suggested to participate in the accelerated development of arteriosclerosis seen in patients
with chronic kidney disease (CKD). We have previously shown that measures of vascular
stiffness were significantly reduced after 24 weeks of treatment with renin-angiotensin

Poster/Saturday

system (RAS) blocking agents. The aim of this longitudinal post hoc study was to investigate
whether serum levels of OPG, OPN and fetuin-A were associated with these same changes
in markers of arterial stiffness found in CKD patients treated with RAS blocking agents.
Methods: Serum OPG, OPN and fetuin-A levels were measured in 57 patients with
CKD stage 3-5, mean eGFR 29 ml/min, as a post hoc analysis of data acquired during a
24-week controlled trial in which patients were randomized to treatment with 16 weeks of
monotherapy with either enalapril or candesartan followed by 8 weeks of dual blockade.
Serum levels were obtained upon study entry and after 16 and 24 weeks of RAS blocking
therapy and compared to aortic pulse-wave velocity and augmentation index.
Results: Except for a significant correlation between OPG and central pulse pressure
(p < 0.05), serum levels of OPG, OPN and fetuin-A did not correlate to markers of vascular
stiffness. There were no significant changes in serum levels of OPG, OPN and fetuin-A
when monotherapy with enalapril or candesartan was compared to dual blockade.
Conclusions: The present results do not corroborate the use of OPG, OPN and fetuin-A
as surrogate markers for vascular stiffness in patients with CKD.

SA-PO601
Hyperuricemia Is Significantly Associated with Coronary Artery
Calcification and Vascular Stiffness in Asymptomatic Subjects Undergoing
General Health Examination Ah Ran Choi, Hae Yeul Park, Seok-Hyung Kim,
Hoon Young Choi, Sung-Kyu Ha, Hyeong Cheon Park. Nephrology, Gangnam
Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea.
Background: Recent studies suggest that hyperuricemia may be associated with
increased adverse cardiovascular events even in healthy subjects. Quantity of coronary artery
calcium (CAC) correlates with atherosclerotic plaque burden and increased cardiovascular
events. This study aimed to determine the relationship between serum uric acid level(sUA)
and brachial-ankle pulse wave velocity (ba-PWV), coronary artery calcium score (CACS)
as well as other traditional cardiovascular risk factors in asymptomatic subjects.
Methods: We consecutively enrolled 4,703 asymptomatic subjects who underwent
ba-PWV and coronary CT angiography as part of a general health examination. A high baPWV group, those having increased vascular stiffness, was defined as ba-PWV greater than
1497.5 cm/s (75th percentile). The subjects were stratified into four groups according to sUA.
Results: Mean age of enrolled subject was 52.8 ± 9.4 years, 61 % of the study
participants were male. Eight point four percent of the study participants showed CACS
greater than 100. The adjusted odds ratio (OR, 95% confidence interval) for the presence
of high ba-PWV in the second to fourth sUA quartile vs. first sUA quartile was 1.45 (1.1371.840, P<0.003), 1.42 (1.081-1.866 P<0.012), 1.66 (1.246-2.218, P<0.001), respectively
after adjusting for age, gender, diabetes, hypertension, smoking, body mass index (BMI),
estimated glomerular filtration (eGFR), fasting blood sugar (FBS) and calculated LDL.
Moreover, subjects with CACS greater than 100 also showed that fourth quartile of sUA
was associated with high ba-PWV compared with the first quartile of sUA [OR 2.4, (1.653.47, P<0.001)]. Multivariate linear regression analysis demonstrated that old age, male,
hypertension, diabetes, BMI, FBS, eGFR and sUA were significantly associated with mean
ba-PWV and log transformed CACS.
Conclusions: Our results show that sUA is an independent risk factor for increased
vascular stiffness and coronary atherosclerosis in asymptomatic adults undergoing health
examination.

SA-PO602
Abdominal Aortic Calcification Score on Plain Radiograph as a Predictor
of Coronary Artery Calcification Score on Computed Tomography and
T-Score on BMD in Dialysis Patients Eu Gene Jeong,1 Su Mi Lee,1 Young
Ki Son,1 Dongyeol Lee,2 Hansae Kim,2 Sung Hyun Son.3 1Dept of Internal
Medicine, Dong A Univ Hospital, Busan, Republic of Korea; 2Dept of Internal
Medicine, Bong Seng Memorial Hospital, Busan, Republic of Korea; 3Dept of
Internal Medicine, BHS Han Seo Hospital, Busan, Republic of Korea.
Background: Not only coronary artery calcification scores (CACS) on computed
tomography (CT) but also several VC scores on plain radiographs can predict cardiovascular
events. However, there is no study about the correlation between CACS on CT and VC
scores of several sites on plain radiographs. Therefore, we evaluated which VC scores among
several VC scores on plain radiographs are a predictor of CACS on CT in dialysis patients.
We also investigated the association between VC scores and bone mineral density (BMD).
Methods: We conducted this single center cross-sectional study from March 2013 to
September 2014. We checked the plain radiographs of the feet, hands, pelvis, and lateral
lumbar spine and estimated the VC scores. CACS on CT and BMD were evaluated. We
defined severe CACS as CACS > 1000. FGF-23, fetuin-A, osteoprotegerin (OPG) and
receptor activator of NF-κB ligand (RANKL) were analyzed with ELISA.
Results: The mean ages of 61 patients including 38 hemodialysis(HD) and 23 peritoneal
dialysis(PD) patients were 58.6±10.2 years. The prevalence rate of significant VC was 75.4%
and prevalence rate of severe CACS was 26.2%. The OPG levels were higher in patients
with severe CACS(p=0.019) and significant VC(p=0.009). Patients with AAC score≥5 had
lower T score of wrist and hip than patients with AAC score<5. CACS is positively correlated
with AAC score(r=0.639, p< 0.001), VC score of the hands and pelvis (r=0.494, p< 0.001).
AAC score is negatively correlated with T score of wrist(right: r=-0.286, p=0.027) and
hip(right: r=-0.259, p=0.045)on BMD. AAC score(B=59.4, C.I.=18.3-100.6, p=0.006) and
VC score of the hands and pelvis(B=225.8, C.I.=69.7-381.8, p= 0.006)on plain radiographs
were independently associated with CACS on CT.
Conclusions: AAC score among several VC scores on plain radiographs is the most
reliable predictor of CACS on CT and T score on BMD in dialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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of and after 12 months Kaupilla and Adragao study was to evaluate the influence of bone mineral disorders in VC and its progression patients; vascular calcification (VC) is common among them. The main objective of this study was to evaluate the influence of bone mineral disorders in VC and its progression in a prospective cohort of patients. Secondarily, we intend to identify clinical, laboratory, and imaging predictors of the presence and progression of VC.

Methods: Adult patients undergoing HD for ≥90 days were included. At the beginning of and after 12 months Kaupilla and Adragao methods were used to determine the VC score (VCS); and clinical, hormonal, inflammatory, biochemical, and nutritional markers were measured. Bone biopsy and histomorphometric analysis were performed at the beginning of follow up.

Results: Sixty patients completed the study; of them 41.7% were male, 43.4% diabetic, and the mean age was 56. 73±1.8 years. At the beginning of the follow-up, 75% of the participants had VC. Age >60 years (Odds ratio=5.2, 95%CI= 4.1-6.184, p<0.002), FG232 levels >3000 Ru/ml (Odds ratio=5.7, 95%CI= 1.00-3.29, p=0.05), and serum fetuin A >673 g/l (Odds ratio=7.3, 95%CI=1.26-43.7, p=0.03) were independent predictors of VC. Regarding VC progression age >60 years (Odds ratio=4.3, 95%CI=1.003-8.15, p=0.049), higher serum 1,25-dihydroxyvitamin D3 (Odds ratio=4.7, 95%CI= 1.47-27.9, p<0.01) no use of statins (Odds ratio=5.6, 95%CI= 1.13-28.1, p=0.03) were the only independent predictors. Bone turnover and histomorphometric findings were not associated with VC and its progression, which deserves new and more specific investigations.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: In this population of incident HD patients at high risk of PAD, OPG was significantly associated with odds of PAD. Whether the elevation of OPG is causal to the development of PAD or whether it serves as a marker of disease severity needs to be explored.

Funding: NIDDK Support

SA-PO608

Association of Vascular Calculcation Biomarkers with Odds of PAD

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG, per 1 pmoI/L higher</td>
<td>1.06 (1.02-1.11)</td>
<td>1.07 (1.01-1.13)</td>
</tr>
<tr>
<td>Fetuin A, per 1 g/L higher</td>
<td>0.88 (0.24-3.26)</td>
<td>1.25 (0.27-5.81)</td>
</tr>
<tr>
<td>MGP, per 1-log ph higher</td>
<td>0.98 (0.75-1.28)</td>
<td>0.91 (0.66-1.25)</td>
</tr>
</tbody>
</table>

Conclusions: In this population of incident HD patients at high risk of PAD, OPG was significantly associated with odds of PAD. Whether the elevation of OPG is causal to the development of PAD or whether it serves as a marker of disease severity needs to be explored.

Funding: NIDDK Support

SA-PO609

Increased Peripheral Arterial Calcification in Patients Receiving Warfarin

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Background: Matrix gla-protein is a vitamin K-dependent inhibitor of vascular calcification. Factors including genetic deficiency or inhibition with warfarin produces medial vascular calcification in animals, raising concerns that warfarin may promote vascular calcification in humans. We recently showed that warfarin use is associated with increased breast arterial calcification but whether this is reflective of other arteries or occurs in men as well is unclear. Therefore, we compared the prevalence of calcification in peripheral arteries in patients with and without warfarin therapy.

Methods: A random sample from a computerized search of medical records yielded 430 patients with x-rays performed during or after warfarin therapy. Each was matched to a patient without warfarin exposure based on age and diabetes. Patients with warfarin exposure <1 month, history of ESRD, or serum creatinine > 2.0 were excluded. X-rays were reviewed visually for arterial calcification.

Results: Mean age was 66.9 ± 0.8, 41% were males, and 34% had diabetes. The indication for warfarin was atrial fibrillation in 45% and venous thrombosis or embolism in 44%, and mean duration of warfarin was 4.8 yrs (range: 1 month to 38 yrs). 68% were on warfarin at the time of the x-ray and the remainder had been off warfarin for a mean of 2.4 yrs (range: 1 day to 25 yrs). Serum calcium was slightly lower (9.04 +/- 0.3 vs. 9.17 +/- 0.2, p=0.003) in the warfarin patient but serum creatinine and phosphorus did not differ. Prevalence of arterial calcification was 44% greater in warfarin patients (30.2% vs. 20.9%, p=0.0023) but not on x-rays performed prior to warfarin (26.4% vs. 22.4%, p=0.156), indicating that the increase was due specifically to the warfarin and not to underlying disease or other patient characteristics. The increase in calcification was seen only after >3 yrs of warfarin and only in the ankle and foot. It was similar in men and women and greatest (2.4-fold) in patients under age 60 (15% vs. 6.3%, p=0.04).

Conclusions: Warfarin use is associated with lower extremity arterial calcification in both men and women independent of age, diabetes, and other patient characteristics.

Funding: Clinical Revenue Support

SA-PO610

Matrix Gla Protein and Vascular Calcification in Patients with End Stage Renal Disease

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Background: Vascular calcification (VC) is a common and severe consequence of end-stage renal disease (ESRD). Matrix Gla protein (MGP) is a calcification inhibitor expressed by the vasculature that counters the development of VC.

Methods: In 84 ESRD patients undergoing LD-Tx at Karolinska University Hospital, biopsies from the inferior epigastric artery were obtained during surgery. Vascular calcification was assessed by von Kossa staining both by manual scoring (0-3) and by semi-automated analysis (%). Total uncarboxylated MGP (t-ucMGP) and dephospho-uncarboxylated MGP (dp-ucMGP) were measured in plasma. Tissue MGP expression was quantified in arterial biopsies by TaqMan RT-PCR. DNA methylation of the MGP gene was assessed in peripheral blood from 12 ESRD patients and 12 healthy controls.

Results: 50 patients (59.5%) had low VC scores (0 and 1) and 34 (40.5%) patients high VC scores (2 and 3). Plasma levels of dp-ucMGP were higher in patients with high VC scores compared to patients with low VC scores (2214 [1413-2995] vs. 1701 [1275-2233] pmoI/mL, p=0.005) and also associated with calcification (%) (Fig 1A: β [95%CI]: 26 [7 to 43] p<0.01). Additionally, calcification (%) associated with arterial expression of MGP (Fig 1B: β [95%CI]: 0.04 [0.02 to 0.06] p<0.0001). t-ucMGP levels were not associated with measures of VC. DNA methylation of the MGP gene was significantly lower in patients with ESRD compared to healthy controls (adjusted p<0.01).

Figure 1

**SA-PO611**

A Nationally Representative Case Control Study of Calciphylaxis Risk Factors

Sagar U. Nigwekar,1 Sophia Zhao,1,2 Julia Beth Wenger,1 Franklin W. Maddux,2 Jeffrey L. Hymes,2 Ravi I. Thadhani,1 Kevin Chan,1,2 1MGH; 2Fresenius Medical Care North America.

Background: Prior studies evaluating calciphylaxis risk factors suffer from sample size limitations and none examine whether characteristics at dialysis initiation predict calciphylaxis risk.

Methods: Data for this matched case control study were derived from hemodialysis (HD) population at the Fresenius Medical Care North America (FMCNA). Cases were identified from FMCNA calciphylaxis prospective database. Controls (HD patients without calciphylaxis) were matched to cases on age, sex, and race. Data on variables at HD initiation were abstracted. Variables for multivariable logistic regression analyses were identified using stepwise selection.

Results: We analyzed 1,025 calciphylaxis cases (52% biopsy-confirmed) and 2,050 controls. Body mass index, diabetes mellitus (DM), serum parathyroid hormone (PTH) level, use of warfarin and phosphate binders were higher whereas serum calcium and active vitamin D use were lower at HD initiation in cases compared to controls.

Figure 1: The association between calcification % (as assessed by semi-automated analysis) and A) plasma dp-ucMGP levels, and B) tissue MGP expression.

Conclusions: Tissue and plasma levels of dp-ucMGP were higher in patients with VC versus those without, possibly indicating a compensatory up-regulation of MGP to prevent further progress. The observation that the methylation of the MGP gene was lower in ESRD than in controls suggests that the altered expression could be due to epigenetic regulation.

Funding: Government Support - Non-U.S.
No significant differences were noted for serum phosphorous, diatelyse calcium, use of statins and calcitriol. In DM subgroup, insulin injection use was more common in cases. In multivariable analyses, obesity (OR: 2.55, 95% CI: 1.82-3.50), DM (OR: 2.63, 95% CI: 1.88-3.69), use of warfarin (OR: 3.60, 95% CI: 2.40-5.41) and insulin injections (OR: 1.29, 95% CI: 1.07-1.89) were associated with higher risk. Similar results were noted in analyses restricted to biopsy-confirmed cases.

Conclusions: Obese, diabetic HD patients treated with insulin injections or warfarin are at high risk for calciphylaxis.

Funding: Private Foundation Support

SA-PO612
Calciphylaxis Quality Improvement Project and Case Series Rohan V. Mehta, Jean Luc Franck, Jason Cobb. Renal Div, Emory Univ, Atlanta, GA.

Background: Calciphylaxis (Calcific Uremic Arteriopathy) is a serious condition characterized by extended length of stays and multiple hospital admissions. The treatment of calciphylaxis can become a burden on the healthcare system especially with the demands on hospital systems to become more efficient. The lengths of stay & 30 day readmission rates are becoming a measure of hospital quality. We developed a multidisciplinary team including nephrologists, hospitalists, dermatologists, hospital administration, nurses, wound care staff, social workers, dieticians, and palliative care. The purpose of the team is to improve the quality of care of our calciphylaxis patients. In development of this quality improvement project we began by examining our baseline patient population. We are reporting our baseline data as a case-series.

Methods: Retrospective chart review of calciphylaxis patients from 2001-2014 in our single center hospital which includes academic and community physicians. Baseline data reported included age, calcium, phosphorus, PTH, albumin, hemoglobin, creatinine, BUN, and the use of warfarin. Treatment options, the length of stay, and number of admissions were reported.

Results: In 20 reported patients, 19 were African-American. Average age was 61 years old. Average calcium levels of 8.8 mg/dl and phosphorus of 5.5 mg/dl. The average PTH was 573, albumin 2.75 g/dl, hemoglobin of 10.4 g/dl, BUN of 42, and creatinine 6.5 mg/dl. 13 patients received hyperbaric oxygen treatment, 9 patients received sodium thiosulfate infusions, and 6 patients received calcitriol. 11 patients were using warfarin for medical conditions including atrial fibrillation and deep venous thrombosis. The average length of stay was 45 days and 3 admissions per patient.

Conclusions: We reported one of the largest single center and predominant African-American calciphylaxis case series. In comparison to other reported calciphylaxis series our average PTH was lower and a high percentage of our patients were using warfarin at time of diagnosis. Future tasks include testing if the multidisciplinary quality improvement team interventions can improve our patient quality of care and hospital goals such as reductions in length of stay and 30-day readmission rates.

SA-PO614
Calciphylaxis – A Multi-Interventional Treatment Regimen Including Vitamin K Supplementation Might Reduce Mortality in Chronic Kidney Disease Patients Daniel A. Hochfellner, Barbara Binder, Werner Ribitsch, Alexander R. Rosenkranz, Gernot Schilcher. 'Clinical Div of Nephrology, Dept of Internal Medicine, Medical Univ of Graz, Graz, Austria; 'Dept of Dermatology, Medical Univ of Graz, Graz, Austria.

Background: Calciphylaxis is a rare disease predominantly affecting patients with chronic kidney disease (CKD) with a high mortality mainly due to wound infection. Recently, multimodal therapy schemes including sodium thiosulfate (STS) have been established. The role of a standardized Vitamin K supplementation remains unclear.

Methods: In a retrospective study we evaluated the impact of a standardized, multi-interventional treatment regimen on the mortality of calciphylaxis patients treated at the Clinical Department of Nephrology, Medical University of Graz, Austria between January 2009 and February 2014. Patients were treated with STS, dermatological wound management and high dose supplementation of vitamin K1 (Phytonadione 30mg/week). The primary endpoint was mortality compared to the present literature. Second endpoints included gender distribution, number of biopsy proven cases, analysis of triggering events and time from event to diagnosis. Data were collected from medical records.

Results: 20 patients with newly diagnosed Calciphylaxis at different CKD stages (CKD 5, n=15; CKD 4, n=3; CKD 3, n=1; no CKD, n=1) were included. The mortality was 25% versus 52% compared to recent literature. Gender distribution and amount of biopsy proven cases were comparable to other retrospective studies. 12 patients (60%) had a known preceding event such as trauma possibly having triggered development of calciphylaxis. The period from event to diagnosis was 103±94 days. 19 patients (95%) received STS. In contrast to other multimodal therapeutic concepts 95% (19) of our patients additionally received high dose vitamin K1 supplementation.

Conclusions: In our cohort calciphylaxis was associated with a markedly reduced mortality as compared to published outcome data. We hypothesize that supraphysiological support therapy and our multi-interventional treatment regimen play an important role in the treatment of calciphylaxis.

SA-PO615
The German Calciphylaxis Registry Vincent Brandenburg, Jürgen Floeg, Joanna Korbiel, Markus Ketteler. 'Cardiology, RWTH Aachen Univ Hospital, Aachen, Germany; 'Nephrology, RWTH Aachen Univ Hospital, Aachen, Germany; 'Nephrology, Klinikum Coburg, Coburg, Germany.

Background: Calciphylaxis (CUA) is a rare disease and for patients a devastating condition associated with high morbidity and mortality. CUA is characterised by painful, ischemic, partly necrotic skin ulcerations. Pathomorphologically, media calcification of cutaneous arteries and extracellular matrix remodelling are the hallmarks of CUA. Epidemiology and risk factors are incompletely understood. Referring patients to specialized units is limited due to high disease burden.

Methods: Therefore, we established an internet-based observational registry in 2006 (www.calciphylaxie.de) to allow online notification for pts with CUA. The registry includes a comprehensive data base with 71 parameters concerning patient and laboratory data, clinical background and presentation as well as therapeutic strategies. The diagnosis of CUA is made on clinical and/or histological grounds by the referring physician.

Results: Until Feb 2015 n=233 patients with CUA have been recorded (~ 30 pts/ year at constant rate) with a median delay of 28 days after onset: 99% Caucasians, 60% females; 76% HD and 10% PD patients; median age 66 (IQR 61-76) years. Co-medication at the time of diagnosis: 75% ESA, 51% vitamin K antagonists (VKA). Skin biopsy was done in 45%, prior PEX in 12%; major skin lesion in 80% at the legs. Median lab data upon diagnosis of CUA: AK Phos 113 u/L (IQR 86 - 167); PTX 173 g/mL (IQR 73-390), total calcium 2.20 mmol/L (IQR 2.04-2.36); phosphorus 1.62 mmol/L (IQR 1.28-2.00).

Conclusions: CUA is a rare disease among ESRD pts with high mortality. Therapeutic strategies vary significantly among centers; EBMs guidelines are absent. VKA usage appears to be a risk factor for CUA in ESRD pts. The German CUA registry is a valuable tool to collect data and may become a basis for a European registry (EuCalNet).

Funding: Pharmaceutical Company Support - Sanofi, Amgen

SA-PO616
Evaluation of the Effects of Sodium Thiosulfate Treatment on Calciphylaxis Pain Guillermo Ortiz, Joshua Wibecan, Julia Beth Wenger, Ravi I. Thadhani, Barbara Baer, Gernot Schilcher, Barbara Binder. 'Clinical Div of Nephrology, Medical University of Graz, Graz, Austria; 'Vascular Calcification: From Bench to Bedside, Emory Univ, Atlanta, GA.

Background: Intravenous sodium thiosulfate (STS) is commonly prescribed to treat calciphylaxis, a highly fatal disease that presents with excruciating painful skin lesions. Anecdotal reports suggest that STS may improve calciphylaxis associated pain (CAP) within 2 weeks of initiation; however, systematic evaluation of effects of STS on CAP is lacking.

Methods: This observational study included 22 patients with biopsy-confirmed calciphylaxis who were hospitalized at our center for ≥ 2 weeks during 2012-2014 for newly diagnosed calciphylaxis and were treated with STS. Medical records were reviewed to abstract clinical data including CAP severity (0-10 scale) and analgesic use. CAP scores restricted to biopsy-confirmed cases.

Results: Two patients with newly diagnosed calciphylaxis at different CKD stages (CKD 5, n=15; CKD 4, n=3; CKD 3, n=1; no CKD, n=1) were included. The mortality was 25% versus 52% compared to recent literature. Gender distribution and amount of biopsy proven cases were comparable to other retrospective studies. 12 patients (60%) had a known preceding event such as trauma possibly having triggered development of calciphylaxis. The period from event to diagnosis was 103±94 days. 19 patients (95%) received STS. In contrast to other multimodal therapeutic concepts 95% (19) of our patients additionally received high dose vitamin K1 supplementation.

Conclusions: In our cohort calciphylaxis was associated with a markedly reduced mortality as compared to published outcome data. We hypothesize that supraphysiological support therapy and our multi-interventional treatment regimen play an important role in the treatment of calciphylaxis.
predict 6-month outcomes. Baseline to 2-weeks (figure 1) despite steady doses of opiate medications. No significant predictors of CAP response were observed and CAP improvement at 2-weeks did not predict 6-month outcomes.

Conclusions: A large prospective trial is needed to ascertain the effects of STS on CAP.

SA-PO616

Long-Term Impact of Strict Blood Pressure Control During CKD on Mortality Risk After ESRD

Elaine Ku,1 Lawrence J. Appel,2 Jennifer J. Gassman,3 Miroslaw Smorodzinski,2 Mark J. Sarna,2 David V. Glidden,4 Chi-yuan Hsu,1 1UCSF; 2AASK; 3Tufts.

Background: In extended follow-up of the Modification of Diet in Renal Disease (MDRD) study, we reported that strict BP control did not lower risk of ESRD but associated with lower mortality risk after ESRD (HR 0.72 [95% CI 0.58-0.89]) (Ku Ki 2015). To further address this issue, we conducted parallel analyses in the African American Study of Kidney Disease (AASK) and post-hoc pooled analyses of AASK and MDRD.

Methods: AASK randomized 1094 persons with CKD attributed to hypertension to either intensive (70/100mmHg) or conventional (90/120mmHg) antihypertensive therapy. In extended follow-up, we evaluated the effect of time-updated exposure to RAS blockade versus all other antihypertensive medications in obese, hypertensive, non-diabetic patients with normal or mildly reduced kidney function using a Cox proportional hazards model as estimated by pooled logistic regression to assess the hazards of developing a 50% reduction in estimated glomerular filtration rate (eGFR) or end stage renal disease. In addition to adjusting for baseline comorbidities including age, gender, socioeconomic status, cardiovascular disease, and body mass index (BMI), we adjusted for time-varying covariates including systolic blood pressure (SBP), number of antihypertensive medications, use of mineralocorticoid antagonists, and eGFR.

Results: There were 219,701 patients that met inclusion criteria, with a median 4.9 years of follow-up. Median baseline eGFR was 72.6 mL/min/1.73m², median SBP was 146 mmHg, and median BMI was 32.8 kg/m². 59% of patients were on RAS blockade at baseline, and 69% of patients were on it for at least half the duration of follow-up. Taking into account time-updated exposure, there was a significantly reduced hazard of adverse renal outcomes in patients treated with RAS blockade compared to those treated with other antihypertensive medications (HR 0.93, p<0.01).

Conclusions: This study, conducted in a large real-world cohort of patients with detailed and time-updated data about blood pressure treatment, provides important evidence that RAS blockade may protect against deterioration in renal function among obese, hypertensive, non-diabetic patients.

Funding: NIDDK Support

SA-PO617

Obesity, Renin-Angiotensin System Blockade, and Chronic Kidney Disease: A Population-Based Cohort Study


Background: Obesity substantially increases the risk of the development and progression of chronic kidney disease. Adipose tissue expresses all of the components of the renin-angiotensin system (RAS), which is an important contributing factor to the high prevalence of hypertension in obese patients, and drives renal hyperfiltration and subsequent glomerular injury.

Methods: We performed a retrospective cohort study using the Health Improvement Network, a primary care database with comprehensive demographic, laboratory, and pharmacy data on 300,000 patients. We evaluated the effect of time-updated exposure to RAS blockade versus all other antihypertensive medications in obese, hypertensive, non-diabetic patients with normal or mildly reduced kidney function using a Cox proportional hazards model with time-varying covariates including systolic blood pressure (SBP), antihypertensive medications, use of mineralocorticoid antagonists, and eGFR.

Results: There were 397 cases of ESRD and 475 deaths (208 after ESRD). The risk for ESRD was 0.94 (95% confidence interval [CI] 0.77-1.14), risk for death after ESRD onset was 0.78 (95% CI 0.63-0.98), overall mortality risk was 0.92 (95% CI 0.77-1.10), and risk for death after ESRD was 0.82 (95% CI 0.66-1.02). Taking into account time-updated exposure to RAS blockade versus all other antihypertensive medications in obese, hypertensive, non-diabetic patients using a Cox proportional hazards model with time-varying covariates including systolic blood pressure (SBP), antihypertensive medications, use of mineralocorticoid antagonists, and eGFR, there was a significantly reduced hazard of adverse renal outcomes in patients treated with RAS blockade compared to those treated with other antihypertensive medications (HR 0.93, p<0.01).

Conclusions: In this population-based cohort study, obesity was a significant risk factor for ESRD and death after ESRD. These data provide the most persuasive evidence to date that aggressive management of BP prior to ESRD may have a persistent benefit after ESRD onset.

Funding: NIDDK Support

SA-PO618

Distribution and Prognostic Value of Central Blood Pressure in Chronic Kidney Disease

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Background: Central blood pressure (CBP) has been shown to be a better predictor for cardiovascular events and target organ damages than brachial blood pressure. However, little is known about comparative values of CBP and brachial BP in chronic kidney disease (CKD) population. We investigated the distribution of CBP and evaluated the comparative value between CBP and brachial BP for the prediction of renal progression in both CKD and non-CKD population.

Methods: We conduct this study using data from 868 subjects who underwent CBP measurement by the radial artery tonometric method between 2009 and 2013. Demographic and clinical characteristics were obtained from a review of the medical records at the time of CBP measurement. The outcome was renal progression defined as decline of estimated glomerular filtration rate at least 30% from baseline follow-up.

Results: In overall, estimated central systolic BP (cSBP) was higher than brachial systolic BP (bSBP). The cSBP was significantly increased with age in non-CKD group, but such a correlation was not observed in CKD group. In CKD population, high cSBP group with greater than mean cSBP value (+150mmHg) had significantly increased probability of renal progression (P=0.016), while high bSBP (+140mmHg) did not predict the outcome (P=0.370). In contrast, the predictor of renal progression was high bSBP not cSBP in non-CKD population. In Cox analysis adjusted for covariates, high cSBP remained a predictor of renal progression in CKD population (HR 5.408; 95% CI 1.008-29.030; P=0.049), whereas high bSBP was not a significant predictor in non-CKD population (HR 2.891; 95% CI 0.786-10.650; P=0.110).

Conclusions: The CBP had different correlation with age and clinical significance according to presence or absence of CKD, and the high cSBP was strong independent predictor of kidney disease progression in CKD patients.

Funding: NIDDK Support

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Underline represents presenting author.
SA-PO619
Clinical Characteristics and Outcomes Associated with Resistant Hypertension in a Large Cohort of U.S. Veterans Caoba P. Kovesdy,1,2 Miklos Zsolt Molnar,3 Adriana Hung,4 Jan Ling Lu,5 John J. Sim,6 Robert B. Canada,2 Elvira Gosmanova,3 Fredjth Thomas,7 Kamary Kalantar-Zadeh.1,2 1VA Medical Center, Memphis, TN; 2Univ of Tennessee Health Science Center, Memphis, TN; 3VA Medical Center, Nashville, TN; 4Kaiser Permanente, CA; 5Univ of California, Irvine, CA.

Background: The prevalence of true resistant hypertension (RH), the characteristics of patients with RH and its association with clinical outcomes is unclear.

Methods: From 2,398,778 patients with essential HTN, we identified 95,334 (4%) with RH, defined as: Failure to achieve BP>140/90 mmHg with >=3 antihypertensives (one being a thiazide diuretic) or success with >=4 drugs; excluding measurements when patient score was <5; when interfering medications were prescribed and excluding those with confounding conditions (CKD, secondary HTN, sleep apnea, urinary obstruction, arterial, thyroid and parathyroid over-activity). We examined with mortality, incident CKD, ESRD, steeper slopes of eGFR, incident coronary heart disease (CHD) and stroke in Cox models and logistic regression models adjusted for demographic and socioeconomic factors, comorbidities, BP, and antihypertensives.

Results: The mean SBP/DBP in RH and non-RH patients were 148±22/81±14 vs. 137±19/78±12 mmHg. Compared to non-RH, patients with RH were older (64±11 vs. 62±13), more likely to be black (25 vs. 17%) and had a higher prevalence of DM and CVD. Crude mortality was similar and the incidence of the renal and cardiovascular end points was higher in RH. After full adjustment the risk of CHD and stroke associated with RH remained significant, but the risk of renal outcomes was reversed (Figure).

Conclusions: RH is relatively infrequent (4%) among patients with essential HTN, and is associated with older age and a higher comorbidity burden. Patients with RH have a higher risk of incident CHD and stroke.

Funding: NIDDK Support, Veterans Administration Support

SA-PO620
Association of Components of Body Mass Index with Treatment-Resistant Hypertension in Men and Women with Chronic Kidney Disease Toshiyuki Aoki,1 Yasushi Ohashi,2 Reibin Tai,3 Kiyoto Koibuchi,4 Atsushi Aikawa,5 Ken Sakai,6,7 1Nephrology, Toho Univ School of Medicine, Ohta-ku, Tokyo, Japan; 2Nephrology, Saiseikai Eastern Hospital, Yokohama, Kanagawa, Japan.

Background: Treatment-resistant hypertension is a risk for cardiovascular disease and end-stage renal disease. However, the appropriate clinical management strategies remain unclear in patients with CKD. Our objective is to investigate the association of components of body mass index (BMI) with treatment-resistant hypertension in patients with CKD.

Methods: Body fluid composition was measured in 310 patients with CKD from 2005 to 2014, and BMI was separated into 3 components – (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW), and (c) extracellular water (ECW). Treatment-resistant hypertension was defined as an office BP of ≥130/80 mmHg, despite receiving ≥3 antihypertensives including diuretics, or ≥4 drugs usage. Patients with resistant hypertension were more adverse renal outcomes, as defined by a decline of 50% or more from baseline GFR (one being a thiazide diuretic) or success with ≥4 drugs; excluding measurements when patient score was <5; when interfering medications were prescribed and excluding those with confounding conditions (CKD, secondary HTN, sleep apnea, urinary obstruction, arterial, thyroid and parathyroid over-activity). We examined with mortality, incident CKD, ESRD, steeper slopes of eGFR, incident coronary heart disease (CHD) and stroke in Cox models and logistic regression models adjusted for demographic and socioeconomic factors, comorbidities, BP, and antihypertensives.

Results: 19 patients (10 men; median age 56 (48; 57) years; BMI 30.9±2.8 kg/m²) with resistant hypertension were enrolled in the study. In all patient plasma renalase concentration was measured before and after 4 months. The average number of antihypertensive agents prescribed was 4.8 ± 0.8 classes per patient. 3 (17%) and 2 (11%) patients were considered adherent by direct method and pill count, respectively. However, the agreement between methods was poor (Kappa correlation coefficient -0.15).

Conclusions: Adherence to therapy in patients with resistant hypertension was very low in both methods. There was no agreement between pill count and direct method. The best method to assess adherence in resistant hypertension is yet to be determined.

Funding: Government Support - Non-U.S.

SA-PO621
Adherence Assessment in Resistant Hypertension: A Comparison Between Pill Count and Direct Method of High Performance Liquid Chromatography Analysis in Urine Patricio Cardoso Alarcon Horí, Silvana de Barros, Indira Fernandes Braga Azam, Andrea Pio de Abreu, Andrea Cassia Perreira Sforsin, Vanusa Barbosa Pinto, Décio Mion Junior, Giovanio Vieira da Silva. Nephrology and Pharmacy, General Hospital of Sao Paulo Univ, Sao Paulo, Brazil.

Background: Poor adherence to antihypertensive therapy is one of possible causes of resistant hypertension. Pill count is currently considered the standard for assessing drug adherence, but as an indirect method, it is inaccurate. The aim of this study was to compare the pill count with the direct method of toxicological urine screening in patients with resistant hypertension.

Methods: Patients with resistant hypertension criteria were included: office blood pressure (BP) above goal (systolic BP> 140mmHg and/or diastolic BP> 90mmHg) taking 3 or more antihypertensive agents of different classes, one of them diuretic, or office BP below goal taking 4 or more classes. Adherence was assessed by direct method of high performance liquid chromatography analysis for antihypertensive drugs or their metabolites in 4 different urine samples, with 30-day interval between them. Simultaneously, pill count was also performed. Patient was considered adherent by direct method if it was found every prescribed agents in at least 3 urine samples. Regarding pill count, patient was considered adherent if he consumed at least 90% of prescribed agents.

Results: 18 patients were selected: 78% women, age 57.5 ± 5.7 years, body mass index 29.3 ± 3.6 kg/m², office mean BP 151/88 ± 20/15 mmHg and 24 hours mean BP by ambulatory blood pressure monitoring 132/85 ± 21/12 mmHg. The average number of antihypertensive agents prescribed was 4.8 ± 0.8 classes per patient. 3 (17%) and 2 (11%) patients were considered adherent by direct method and pill count, respectively. However, the agreement between methods was poor (Kappa correlation coefficient -0.15).

Conclusions: Adherence to therapy in patients with resistant hypertension was very low in both methods. There was no agreement between pill count and direct method. The best method to assess adherence in resistant hypertension is yet to be determined.

Funding: Supported by FAPESP, CNPq.

SA-PO622
Plasma Renalase Concentration Before and After Radiofrequency Renal Denervation in Patients with Resistant Hypertension: Preliminary Results Marcin Adamieczak,1 Beata Czerwińska,1 Maciej T. Wybraniec,1 Michal Lelek,1 Katarzyna T. Mizia-Stec,2 Andrzej Wieciec,1 1Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland; 21st Dept of Cardiology, Medical Univ of Silesia, Katowice, Poland.

Background: Renalase is a catecholamine-metabolizing enzyme produced by proximal tubular cells in kidney which is supposed to be involved in blood pressure regulation. The aim of the study was to evaluate plasma renalase concentration after radiofrequency renal denervation (RDN) in patients with resistant arterial hypertension (HTN).

Methods: 19 patients (10 men; median age 56 (48; 57) years; BMI 30.9±4.4 kg/m² and eGFR 89±17.7 ml/min/1.73 m²) with resistant HTN were enrolled in the study. In all patient plasma renalase concentration was measured before and after RDN by ELISA method (Cloud-Clone Corp, Houston, USA).

Results: A significant decrease of both office systolic and diastolic blood pressure 6 months after RDN was found (192±31 vs. 177±28 mmHg, p=0.03; 113±23 vs. 99±21 mmHg, P=0.002, respectively). One and 3 months after RDN plasma renalase concentration decreased significantly, with a subsequent return to values comparable with baseline at 6- and 12-month follow-up (median of 22100 vs. 18550 vs. 17600 vs. 20750 vs. 20500 ng/mI respectively; Friedman analysis of variance p=0.054).

Conclusions: Plasma renalase concentration decreased significantly, with a subsequent return to values comparable with baseline at 6- and 12-month follow-up. These findings emphasize the importance of adequate weight and volume status.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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767A
Conclusions: RDN leads to the temporary decrease of plasma reninase concentration in patients with HTN. Lower plasma reninase concentrations seems to be a counteracted reaction to the antihypertensive effects of RDN.

Funding: Government Support - Non-U.S.

SA-PO623

A Non-Vascular Treatment for Resistant Hypertension  Richard R. Heuser,1 Adam Gold,2 1Cardiology, St. Luke’s Medical Center, Phoenix, AZ; 2Verve Medical, Scottsdale, AZ.

Background: Systematic arterial hypertension remains the most common and important risk factor for cardiovascular and renal disease. A safe and effective medical device effecting a significant and immediate fall in arterial BP addresses an unmet clinical need. Early clinical experience with the Verve non-vascular device causes an immediate BP drop in patients with resistant hypertension.

Methods: In humans, there is a greater abundance of efferent compared with afferent nerve fibers and the afferent nerves are much less abundant in general and are much less abundant as one goes away from the aorta. In contrast to the widespread distribution of EFFERENT Sympathetic nerve fibers in the kidney, the majority of the AFFERENT Renal Sensory nerves are located in the renal pelvic area. With our first generation device, we treated patients with resistant hypertension. Four patients with resistant hypertension were treated. They had immediate blood pressure drop (Systolic Mean 44mmHg, Diastolic Mean 13mmHg), which was maintained for 3 months. Because of the possibility of calyceal damage noted in follow-up in our animal model, we have redesigned the probe and shortened the duration of therapy.

Results: In over two dozen animals, it appears that we get a similar histopathologic results with our first generation probe without late pelvic or calyceal damage. In our first clinical application of this helical probe, there also is an immediate blood pressure drop.

Conclusions: Unlike other renal denervation treatments, the Verve natural orifice approach appears to treat the afferent nerves and results in an immediate blood pressure drop. More patients will need to undergo treatment to confirm these encouraging results. We will present our first series of resistant hypertensive patients treated with the helical device.

SA-PO624


Background: Preeclampsia is a hypertensive disorder of pregnancy associated high morbidity and mortality. Hallmarks of preeclampsia are endothelial damage and functional (e.g. proteinuria) and morphological renal aberrations. The only known remedy against this is the delivery of the placenta. Cell derived microparticles (MP) of different origins are elevated in preeclampsia but their mechanistic relevance is unknown. Preeclampsia is also associated with a pro-inflammatory condition but there are meager mechanistic insights into this as well.

Methods: To address these questions MP (endothelial or platelet derived) were injected into C57BI/6 pregnant mice and the pregnancy outcome (embryonic survival and growth, placenta morphology) was studied. Morphology of the kidney was studied using PAS staining and electron microscopy. Proteinuria was studied as a measure of renal dysfunction. To address mechanistic questions, inflammasome activation by MP in placenta and trophoblast cells was studied using western blotting and immunohistochemistry. Human trophoblast derived cells and placentas from pregnancies complicated with pre-eclampsia were also studied for activation of inflammasome. NLRP3 and Casp-1 KO mice were used to rescue the mice from disease conditions and establish causality of the mechanism.

Results: MP caused preeclampsia associated with fetal loss and embryonic growth restriction in mice. This was associated with renal damage indicated by proteinuria, glomerular enlargement, thickness of glomerular basement membrane, and podocyte effacement in the kidney. Human and mouse placenta analysis indicated inflammasome activation seen by elevated expression of NLRP3, cleaved casp-1 and IL-1β. The pregnancy outcome and renal function was rescued in NLRP3 and Casp-1 KO mice.

Conclusions: Our results establish that MP are causative of preeclampsia, fetal death, embryonic growth restriction, and renal injury. These pathogenic effects of MP are mechanistically linked with inflammasome activation in the placenta.

Funding: Government Support - Non-U.S.

SA-PO625

Short Term Sequela of Preeclampsia  Michael Yannik Girsberger,1 Irene Mathilde Hoelsi,2 Michael Dickenmann. 1Clinic for Transplantation Immunology and Nephrology, Univ Hospital Basel, Basel, Baselstadt, Switzerland; 2Dept of Gynaecology and Obstetrics, Univ Hospital Basel, Basel, Baselstadt, Switzerland.

Background: Data on sequela in the first year after preeclampsia are scarce. We investigated kidney function, blood pressure, proteinuria and urine sediment in women with preeclampsia six month after delivery.

Methods: From January 2007 to July 2014 all women with preeclampsia and 6-months follow up at the university hospital Basel were prospectively analysed. Preeclampsia was defined as new onset of hypertension (³140/90 mmHg) or worsening hypertension and either proteinuria or signs of end-organ dysfunction. Hypertension was defined as a blood pressure (BP) ³140/90 or the use of antihypertensive medication. Proteinuria was defined as a protein-to-creatinine ratio in a spot urine > 11 mg/ml. Urine sediment was evaluated by a nephrologist.

Results: 202 women were included. Baseline characteristics are shown in Table 1 and follow up data are shown in Figure 1. The mean time of the follow up visit was 172 days (+/- 39.6) after delivery. The mean blood pressure at follow up was 124/76 mmHg (+/- 14/11, range 116-182/63-110) and the mean serum-creatinine was 61.8 umol/l (+/- 11.6). Mean estimated glomerular filtration rate (CKD-EPI) was 110.7 ml/min/1.73m2 (range 59.7-142.4 ml/min/1.73m2). No active urine sediment (e.g. signs of glomerulonephritis) was observed.

Conclusions: The findings stress the importance of a close follow up to identify those women who need further care.

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SA-PO626  
Preeclampsia: Long-Term Effects on Pediatric Neurologic Disability  
Alberto Tejedor Jorge, Clara Nicolas, Patrocínio Rodrigues Benitez, Olga Arroyo, María Silva, Laura Matesanz, Carmela Mercurio, Manuel Sánchez Luna.  
*Hospital General Univ Gregorio Marañón.*

**Background:** Preeclampsia affects up to 10% of pregnancies worldwide and is one of the main causes of fetal morbidity and mortality. Although it has been linked to developmental delay, its long-term effects on neurologic development in children have yet to be sufficiently quantified. Our aim is to evaluate whether the preeclampsia’s severity and the therapeutic options used to manage it correlate to the degree of developmental delay in these infants.

**Methods:** This is an observational and descriptive study performed on a population of 96 women who were diagnosed with preeclampsia at Hospital General Universitario Gregorio Marañón between 2007 and 2014, and their 111 children. To evaluate the mother, we gathered data pertaining to her medical history, renal function markers, and medical management of the preeclampsia. To assess the children, we collected fetal growth measurements, acute fetal distress markers and main diagnoses at birth. We used the Pediatric Disability Inventory in its computerized adaptive test version (PEDI-CAT) to study neurologic development, and the TNO-AZL Preschool children Quality of Life (TAQPOL) to estimate health-related quality of life.

**Results:** Early-onset and more severe preeclampsias were associated with higher preterm birth and perinatal mortality rates. Preeclampsias with a greater impact on maternal organ function showed a clear correlation to higher periventricular-intraventricular hemorrhage rates in the newborn. In terms of neurologic development, PEDI-CAT percentiles were consistently lower in the Social/Cognitive domain than in other areas. Lower Social/Cognitive percentiles were associated to both lower maternal IgG levels and presence of necrotizing enterocolitis during the neonatal period.

**Conclusions:** Early-onset preeclampsias have a greater negative impact on both maternal renal function and fetal morbimortality. A connection between preeclampsia and poor social/cognitive outcomes exists that warrants further research, as does the possible link between between preeclampsia, immaturity, and autistic features.

SA-PO627  
Do Hypertension Providers Inquire About Hypertension in Pregnancy?  
Andrew G. Kattah, Vesna D. Garovic. *Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

**Background:** Hypertensive pregnancy disorders are increasingly recognized as a risk factor for future hypertension and cardiovascular disease. However, knowledge of this risk may be inadequate among internal medicine providers.

**Methods:** We reviewed all new consults in a 2-month period in a hypertension subspecialty clinic. We determined the frequency with which providers documented a reproductive history, a history of hypertension in pregnancy and known cardiovascular risk factors. We also studied whether there were differences according to gender and level of training of the provider (consultants vs. residents/fellows) using the chi-square test.

**Results:** There were 102 consults for hypertension in the study period. The majority of consults were by consultants, 55/102 (53.9%), and 23/102 (22.6%) were by female providers. A reproductive history, including number of pregnancies, infertility and/or intent of pregnancy, were documented in 37/102 (36.3%) of notes. Chart review revealed that 85/96 (89%) of women had live births, but it was documented in only 31 (36.3%) of notes. Female providers were more likely to document pregnancies (36.3% vs. 30.3%, p=0.03). Of the women who had live births, 15/85 (17.7%) of providers inquired about hypertension of pregnancy, were documented in 37/102 (36.3%) of notes. Chart review revealed that knowledge of this risk factor for future hypertension and cardiovascular disease. However, knowledge of this risk may be inadequate among internal medicine providers.

**Conclusions:** Even in a minority, inner city population we found significant correlation between the 24 hour protein excretion and the SP/Cr ratio, especially in the 2nd and 3rd trimesters of preeclampsias. Our findings are in line with the literature despite a minority patient population.

SA-PO628  
Thiazide Diuretics for Hypertension in Kidney Transplant Recipients Using Tacrolimus  
Arthur David Moes, Dennis Alexander Hesselink, Anton H. van den Meiracker, Robert Zietse, Ewout J. Hoorn. *Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands.*

**Background:** Hypertension after kidney transplantation is common and associated with poorer graft and recipient outcomes. Recently, we and others showed that tacrolimus activates the thiazide-sensitive sodium chloride cotransporter to cause hypertension. This suggests that thiazide diuretics may be especially effective drugs in this context, but prospective data are lacking.

**Methods:** We conducted a non-inferiority crossover trial to compare chlorthalidone (CT, 12.5-25 mg) with amlopidine (AML, 5-10 mg). Patients were invited for ambulatory blood pressure measurement (ABPM) if office BP >140/90 mmHg. Other criteria included eGFR >30 ml/min, proteinuria > 1 g, and no use of glucocorticoids. The treatment periods were randomized, lasted 8 weeks (allowing dose titration after 2 weeks), and were separated by a 2-week wash-out. Background anti-hypertensive drugs were allowed except for other diuretics.

**Results:** 71 patients underwent initial ABPM of whom 45 patients (63%) with average wake SBP >140 mmHg were enrolled (median 2.6 years after transplantation). 38 patients completed the study (5 patients stopped during CT mainly due to electrolyte disorders vs. 2 during AML, p=0.4). CT and AML both markedly reduced ABPM after 8 weeks (151/85 ± 119/81 ± 12/9 mmHg vs. 151/84 ± 13/9/79 ± 14/7 mmHg). There was no statistically significant in blood pressure response between the two drugs (p=0.3 by 2-way ANOVA). Dose titration rates were similar (42% for CT vs. 37% for AML, p=0.8). CT decreased eGFR (53 ± 17 to 46 ± 15 ml/min), whereas amlopidine increased it (50 ± 16 to 53 ± 17 ml/min, P=0.001). The first post-CT eGFR returned to baseline (51 ± 17 ml/min). Treatment with CT resulted in less proteinuria (median 14 vs. 19 mg/mmol, p=0.03) and less edema (8 vs. 31%, p=0.02). Regression analysis showed that a higher aldosterone to renin ratio, lower baseline serum potassium, and higher baseline serum bicarbonate predicted a better anti-hypertensive response to CT.

**Conclusions:** Thiazide diuretics effectively lower blood pressure in kidney transplant recipients using tacrolimus. Thiazides are especially effective in patients with more aldosterone effect.

<table>
<thead>
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<th>Risk Factor, n(%)</th>
<th>Resident/Fellow (n=47)</th>
<th>Consultant (n=55)</th>
<th>P-value</th>
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<tr>
<td>Dietary issues</td>
<td>29 (62%)</td>
<td>32 (58%)</td>
<td>0.72</td>
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<tr>
<td>Alcohol Use</td>
<td>37 (79%)</td>
<td>36 (55%)</td>
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<td>Illicit Drug Use</td>
<td>16 (34%)</td>
<td>2 (4%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Smoking</td>
<td>41 (87%)</td>
<td>47 (85%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Exercise</td>
<td>27 (55%)</td>
<td>29 (53%)</td>
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<tr>
<td>Medication-related effects</td>
<td>32 (68%)</td>
<td>31(56%)</td>
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</tr>
<tr>
<td>Family History of Hypertension</td>
<td>43 (92%)</td>
<td>38 (69%)</td>
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<td>Renal Disease</td>
<td>44 (94%)</td>
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<td>Dyslipidemia</td>
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<td>Obstructive Sleep Apnea</td>
<td>22 (47%)</td>
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<tr>
<td>Hypertension in Pregnancy*</td>
<td>5/36 (14%)</td>
<td>10/49 (20%)</td>
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</tbody>
</table>

*Only in women with live births
SA-PO630

The Detrimental Effects of Beta-Blockers on Central Hemodynamic Parameters: A Propensity Score Analysis

Reemi Gouni,1 Dominique Dupuis,1 Stephan Troyanov,1 Francois Madore,1 Mohsen Agharazi,2 1Hôpital du Sacré-Cœur de Montréal, Montréal, QC, Canada; 2CHU de Québec, Hôtel-Dieu de Québec, Québec City, QC, Canada.

Background: Central blood pressure (BP) and arterial stiffness are better predictors of the cardiovascular burden than peripheral BP. Beta-blockers (BB) are known to reduce central BP to a lesser extent than peripheral BP, a hypothesized consequence of heart rate (HR) reduction. Therefore, the association between BB use, HR and central hemodynamics indices were studied in the treated hypertensive participants of the CARTAGENE study.

Methods: Using propensity score analyses, BB users (n=605) were matched to controls having similar clinical characteristics with (Model 1) and without (Model 2) adjustment for HR. This resulted in 457 and 510 pairs with adequate balance, except for a different HR in Model 2 (62.5 ± 10.5 vs. 70.4 ± 11.5 bpm, p<0.001).

Results: In Model 1, the difference between peripheral and central systolic BP (DSBP) was 8.3 mmHg (IQR 5.8, 11.6) with BB compared to 9.7 mmHg (7.1, 13.5) without (p<0.001), indicating that for any given peripheral BP, BB use resulted in higher central systolic BP. Pulse pressure amplification, augmentation index and augmented pressure were also less favorable with the use of BB. The different HR in Model 2 further increased the detrimental DSBP observed with BB to 7.9 (5.6, 11.0) vs. 10.6 (8.1, 14.3) without (p<0.001) and was associated with a higher central pulse pressure (46.5 ± 13.0 vs. 43.3 ± 11.3, p<0.001).

Conclusions: This study shows that the unfavorable central hemodynamic profile of BB has both a HR-dependent and a HR-independent component.

Funding: Government Support - Non-U.S.

SA-PO631

Risk of Development of Dementia During Treatment of Hypertension with Different Calcium Channel Blockers

Leonid Feldman,1 Shai Efrati,2 Ilia Beberashvili,1,2 Shlomo Vinker,2,3 Michail Shami,3 1Assaf Harofeh Medical Center, Israel; 2Tel Aviv Univ, Israel; 3Clalit Health Services, Israel.

Background: Arterial hypertension (HTN) is a risk factor for development of dementia. Medical treatment of HTN may decrease the risk of dementia. Experimental study pointed to the possibility of difference between different calcium channel blockers (CCB) in their neuro-protective effect. The aim of our study was to evaluate the risk of dementia during treatment of HTN with one of three different CCBs.

Methods: This is a retrospective cohort study based on electronic database of Clalit Health Services, Central District. Study period was 11 years (2002-2012). Inclusion criteria: age 40-75, diagnosis of HTN without diagnosis of “Dementia” at the starting point, minimal duration of treatment >30 months with single specific CCB. New diagnosis of dementia was established according to appearance of its diagnostic code in the chronic diseases register or prescription of medication for its treatment – whatever occurred first.

Results: 15,664 patients were included in the study: 3,884 were treated with amlodipine, 2,062 - with nifedipine, 699 – with lercanidipine and 9,109 never received CCBs. The mean age was 60.7 years, 52.9% were females and the mean baseline creatinine was 1.0 mg/dL. 2,062 - with nifedipine, 609 – with lercanidipine and 9,109 never received CCBs. The mean age was 60.7 years, 52.9% were females and the mean baseline creatinine was 1.0 mg/dL.

Conclusions: The unfavorable central hemodynamic profile of BB has both a HR-dependent and a HR-independent component.

Funding: Government Support - Non-U.S.

SA-PO632

The Association Between Antihypertensive Agents and Postural Blood Pressure Response Using Beat-to-Beat Data: Results from the Irish Longitudinal Study on Ageing

Mark N. Conneely,1 Matthew DI O’Connell,1 Catriona M. Murphy,2 Mark Alan Little,2 Conall M. O’Seaghdha,2 Rose Anne M. Kenny,1 1The Irish Longitudinal Study on Ageing, Trinity College Dublin; 2Trinity Health Kidney Centre, Tallaght Hospital Dublin, 3Dept of Nephrology, Beaumont Hospital Dublin.

Background: Beat-to-beat blood pressure (BP) measurements provide a dynamic picture of BP behavior during postural change. Impaired BP stabilization after standing is associated with substantial morbidity and mortality. We aimed to define the relationship between class of antihypertensive drug and BP stabilization during an active stand.

Methods: Cross-sectional analysis from The Irish Longitudinal Study on Ageing, a nationally representative cohort study of 8175 adults ≥50 years. Beat-to-beat BP was recorded in participants undergoing an active stand test. We defined grade 1 hypertension according to European Society of Cardiology criteria (systolic BP [SBP] ≥140-159mmHg or diastolic BP [DBP] ≥90-99mmHg). Orthostatic hypotension (OH) was defined as a drop in SBP ≥20mmHg or DBP ≥10mmHg. Outcomes were sustained OH (OH throughout the test) and impaired BP stabilization (OH at each 10-second (s) interval during the test [total 110s]). Outcomes were assessed using logistic regression models adjusted for potential confounding variables.

Results: A total of 536 participants with self-report hypertension were receiving monotherapy with a renin-angiotensin-aldosterone-system inhibitor (317), beta-blocker (89), calcium channel blocker (89) or diuretic (41). Betablockers were associated with increased odds of sustained OH vs untreated grade 1 hypertension (OR 3.4, 95% CI 1.9-6.0). This was evident from 20s after starting the study. Multivariable adjustment did not attenuate the association. No significant association was detected among the other drug classes.

Conclusions: In older hypertensive adults beta-blocker monotherapy was associated with a 3-fold increased odds of OH compared to subjects with untreated grade 1 hypertension. The effect was evident from 20s after standing and was sustained. This should inform decision-making regarding appropriate choice of antihypertensive agent in older adults.

Funding: NIDDK Support

SA-PO633

Effect of Vitamin D on 24 Hour Ambulatory Blood Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Ciaran Joseph McMullan,1 Lea Borgi,2 Gary C. Curhan,2 Naomi D.L. Fisher,3 John P. Forman.2 1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Endocrine Div, Brigham and Women’s Hospital, Boston, MA.

Background: Lower levels of 25-hydroxyvitamin D (25(OH)D) have been associated with an increased risk of hypertension in prospective cohort studies, suggesting that vitamin D might be a modifiable target for the prevention of hypertension. Vitamin D supplementation has also been shown to decrease clinic blood pressure (BP) in some studies.

Methods: We performed a randomized, double-blind, placebo-controlled trial of nonhypertensive participants with body mass index ≥25, and 25(OH)D<20ng/ml; subjects were randomized to receive either ergocalciferol 50,000 units or placebo, once a week for 8 weeks. Mean 24 hour BP was measured using 24 hour ABPM at baseline and 8 weeks after starting the study.

Results: By the end of the trial, 29 and 27 participants randomized to receive vitamin D and placebo, respectively, had adequate 24 hour ABPM at both baseline and at 8 weeks. Mean vitamin D levels increased from 14.9 to 30.3 ng/ml in the intervention group and from 14.4 to 17.4 ng/ml in the placebo group. Vitamin D supplementation did not lower BP at 8 weeks; 24 hour systolic BP changed from 120±10 to 122±18 mmHg in the intervention group (p-value=0.29), and from 124±8 to 125±10 mmHg in the placebo group (p-value=0.38), with a treatment effect p-value of 0.92.

Conclusions: In this randomized, double-blind, placebo-controlled trial of overweight/ obese normotensive individuals, there was no improvement in mean 24 hour blood pressure after repletion of vitamin D. These findings are not consistent with vitamin D being a modifiable target for prevention of hypertension.

Funding: NIDDK Support

SA-PO634

Effect of Uric Acid Lowering on Intrinsic Renal and Systemic Renin Angiotensin System Activity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Ciaran Joseph McMullan,1 Lea Borgi,2 Gary C. Curhan,2 Naomi D.L. Fisher,2 John P. Forman.2 1Renal Div, Brigham and Women’s Hospital, Boston, MA; 2Endocrine Div, Brigham and Women’s Hospital, Boston, MA.

Background: Higher levels of uric acid have been associated with an increased activity of the renin-angiotensin system (RAS) in animal models of hypertension and kidney disease. Similarly, individuals with high levels of circulating uric acid have increased renal specific RAS activity measured using renal plasma flow (RPF). However, the effect of lowering serum uric acid on RAS activity in humans is unknown.

Methods: We performed a randomized, double-blind, placebo-controlled trial analyzing the Modifiable Effectors of Renin System Activation Treatment Evaluation (MODERATE). Normotensive individuals with body mass index (BMI) ≥25 and uric acid level ≥ 5.0 mg/
Effect of Vitamin D Supplementation on Intrinsic Renal and Systemic Renin Angiotensin System Activity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial  

Background: Disruption of vitamin D signaling in rodents causes activation of the renin-angiotensin system (RAS). In humans low circulating 25[OH]D is associated with increased renal specific RAS activity (measured using renal plasma flow [RPF]; in addition, a small, open label, uncontrolled study found that vitamin D supplementation decreased renal specific RAS activity. However, the effect of vitamin D supplementation on the RAS in humans with vitamin D deficiency has never been examined in a rigorous manner.

Methods: We performed a randomized, double-blind, placebo-controlled trial of normotensive individuals with body mass index <25 and vitamin D deficiency (25[OH]D ≤20ng/ml). Subjects were assigned to receive either ergocalciferol 50,000 units or placebo, once a week for 8 weeks. Renal specific (assessed by RPF response to captopril in high sodium balance) and systemic RAS activity (plasma renin activity [PRA] and angiotensin II levels [AngII]) were measured at baseline and 8 weeks after starting the study.

Results: By the end of the trial, 43 and 41 participants allocated to receive vitamin D and placebo, completed the study with measurement of renal and systemic RAS activity. Mean vitamin D levels increased from 14.9 to 30.3 ng/ml in the ergocalciferol group and from 14.4 to 17.4 ng/ml in the placebo group. Renal specific RAS did not significantly change after vitamin D repletion: the RPF response to captopril was 33.9±56.1 ml/min at baseline and 35.7±47.7 ml/min at 8 weeks in the ergocalciferol group (p-value=0.26); and was 37.3±46.9 ml/min at baseline and 35.9±26.2 ml/min at 8 weeks in the placebo group (p-value=0.70), with a treatment effect p-value of 0.27. Similarly, vitamin D supplementation had no effect on PRA or AngII levels.

Conclusions: In contrast to animal experiments, observational studies, and open-label uncontrolled interventions, this randomized, double-blind, placebo-controlled trial found no effect of vitamin D supplementation on RAS activity in vitamin D deficient individuals.

Funding: NIDDK Support

Comparison of Office Orthostatic Blood Pressure and 24-Hour Ambulatory Blood Pressure Measurements in the Prediction of Autonomic Dysfunction  

Background: Evaluation of orthostatic hypotension (OH) may involve office orthostatic blood pressure (BP) measurements, 24-hour ambulatory BP (ABP) and autonomic reflex screen (ARS). We investigated the predictive performance of BP and the variables of ABP, i.e., reversal of circadian pattern (RCP), postprandial hypotension (PPH) and noncompensatory heart rate variability (HRV), to predict autonomic dysfunction as measured by the AUC of the ROC curves.

Methods: Data from previously published study were analyzed. Ninety-four patients were included for analysis. BP\textsubscript{OP}, RCP, PPH, HRV were investigated for the presence or absence of autonomic dysfunction. Autonomic dysfunction was defined as a CASS (composite autonomic scoring system) score of 1. Comparisons of the AUCs of the ROC curves of the candidate parameters were performed.

Results: ROCs of candidate parameters are shown in Fig. 1.

Funding: Government Support - Non-U.S.

Comparison of Office Orthostatic Blood Pressure and 24-Hour Ambulatory Blood Pressure Measurements in the Prediction of Autonomic Dysfunction  

Background: Blood pressure measurement (BPM) is a common procedure in clinical practice but in children (C) obtaining reliable values can be challenging. Casual office BPM, the standard of care, is all but accurate and ABPM may be difficult to perform or even misleading.

Methods: Office Blood Pressure Monitoring (OBPM) was developed at our Center in 2010 for evaluating BP in C with serial and automated ABPM (10 in at least 30 min)

The diagnostic performance to predict autonomic dysfunction for HRV was superior to PPH. Both were superior to RCP. RCP was a better predictor of autonomic dysfunction than office BP.

Conclusions: Our data suggests that ABP is a reliable, simple and inexpensive predictor of autonomic dysfunction in routine clinical practice.
with a standard oscillometric device. BP values are uploaded in a software to calculate the coefficient of variation (CV) after having excluded outlier values (< 5% and > 95% centiles of the recorded values).

Results: Since 2010 a total of 402 OBPMs have been performed but only the 282 in 110 C (59% Males) aged <18 yrs old (IQR 4.8-12.1) with a CV <10% for both syst and diast BP were considered for the analysis. The table compares BP as measured by OBPM with a single BPM (1st and 3rd) and with the mean of the 3 initial measurements (*: p<0.01 vs. others BPMs with student’s t test for paired data and c²).

Conclusions: OBPM provides significantly lower BP values, leading to a diagnosis of poor BP control in a smaller number of patients (~10%). Given the lack of a gold standard, the present analysis doesn’t demonstrate that OBPM is more reliable than standard procedures however serial BPM have the potential of reducing measurement biases and white coat effect. We recommend the routine use of OBPM for measuring BP in C at risk of hypertension rather then relying upon few measurements.

SA-PO639
A Simple Prediction Score for Incident Hypertension in a Korean Population
Jong-Hwan Jung, Sung Kwang Park, Won Kim, Kyung Pyo Kang, Sik Lee.
Dept of Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Republic of Korea.

Background: We aimed to develop a simple prediction model for incident hypertension that could help to prevent or delay the onset of hypertension for some patients who did not experience hypertension yet.

Methods: The Korean Genome and Epidemiology Study was used for the model development (n=3533) and internal validation (n=1069). Hypertension was defined when experience hypertension yet.

Results: OBPM, age and DBP, parental hypertension, obesity, high density lipoprotein (HDL), current smoking and fasting glucose were significantly associated with incident hypertension. Integer scores were assigned to variables based on the magnitude of the coefficient of variation (CV) after having excluded outlier values (< 5% and > 95% centiles of the recorded values).

Conclusions: OBPM provides significantly lower BP values, leading to a diagnosis of poor BP control in a smaller number of patients (~10%). Given the lack of a gold standard, the present analysis doesn’t demonstrate that OBPM is more reliable than standard procedures however serial BPM have the potential of reducing measurement biases and white coat effect. We recommend the routine use of OBPM for measuring BP in C at risk of hypertension rather then relying upon few measurements.

SA-PO640
Hemodynamics and Cardiovascular Autonomic Efficiency During Blood Pressure Variations in Hemodialysis
Dan Sapoznikov, Rebecca Backenworth, Dvora Rubinger. Nephrology and Hypertension Services, Hadassah Univ Medical Center, Jerusalem, Israel.

Background: Chronic hemodialysis (HD) is associated with hematologic instability and with reduced cardiovascular autonomic efficiency (CaE).

Methods: To define hemodynamic changes associated with intradialytic blood pressure variations, beat-to-beat systolic blood pressure (SBP) and interbeat interval (IBI) monitoring using Finometer device and Beatscope software was performed during HD sessions in 69 non-diabetic patients (Pts), age 56±15 yrs. Cardiac output (CO) and total peripheral resistance (TPR) were calculated using the Modelflow simulation method. Differences in variability indices during SBP periods, 10% above (high) or below (low ) the mean SBP were considered representative of CaE.

Results: During low to high SBP periods, two patterns of changes were noted: increased CO and decreased TPR (18 Pts,TPR↓), and relatively stable CO with increased TPR (51 Pts, TPR↑). Low frequency (LF) range variability of SBP and IBI, CO and TPR (median and interquartile ranges) were:

Conclusions: OBPM provides significantly lower BP values, leading to a diagnosis of poor BP control in a smaller number of patients (~10%). Given the lack of a gold standard, the present analysis doesn’t demonstrate that OBPM is more reliable than standard procedures however serial BPM have the potential of reducing measurement biases and white coat effect. We recommend the routine use of OBPM for measuring BP in C at risk of hypertension rather then relying upon few measurements.

SA-PO641
Antihypertensive Medications and Blood Pressure Control in Chronic Kidney Disease: A Cross-Sectional Analysis from the German Chronic Kidney Disease (GCKD) Study
Karl F. Hilleger,1 Matthias Schmid,2 Silvia Huebner,1 Martin Busch,1 Seema Baid-Aigrawal,1 Anna Kottgen,3 Georg Schlieper,1 Claudia Sommerer,1 Gunter B. Wolf, MHBA,1 Uwe Eckardt,3 Univ Hospital Erlangen;3 Univ of Bonn;1 Univ Hospital Jena;1 Charite Medical School;1 Univ of Freiburg; 2RWTH Univ Hospital, 3Univ Hospital Heidelberg, Germany.

Background: We reported low rates of blood pressure (BP) control in a large German cohort of patients with chronic kidney disease (CKD). Here, we analyzed the antihypertensive drug therapy to assess the prevalence of resistant hypertension, and to determine associations with control of BP.

Methods: The German Chronic Kidney Disease (GCKD) study is a prospective observational cohort study which enrolled 5217 patients with CKD in Germany. Inclusion criteria were an estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m2 or overt proteinuria. At enrollment, office BP was measured by trained study nurses, and information on medications was collected from patients.

Results: Office BP was obtained from 5181 participants, 4958 (95% ) were classified as hypertensive (>= 140/90 mmHg or use of antihypertensive medication). In 2410 (49%) hypertensive patients, BP was controlled (defined as < 140/90 mmHg). Inhibitors of the renin-angiotensin system (RAS; ACE inhibitors, sartans and aliskiren) were the most prescribed class of antihypertensive drugs (56%), followed by beta-blockers (29%), diuretics (16%), calcium channel blockers (12%) and CCB (8%). In addition, 23% of patients received 2 or more different antihypertensive substances. Of the patients with uncontrolled hypertension, 49.9% met the definition of resistant hypertension (uncontrolled diastolic BP ≥ 90 or use of antihypertensive substances, including a diuretic). In multivariate analysis, RAS inhibitors were associated with better control of BP (odds ratio 1.48, p<0.001), as were diuretics (odds ratio 1.16, p=0.036).

Conclusions: Resistance hypertension was present in 49.9% of CKD patients whose BP was not controlled. RAS inhibitors were widely used and associated with better odds for controlled BP whereas the use of diuretics was less frequent than expected.

Funding: Private Foundation Support, Government Support - Non-U.S.
SA-PO642

Associations Between Cystatin C Based eGFR, Ambulatory Blood Pressure Parameters, and In-Clinic versus Ambulatory Blood Pressure Agreement in Older Community-Living Adults

Tyler Woodell, Jan M. Hughes-Austin, Tiffany Tran, Atul Malhotra, Joseph A. Abdelmalek, Dena E. Rifkin.
UC San Diego.

Background: Although CKD IV-V has been associated with abnormal ambulatory blood pressure (ABP) patterns, the associations with milder CKD have not been determined. We examined the relationship between mild chronic kidney disease (measured by cystatin C-based eGFR) and abnormal ABPM (including nocturnal dipping) in healthy older adults. Further, we assessed agreement between clinic and ambulatory blood pressure monitoring.

Methods: 334 older community-living adults had clinic BP and 24-hour ABPM measured. Serum cystatin C levels were used to calculate eGFRs using the CKD-EPI equation. Multiple linear regression was performed to examine associations between eGFR < 60 ml/min/1.73m2 (CKD-eGFR) and ABPM parameters. Bland-Altman analysis was performed to evaluate agreement between clinic and ambulatory measurements.

Results: Average age was 72. Average eGFRs were 78 ± 20, and 60 individuals with CKD-eGFRs. Compared to those without CKD-eGFRs, individuals with CKD-eGFRs were older, more likely to have clinic-based hypertension and less likely to be dipper. After multivariable analysis, the presence of CKD-eGFRs was significantly associated with lower mean ambulatory diastolic blood pressure (DBP) (-2 mm Hg, p = 0.048), but not with nocturnal dipping or other ABPM parameters. Analyses using creatinine-based eGFR yielded similar results. Clinic systolic blood pressure (SBP) significantly overestimated mean wake time ambulatory SBP; mean difference was 11 mmHg for those without CKD-eGFRs (95% limits of agreement -5 to 35 mmHg) and 14 mmHg for those with CKD-eGFRs (95% limits of agreement -13 to 41 mmHg); there was no statistically significant effect modification by CKD status.

Conclusions: In older community-living adults, mild CKD as detected by cystatin C was associated with lower ambulatory DBP but not with dipping status. This result is in contrast to findings with more advanced CKD in other studies and suggests that abnormal ABPM may only emerge at more advanced stages of CKD. The presence of CKD did not affect interpretation of clinic vs. ABPM pressures, although accuracy of clinic SBP was poor in this older cohort.

Funding: NIDDK Support

SA-PO643

Serum MicroRNA Biomarkers for Obese Children with Hypertension
Scott Saint-Amour, Santosh Kumar Patnaik, Sudha Garamella. Pediatric Nephrology, Univ at Buffalo, Buffalo, NY; Cardiothoracic Lab, RPCI, Buffalo, NY.

Background: Childhood obesity is a major health problem and 30% of obese children may develop hypertension. There is no clinical method to identify high risk obese children before they develop hypertension. MicroRNAs are non-coding RNAs that are implicated in pathways of inflammation and vascular injury. There has been no characterization of miRNA profiles of obese children with hypertension. This study aims to characterize miRNA profiles as a first step toward evaluating miRNAs as biomarkers for obesity-related hypertension.

Methods: 39 patients ages 3-21 were placed in four cohorts based on presence or absence of obesity and hypertension. Total serum RNA was isolated using miRcURYBiofluids kit Exiqon®, and examined for miRNAs by RT-PCR. Cβ values were normalized by the global mean method. Rates of false discovery (FDR) arising from multiple testing were assessed from P values with the Benjamini-Hochberg method.

Results: 69 of 179 examined miRNAs were detected in all samples. MiRNA measurements were globally reduced in sera of obese normotensive Vs. controls. Four miRNAs were identified as differentially expressed between these two groups at FDR <10%, whereas no miRNA was identified as differentially expressed between controls and hypertensive obese. Tukey plots of miRNAs in the cohorts are shown.

Conclusions: Serum levels of four miRNAs appear to be reduced in patients with obesity alone, but not in those with obesity and hypertension. While it is possible that these serum miRNA differences were because of variables such as serum lipid content and medications, our study suggests that serum miRNAs have utility in detecting hypertension risk in obese children. This should be validated in a larger study, and the biomarker value of the serum miRNAs correlated with ambulatory blood pressure monitoring data as well as left ventricular hypertrophy.

Funding: Pharmaceutical Company Support - Roswell Park Cancer Institute Support to Dr. Sai Yendamuri in the Cardiothoracic Lab at RPCI was used for this study.

SA-PO644

Effect of Prenatal and Childhood Lead Exposure on Blood Pressure at 4 Years of Age

Background: Prenatal lead (Pb) exposure occurs during a susceptible period of renal development and may program later life cardiovascular and renal disease.

Methods: Systolic and diastolic blood pressure (SBP and DBP) was obtained using an automated oscillometer from 397 children at 4 years of age in the PROGRESS cohort located in Mexico City. Maternal blood samples were previously collected at the 2nd trimester (2T), 3rd trimester (3T), and at delivery and children’s blood samples were collected at birth (cord blood), 1 year, and 2 years of age. Blood lead levels (BLLs) were analyzed via inductively coupled plasma-mass spectrometry. We performed linear regression to examine the associations between longitudinal BLLs and children’s SBP, DBP, and pulse pressure (mSBP + mDBP) adjusting for child’s age, sex, body mass index, maternal education and environmental tobacco smoke.

Results: Maternal 2T BLLs ranged between 0.7 and 18.8 mg/dL, and 89 (22%) prenatal BLLs were above the CDC guideline level of 5 mg/dL. Increased 2T and 3T BLLs were associated with decreased pulse pressure (p<0.05) and modestly associated with increased DBP (p=0.1).

No significant associations were observed for childhood BLLs and BP. Stratification by sex showed that the effect of prenatal Pb (2T and 3T) on decreased pulse pressure was significant only among females.

Conclusions: Prenatal Pb exposure may contribute to subclinical changes in the developing kidney or cardiovascular system leading to elevated BP in childhood. Future studies will assess if the contributions of early life Pb exposure to BP outcomes persist at later life stages.

Funding: Other NIH Support - Supported by grants from the NIHES R42ES016454; R01ES013744; R01ES021357; R01ES020268; P50ES023515.

SA-PO645

Smoking, Microalbuminuria and Renal Function in Essential Never Treated Hypertensive Patients
Dimitrios Petras,1 Vanessa Tzamou,2 Athanasios Bramos,1 Panagiota E. Giannou,2 Stella-Maria Kyvelou,1 Eva Karpanou,1 Gregory Vysoulis.1 Nephrology Dept, Hippokration Hospital, Athens, Greece; 21st Cardiology Clinic, Onassis Cardiac Surgery Center, Athens, Greece; Hypertensive Unit, 1st Cardiology Clinic, Univ of Athens, Hippokration Hospital, Athens, Greece; Microbiology Dept, Hippokration Hospital, Athens, Greece.

Background: The aim of the present study was to identify possible differences depending on patient’s individual smoking history with renal function and microalbuminuria in essential never treated hypertensive patients.

Methods: The study included 6100 consecutive patients with essential hypertension. In each patient the smoking status has been assessed by means of a standard questionnaire. Each patient had renal profile work up including microalbumin levels, albumin creatinine ratio in 24h urine collection (ACR) and 24h creatinine clearance.

Results: The study population was divided according to the smoking status in three groups: Smokers (n=2350), Ex-smokers (n=663) and Non-smokers (n=3121). Microalbumin at ACR was significantly higher in smokers compared to ex-smokers and non-smokers ([26.3±24.3 vs 23.6±21.7 vs 22.0±20.0, p<0.0001], [31.5±30.2 vs 28.8±29.3 vs 27.4±27.2, p<0.0001], respectively). There was no significant difference in creatinine clearance among the three groups of smokers (p=NS)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

773A
Micronutrients (mg/dL) were also higher in Myanmarese than Koreans. Blood pressure was significantly higher in Myanmar adults than Koreans. This study is comparing salt taste thresholds and salt usage behavior scores between Myanmar and Korean adults. Background: Excessive oral salt intake can induce hypertension. According to previous studies, prevalence of hypertension is higher in Myanmar than Korea. We postulated that baseline salt taste thresholds and salt usage behavior scores between Myanmar and Korean adults are different. Methods: This cross-sectional study enrolled the patients who visited volunteer medical service clinic at Assung in Myanmar and Hfeug and Bago in Myanmar in August 2014. We measured salivary sodium, height and weight of each patient and evaluate detection threshold, recognition threshold, salt preference, all patients were urinalysis and checked spot urine Na. They also filled up the salt usage behavior questionnaires. Results: Total 1,371 patients were enrolled and 64 of them were Myanmarese and 67 were Koreans. Blood pressure was significantly higher in Myanmar adults than Koreans. Detection threshold, recognition threshold, salt preference, spot urine sodium and salt usage behavior score was also higher in Myanmar than Koreans.

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</tr>
</tbody>
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We calculated correlation coefficient between spot urine Na and other parameters that related to salt intake. The salt usage behavior score detection threshold was significantly correlated with the spot Urine Na.

Conclusions: All parameters related to salt intake, such as detection thresholds, the recognition thresholds, salt preference, salt usage behavior score and spot urine sodium concentration, of Myanmarese were significantly higher than those of Korean.

SA-PO646

Comparison of Salt Taste Thresholds and Salty Usage Behaviors Between Myanmar and Korean Adults

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Background: Hypertension is associated with worse outcomes, and its treatment improves mortality and cardiovascular disease. Hospitalized patients undergo frequent BP measurements, and hence hospitalization is an opportunity to diagnose and treat hypertension. However, it is unclear if BP measured as inpatient is associated with outcomes.

Results: From 3,499,271 US veterans with normal eGFR, we identified 1,113,515 patients with inpatient and outpatient SBP recordings. We examined the association of baseline outpatient SBP, and baseline inpatient SBP (defined as the SBP obtained on the first day of the first hospitalization following cohort entry) with all-cause mortality in Cox proportional hazards analyses. Models included both in- and outpatient SBP and their interactions, and were adjusted for age, gender, race, eGFR, comorbidities, socioeconomic factors, and antihypertensives.

Conclusions: SBP shows markedly different associations in the outpatient vs inpatient setting, with higher blood pressures in the inpatient setting conferring less mortality risk compared to the outpatient setting. Until randomized controlled clinical trials are done, caution is warranted when treating hypertension in hospitalized patients.

Funding: NIDDK Support, Veterans Administration Support

SA-PO649

Fibroblast Growth Factor 23 and Sodium-Volume Regulation: FGF23 Response to Sodium Restriction in Essential Hypertensive Subjects and to Long Term Extracranial Volume Reduction in Hemodialysis Patients

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Background: Dietary sodium load causes volume expansion and hypertension in mouse models of FGF23 and αKlotho deficiency. FGF23 also associates with ultrafiltration volume in cross-sectional analyses in hemodialysis (HD) patients (pts) further implicating this bone hormone in extracellular volume regulation.

Methods: 32 uncomplicated essential hypertensive pts were randomized to a 2-weeks high-sodium diet (200mmol/day) or to a 2-weeks low sodium diet (10-20 mmol/day). After 1 week wash out, these treatments were crossed-over. At the end of each diet-period, pts underwent 24h urine sodium, 24h ABPM and serum intact FGF23 measurements. The FGF23 response to UF intensification was assessed in 52 hypertensive HD pts. FGF23 also associates with ultrafiltration volume in cross-sectional analyses in hemodialysis (HD) patients (pts) further implicating this bone hormone in extracellular volume regulation.

Results: In essential hypertensives, PRA and aldosterone (P<0.01) rose during low sodium. However, FGF23 remained unmodified [low sodium: median 36.2 pg/mL, inter-quartile range (IQR):32.4-44.0; high sodium: 33.9 pg/mL, IQR:29.5-41.0; P=0.18]. Changes in FGF23 were unrelated to systolic and diastolic ABPM, heart rate, PRA and aldosterone changes. In hypertensive HD pts, baseline FGF23 was 4062 pg/ml (IQR: 1381-12571). BP during the longitudinal study fell from 144 to 139 mmHg (P=0.02) along with a parallel decline in dry body weight (BW) from 63.7 to 62.8 Kg but FGF23 remained unchanged (3688 pg/mL, IQR: 1372-14117, P=0.30). Changes in FGF23 were unrelated (P=0.90) with ongoing changes in dry BW.

Conclusions: Changes in sodium intake that potentially activate the renin-aldosterone system do not alter FGF23 in essential hypertensives. Similarly, extracellular volume

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SA-PO650
Association of Urinary Albumin Excretion and Salt-Sensitivity of Blood Pressure: Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study
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Background: Albuminuria is a marker of early kidney injury and associated with risk of hypertension, cardiovascular disease, end-stage renal disease, and premature death. However, it is unknown whether urinary albumin excretion is associated with salt- and potassium-sensitivity.

Methods: We investigated the association between urinary albumin excretion and salt- and potassium-sensitivity of blood pressure (BP) among GenSalt study participants. The GenSalt dietary intervention consisted of a 7-day low sodium diet (51.3 mmol sodium/day), 7-day high-sodium diet (307.8 mmol sodium/day), and 7-day high-sodium diet with potassium supplementation (307.8 mmol sodium/day and 60 mmol potassium/day).

Results: Urinary albumin-to-creatinine ratio (A/CR, mg/g) was significantly reduced during low-sodium and potassium-supplementation interventions to 2.26 (1.1.1.4.61) and 2.10 (1.46.2.46), respectively, from a baseline ratio of 2.97 (1.20.4.40) and increased during the high-sodium intervention to 3.23 (2.15, 5.73) with P for group difference = 0.005. One standard deviation higher of baseline log-transformed ACR (2.23 mg/g) was significantly associated with 1.5% (95% CI 0.3, 2.7) mm Hg higher in mean arterial BP (P = 0.01) from low-sodium to high-sodium intervention (salt-sensitivity) but not statistically significantly associated with potassium-sensitivity after adjusting for confounding factors.

Conclusions: These data indicate that urinary albumin excretion may be associated with BP salt-sensitivity.

SA-PO651
Effects of Nephrectomy on Blood Pressure and Its Circadian Rhythm
Naro Ohushi, 1 Sayaka Ishigaki, 1 Shinshu Isobe, 1 Takayuki Tsujii, 2 Akihiko Kato, 2 Hideo Yasuda, 1 Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Japan; 2 Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Japan.

Background: Intradural renin-angiotensin system (RAS) activation causes disturbance of sodium excretion from the kidney by increasing sodium reabsorption in the tubulus, with resultant blood pressure (BP) elevation and nocturnal hypertension. However, the effects of nephrectomy on BP and its circadian rhythm have not been clarified in the patients who have various renal functions.

Methods: We investigated 25 nephrectomized patients [17 men and 8 women, age: 61.3±14.7 years, chronic kidney disease stage 1 in 3 patients, stage 2 in 7, stage 3 in 5, stage 4 in 2 patients, stage 5 in 3 patients] on hemodialysis in 3 and peritoneal dialysis in 1]. Body weight (BW), circulating RAS [plasma renin activity (PRA) and plasma angiotensin II (AngII)] and 24-h ambulatory BP monitoring (ABPM) were examined before and after nephrectomy. We divided the daytime and nighttime for 24-h ABPM using sleep and waking times. Renal function [estimated glomerular filtration rate (eGFR)] was evaluated in non-dialysis patients.

Results: In non-dialysis patients, GFPR after nephrectomy was significantly decreased compared with that before nephrectomy [67.8±23.1 ml/min/1.73m²] and after nephrectomy, 47.9±16.5 ml/min/1.73m²; p<0.01]. There were no significant differences in the levels of BW, BP’s during daytime, nighttime and 24-h periods, and circulating RAS before and after nephrectomy.

Conclusions: Nocturnal hypertension may play a role in BP salt- and potassium-sensitivity.

SA-PO654
Uric Acid Levels Are Associated with Peripheral but Not Central Blood Pressure Parameters in Normotensive Individuals
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Background: Uric acid is increasingly recognised as a risk factor for cardiovascular disease. Whether this could be explained by changes in peripheral or central blood pressure (BP) profiles remains controversial. The aim of this study was to assess the association of uric acid levels with peripheral and central hemodynamic parameters in untreated normotensive individuals.

Methods: Of 20,004 CADIENGENe participants, 8,420 were normotensive individuals not treated for hyperuricemia or hypertension with valid pulse wave analysis (46.9% male, 52.6% yo). The associations between uric acid levels and peripheral systolic BP (SBP), pulse pressure (PP) central systolic BP (cSBP), central PP (cPP), pulse pressure amplification (PPA), augmentation index (AIx) and augmented pressure (AP) were tested with linear regressions.

Results: In univariate analyses, uric acid levels were significantly associated with all parameters. In contrast, in multivariate analyses, only SBP and cSBP remained independently associated with uric acid levels. As cSBP is usually highly dependent of SBP, it was further adjusted for peripheral BP, where it was not independently associated with uric acid levels (β coefficient -0.003, p=0.51).

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Hypertension: Clinical
Poster/Saturday
775A

reduction by UF intensification does not materially influence FGF23 in hypertensive HD pts. These findings suggest that nephrectomy (nephrectomy) is unlikely to play a role in the response to changes in sodium intake in human hypertension.

Funding: Government Support - Non-U.S.

SA-PO653
Differences of Carotid Intima-Media Thickness in Hypertensive Patients with Diabetes or Without
Hideo Okonogi, Tetsuya Kawamura, Akira Fukui, Shinnya Yokote, Nobuo Tsuboi, Yoichi Miyazaki, Makoto Ugar, Takashi Yokoo. Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.

Background: Several studies reported that pulse pressure (PP) is the predictor of heart and kidney risks. On the other hand, arterial stiffness negatively correlates with renal function, and is the predictor of all causes mortality and mainly cardiovascular events in chronic kidney disease (CKD). Carotid-ankle vascular index (CA VI) is a non-invasive indicator of arterial stiffness, and is not influenced by the blood pressure (BP) at the time of examination. Therefore, we examined the relationship between various BP indexes and CA VI in patients with non-diabetic CKD.

Methods: Fifty-nine patients with non-diabetic CKD, who were diagnosed by first time biopsy, were included. Relationships between various BP indexes and CA VI were analyzed. Then receiver-operating characteristic (ROC) analysis for diagnosis of the presence of high arterial stiffness (CA VI<9, suggesting the presence of arterial sclerosis) were analyzed.

Results: As a result, systolic BP (SBP) and PP significantly correlated with CA VI (r=0.433, p<0.01 and r=0.624, p<0.01, respectively), while diastolic BP (DBP) and mean BP (MBP) did not correlate with CA VI. The ROC curves for diagnosis of the presence of high arterial stiffness by each index showed that SBP, DBP, MBP and PP had an area under the ROC curve (AUC) value of 0.786 (p<0.01), 0.425, 0.614 and 0.906 (p<0.01), respectively. Then, by two-graph ROC analysis, the threshold values of SBP and PP were obtained as 132.4mmHg (sensitivity 71%, specificity 71%) and 55.5mmHg (sensitivity 82%, specificity 82%), respectively.

Conclusions: These results indicated that PP has the most strong impact on arterial stiffness among various BP indexes. PP may affect renal function and cardiovascular risk via increase in arterial stiffness.
**SA-PO655**

**Blood Pressure Trajectory and Events in the Cardiovascular Health Study**

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**Background:** The association of blood pressure (BP) trajectories with clinical events in elders is not well established. The importance of integrating trajectories of systolic (SBP) and diastolic (DBP) is not known.

**Methods:** Among 4,067 participants in the Cardiovascular Health Study, we used repeated measures from the first 7 years to identify discrete trajectories of SBP, DBP and joint SBP/DBP: (1) concordant increasing, (2) discordant (stable SBP and decreasing DBP) and (3) concordant decreasing. Compared with a concordant increasing, a concordant decreasing and discordant trajectory had increased risk of death. Concordant decreasing was also associated with increased risk for incident CVD and HF, compared with concordant increasing and discordant trajectory had increased risk of death. Concordant decreasing was compared with concordant increasing. Findings did not differ when we stratified by use of antihypertensives.

**Results:** Of the 3828 individuals with treated self-declared hypertension, 155 had hypertension. The mean age was 48.7±8.7 years and majority of the participants were women (71%).

**Conclusions:** In normotensive individuals, uric acid levels were independently associated with SBP, but not with other hemodynamic parameters. Whether the increased risks associated with uric acid levels are explained by these parameters remains uncertain and needs further study.

**Funding:** Government Support - Non-U.S.

**SA-PO656**

**Serum Uric Acid and Vascular Stiffness in African Americans with Hypertension**

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**Background:** Elevation serum uric acid levels as well as vascular stiffness is associated with hypertension and cardiovascular (CV) disease. However, how uric acid affects vascular stiffness is not known. We examined the relationship between uric acid and vascular stiffness in a cohort of African American men and women with well-controlled hypertension.

**Methods:** 120 African-Americans with controlled hypertension were randomized in a double-blind, placebo controlled study to allopurinol (300mg/dl) or placebo for 4 weeks. Vascular stiffness was assessed by augmentation index at baseline and at 4 weeks after allopurinol therapy. Uric acid was characterized as low or high (>7 mg/dl in men and >6 mg/dl in women).

**Results:** The mean age was 48.7±8.7 years and majority of the participants were women (71%). Augmentation index was negatively correlated with uric acid at baseline (R=-0.24 p=0.009). The high uric group as compared to the low uric acid group, had a lower augmentation index (9.07 ± 5.52 vs. 11.22 ± 5.23 p=0.03) while the mean BP (119/75 vs 118/75), age (48.7 vs 48.6), and endothelial function as measured by endoPAT (2.2 ±2.2) were similar. With allopurinol therapy there was a drop in uric acid by 2.23±1.4 mg/dl as compared to placebo -0.15 ± 0.9 mg/dl but there were no significant changes in vascular stiffness or endothelial function.

**Conclusions:** In African Americans with hypertension uric acid is negatively associated with vascular stiffness and short-term therapy with allopurinol does not alter vascular stiffness. These changes are not explained by endothelial function. The mechanistic basis of how uric acid may be protective against vascular stiffness may explain the many conflicting studies on the contribution of uric acid to cardiovascular risk and merits further investigation.

**Funding:** Other NIH Support - NHLBI R01HL079352

**SA-PO657**

**The Impact of Renin-Angiotensin System Blockers on Renal Sodium Handling: An Analysis of CARTaGENE**


**Background:** Renin-angiotensin system blockers (RASB) reduce the effects of angiotensin II, and subsequently aldosterone, leading to vasodilation and natriuresis. The magnitude of the RASB-induced natriuresis compared to diuretics and other anti-hypertensive agents remains uncertain.

**Methods:** We identified patients treated for hypertension from the prospective CARTaGENE cohort, a random sample of the Quebec population aged 40 to 69, who had available urinary sodium levels. We compared the fractional excretion of sodium (FeNa) between patients on beta-blockers or calcium channel blockers without diuretics (Group 1), on RASB without diuretics (Group 2) and on diuretics (Group 3) with ANOVA and a general linear model adjusting for age, gender, estimated glomerular filtration rate (eGFR), diabetes and peripheral mean arterial pressure (pMAP).

**Results:** Of the 3828 individuals with treated self-declared hypertension, 155 had hypertension. Of these 61% were males, their mean age was 59±8 years, 23% had diabetes and the eGFR was 85±14 ml/min/1.73m² and 93±11 ml/min. Group 1, 2 and 3 included 42, 72 and 41 patients, respectively. In unadjusted analyses, patients in Group 1 (0.67±0.33) had lower FeNa than Group 2 (1.02±0.51, p=0.001) and Group 3 (1.25±0.70, p=0.001), while Group 2 had lower FeNa compared to Group 3 (p=0.029). In the adjusted analysis, Group 2 still had higher FeNa than Group 1, but the results were similar to Group 3.

**Conclusions:** After adjustment for important covariables, RASB therapy is associated with a natriuresis similar to diuretics and greater than other antihypertensive drugs in hypertensive patients. Whether the degree of natriuresis parallels the blood pressure response to these agents remains to be determined.

**Funding:** Government Support - Non-U.S.
Background: We previously demonstrated that mitochondrial injury contributes to renal dysfunction in swine renovascular disease (RVD), but its implications in human RVD remain unknown. Fragments of the mitochondrial genome released from dying cells are considered surrogate markers of mitochondrial injury. We hypothesized that RVD would be associated with increased urine mitochondrial DNA (mtDNA) copy numbers.

Methods: We prospectively measured urinary copy numbers of the mtDNA genes COX3 and ND1 by quantitative real-time PCR in essential hypertensive (EH), moderate RVD, and severe RVD patients (based on ultrasound criteria and evident loss of functional reserve). In RVD patients, urinary COX3 and ND1 directly correlated with RVD (R²=0.18, p<0.02 and R²=0.37, p<0.001), proteinuria (R²=0.33, p<0.001 and R²=0.53, p<0.001), and serum creatinine (R²=0.27, p<0.002 and R²=0.16, p<0.02, respectively), and inversely with eGFR (R²=0.10., p<0.05, respectively).

Conclusions: We found progressive increments in urine mitochondrial injury markers with increased severity of RVD, implicating mitochondrial injury in kidney damage in human RVD. Mitochondria might represent a novel therapeutic target in RVD.

SA-PO660

Independent Association of Vitamin D on Endothelial Function: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial Lea Borgi,1 Ciaran Joseph McMullan,2 Gary C. Curhan,1 Naomi D.L. Fisher,1 John P. Forman,1 Nephrology, Brigham and Women’s Hospital, Boston, MA; Endocrinology, Brigham and Women’s Hospital, Boston, MA.

Background: In nonhypertensive individuals, lower levels of 25-hydroxyvitamin D (25(OH)D) have been associated with increased risk of hypertension (HBP). Vitamin D deficiency has been associated with endothelial dysfunction in such individuals. However, the effect of vitamin D supplementation on endothelial dysfunction in nonhypertensive individuals has not been examined in a rigorous fashion.

Methods: In this randomized, double-blind, placebo-controlled trial of nonhypertensive, nondiabetic overweight or obese individuals with vitamin D deficiency (body mass index [BMI] 25 and 25(OH)D<20ng/mL), we assigned subjects to receive either ergocalciferol (1500 IU) or placebo, once a week for 8 weeks. Our primary outcome was endothelial-dependent vasodilation (EDV) measured by brachial ultrasound at baseline and 8 weeks post-randomization.

Results: By the end of the trial, 46 and 47 participants were allocated to receive ergocalciferol and placebo, respectively. Mean 25(OH)D levels increased from 14.9 to 30.3 in the vitamin D group and from 24.9 to 29.3 in the placebo group (p=0.006). EDV did not change significantly with either vitamin D repletion (from 6.3±3.6% at baseline to 6.1±4.6% at 8 weeks; p-value=0.78) or placebo (7.9±4.7% to 6.8±4.7%; p=0.17). The treatment effect p-value (comparing the 8-week change with ergocalciferol to the change with placebo) was 0.35.

Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (measured as EDV) after repletion of vitamin D in overweight/obese non-hypertensive individuals.

Funding: NIDDK Support

SA-PO661

Secondary Hypertension, Primary Hyperaldosteronism, and Renal Cell Carcinoma Nicole Pietro,1 Krishnanath Gaitonde,1 Charuhas V. Thakar,1 Cincinnati VA Medical Center; 2Univ of Cincinnati.

Background: Primary hyperaldosteronism (PH) is the most common cause of secondary hypertension. Renal cell carcinoma (RCC) can cause secondary hypertension, but as a renin-mediated process. We describe 5 cases referred for evaluation of PH (uncontrolled hypertension and hypokalemia), incidentally diagnosed with RCC, and the potential role of RCC as a renin-independent mechanism for hypertension.

Methods: At the initial renal visit, average blood pressure (BP) was 167/87 mmHg, with an average of 4 BP meds (nondiuretic blockers). Average serum levels of potassium, sodium, and bicarbonate were 3.1, 143, and 30 mEq/L respectively. Average plasma renin activity (PRA) was 0.12 ng/ml/hr, average serum aldosterone (sAldo) was 16.6 ng/dL, with a mean sAldo:PRA of 146. 24-hour urine analysis, aldosterone ranged from 11.8 to 30.2 ng/dL and sodium ranged 82-226 mEq/24 hours. All patients required 1 or 2 aldosterone blocking agents to achieve an average BP of 134/75 mmHg. Upon imaging, 4/5 had adrenal adenomas and all 5 patients had incidental solid renal masses with radiological characteristics of RCC. To date, 3/5 have had renal masses treated with partial/total nephrectomy or cryotherapy; all have confirmed pathology of RCC. All those undergoing TF treatment were on improved BP with 2/3 having reduced therapy. At presentation these 3 patients had an average BP of 159/87 mmHg and were on an average of 4.7% to 6.8% of 4.7%; p=0.17). The treatment effect p-value (comparing the 8-week change with ergocalciferol to the change with placebo) was 0.35.

Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (measured as EDV) after repletion of vitamin D in overweight/obese non-hypertensive individuals.

Funding: NIDDK Support

SA-PO659

Association Between Urinary Big Angiotsin-25 and Microalbuminuria in Hypertensive Patients Yasuhiko Yamashita,1 Sayaka Nagata,1 Yui Sato,2 Kazuo Kitamura,1 Shouichi Fujimoto.1 1Dept of Circulatory and Body Fluid Regulation, Dept of Internal Medicine, Faculty of Medicine, Univ of Miyazaki, Miyazaki, Japan; 2Div of Nephrology, Brigham and Women’s Hospital, Boston, MA.

Background: In hypertensive patients, albuminuria is a predictive factor for cardiovascular events. Recently, a newly glycolated angiotensin-related peptide, Big angiotensin-25 (Bang-25), was isolated from human urine (Nagata et al. Biochem Biophys Res Comm 2013), and it was localized to podocytes in kidney tissue. Bang-25 may be involved in the renin-independent pathway for localized angiotension II generation, and can contribute to diagnosis in organ disorders. Using cross-sectional data, we investigated the relationship between urinary Bang-25 and albuminuria in hypertensive patients.

Methods: We examined the data of 408 hypertensive patients (male 50.5%; mean age ±10 years, BMI 25±7 kg/m², diabetes mellitus 36.8%, and eGFR 72±17 ml/min/1.73m²). We evaluated urinary albumin-creatinine ratio (ACR) and we measured urinary Bang-25 by specific AlphaLISA immunoassay. The association between urinary Bang-25/creatinine ratio and microalbuminuria was analyzed by a multivariate logistic ratio.

Results: Thirty patients were excluded because of microalbuminuria (ACR>300 mg/gCr). Of 378 patients, 96 had microalbuminuria (30<ACR<300 mg/gCr). Patients were then divided by quartiles of Bang-25/creatinine ratio. Older patients, females, lower hemoglobin, lower uric acid, and higher HDL were more prominent in higher Bang-25/creatinine quartiles. After adjusting for age, sex, eGFR, and presence of diabetes, the odds ratios (95% confidence intervals) for microalbuminuria per quartile, calculated using multiple logistic regression, were as follows: Q1, reference; Q2, 0.72 (0.33-1.54); Q3, 0.99 (0.49-2.01); and Q4, 2.05 (1.01-4.14).

Conclusions: Higher urinary Bang-25/creatinine quartile was significantly associated with microalbuminuria in hypertensive patients. As Bang-25 is localized to podocytes, it may play some role in the development of albuminuria.

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

Underline represents presenting author.
Methods: In this randomized, double-blind, placebo-controlled trial of nonhypertensive, nondiabetic, overweight or obese individuals with elevated serum uric acid (body mass index [BMI] ≥25 and serum uric acid ≥5 mg/dL), we assigned subjects to receive one of the following: allopurinol 300 mg daily for 4 weeks followed by 600 mg daily for 4 weeks; probenecid 500 mg daily for 4 weeks then 1000 mg daily for 4 weeks; or matching placebo. Our primary outcome was endothelial-dependent vasodilation (EDV) measured by brachial artery ultrasound at baseline and 8 weeks post-randomization.

Results: By the end of the trial, 43, 44 and 47 participants were allocated to receive probenecid, allopurinol and placebo, respectively. Mean serum uric acid levels decreased from 7.9 ± 3.7 to 5.2 ± 2.4 mg/dL in the allopurinol group, and were unchanged in the placebo group (5.6 ± 5.7 mg/dL). EDV did not change significantly with either probenecid (from 7.6 ± 5.1% at baseline to 8.4 ± 5.2% at 8 weeks; p-value = 0.39), allopurinol (from 7.4 ± 6.0% at baseline to 5.9 ± 4.6% at 8 weeks; p-value = 0.09) or placebo (6.8 ± 3.8% to 7.1 ± 4.9%; p = 0.66).

Conclusions: In this randomized, double-blind, placebo-controlled trial, there was no improvement in endothelial function (measured as EDV) after lowering serum uric acid in overweight/obese non-hypertensive individuals.

Funding: NIDDK Support

SA-PO663
Azelnidipine Can Restore the Deceleration Capacity of Heart Rate Variability (DC) in CKD Patients with Preceding Treatment with ARB

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Background: Recently, we have hypothesized that DC, novel measure of cardiac vagal modulations, is also attributable to sympathetic nerve activities. Azelnidipine was reported to decrease non-Gaussianity index of HRV (I kh), which can serve as a marker of sympathetic cardiac overdrive.

Methods: In 43 hypertensive patients with CKD under treatment with an angiotensin receptor blocker (ARB), we tested whether 8-week add-on administration of azelnidipine can increase DC. DC was calculated by Bauer’s signal processing technique of phase-rectified signal averaging. For reference, the power of high frequency (HF, 0.15–0.40 Hz) obtained from frequency measure of HRV was examined as a conventional indicator of vagal activity.

Results: DC increased (6.17 ± 4.85 to 6.92 ± 4.18, p = 0.002) and I kh decreased (0.56 ± 0.15 to 0.17 ± 0.02, p = 0.001), while no significant changes were observed in other HR variability measures including HF (p = 0.9). Change in DC correlated inversely with the change in I kh (r = -0.38, p = 0.01), but not with the change in HF (p = 0.8).

Conclusions: Our findings are consistent with the thesis that DC is not a simple measure of vagal activity but a product of complex interplay between sympathetic and vagal nerve activities.

SA-PO664
Elevated Levels of Podocyte Derived Urinary Microparticles in Angiotensin II Induced Hypertension

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Background: Early and non-invasive biomarkers of kidney damage are needed to identify hypertensive patients at risk for kidney damage. Urinary microparticles (uMPs) have gained significant attention as potential novel biomarkers for kidney damage, and have already been identified in pre-albuminuric diabetic glomerular injury. These vesicles are less than 1 micron in size and carry markers of the parent cell. We hypothesized that podocyte derived uMPs are elevated in angiotensin II-induced hypertension (HTN).

Methods: Wild-type mice were treated with AII (400 ng/kg/min) via mini-osmotic pumps. Untreated WT mice served as controls. Blood pressure was measured with tail-cuff manometry. 24 hour urines were collected after 5 days of all treatment. Enumeration and phenotyping of MPs was done of podocyte culture supernatant and urine. UMP levels were normalized to urinary creatinine concentration. Podocalyxin (Pcal), podoplanin (Ppla) and annexin 5 (AV) were used as surface markers.

Results: Pcal and Ppla positive MPs as well as AV positive and negative MPs were detectable in supernatant from primary podocyte cultures. Compared to untreated controls (n = 3), AII treated mice (n = 2) had an increase in systolic blood pressure (SBP) by 33 ± 6 mmHg in the sulodexide and placebo arm, respectively (p = 0.037). The SBP reduction was most pronounced in the highest UACR tertile (-1.6 ± 1.5 vs 2.9 ± 1.6 mmHg; p = 0.042). Treatment (p = 0.015), baseline SBP (p = 0.001), heart rate (p = 0.007) and UACR (p = 0.007) were associated with SBP change. We found an interaction between treatment and UACR (p = 0.047), indicating that sulodexide and placebo differently affected SBP at various UACR levels. Age, eGFR, BMI, HbA1c and lipid profile (i.e., factors influencing ESL thickness) did not modify the treatment effect. The BP differences persisted during the first year of follow-up (p = 0.047).

Conclusions: Diabetic patients have a thinner endothelial surface layer (ESL), especially when macroalbuminuria is present. Sulodexide, a mixture of glycosaminoglycans (GAGs), increases ESL thickness. Previous data indicate that the ESL is pivotal for BP regulation. In this study, we assessed whether the BP reducing effect of sulodexide is modified by albuminuria severity (a surrogate for the ESL) in type 2 diabetic patients.

Methods: In a post-hoc analysis of the randomized, double-blind, placebo-controlled Sun-MACRO trial, including type 2 diabetic patients with macroalbuminuria and maximal angiotensin II receptor blocker therapy, we studied the BP effects of sulodexide 200 mg/d. We stratified patients in baseline urinary albumin-creatinine ratio (UACR) tertiles. We used ANCOVA to study whether baseline UACR modified the 3-month SBP changes of sulodexide.

Results: Data of 843 patients were available for analysis. Baseline BP was 138 ± 73 mmHg. At 3 months, mean (SEM) SBP change was -0.9 ± 0.9 and 1.7 ± 0.9 mmHg in the sulodexide and placebo arm, respectively (p = 0.037). The SBP reduction was most pronounced in the highest UACR tertile (-1.6 ± 1.5 vs 2.9 ± 1.6 mmHg; p = 0.042). Treatment (p = 0.015), baseline SBP (p = 0.001), heart rate (p = 0.007) and UACR (p = 0.007) were associated with SBP change. We found an interaction between treatment and UACR (p = 0.047), indicating that sulodexide and placebo differently affected SBP at various UACR levels. Age, eGFR, BMI, HbA1c and lipid profile (i.e., factors influencing ESL thickness) did not modify the treatment effect. The BP differences persisted during the first year of follow-up (p = 0.047).

Conclusions: In conclusion, podocyte derived urinary MPs are detectable in all HTN. These findings need to be confirmed in a larger group of animals. Urinary MPs can be potential marker for kidney end-organ damage in HTN.

Funding: Clinical Revenue Support

SA-PO665
Blood Pressure Lowering Effects of Sulodexide Depend on Albuminuria Severity

Hikko Jan Lamberts Heerspink, Dick de Zeeuw, Liffert Vogt, Nephrology, AMC, Amsterdam, Netherlands; ’Clinical Pharmacy and Pharmacology, UMCG, Groningen, Netherlands.

Background: Diabetic patients have a thinner endothelial surface layer (ESL), especially when macroalbuminuria is present. Sulodexide, a mixture of glycosaminoglycans (GAGs), increases ESL thickness. Previous data indicate that the ESL is pivotal for BP regulation. In this study, we assessed whether the BP reducing effect of sulodexide is modified by albuminuria severity (a surrogate for the ESL) in type 2 diabetic patients.

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Funding: Clinical Revenue Support

SA-PO666
Under-Diagnosis of Hypertension in a Large Cohort of Overweight/Obese Adolescents

Brian William Sykes, Divya G. Moodalbail, Christopher J. LaRosa, Joshua Zaritsky. Nephrology, Nemours/A.I. duPont Hospital, Wilmington, DE.

Background: The obesity epidemic in children is strongly associated with increasing prevalence of childhood hypertension (HTN) along with heightened risk for cardiovascular morbidity and mortality in adulthood. Therefore we assessed the identification of HTN in overweight/obese adolescents cared for by a large healthcare system utilizing an EMR system.

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

Underline represents presenting author.
Methods: We performed a retrospective study of patients (pts) in the Nenmours Health Care System aged 12-17 years, with a BMI > 85%, and 3 documented BP > 120/80 in the outpatient setting, between 1/2010 and 12/2014. Pts with established diagnosis of hypertension (HTN) diagnosed 1992-2004, were excluded. Results: Of the 6604 distinct pts identified, only 253 (3.8%) received a diagnosis of HTN during the study period, while 6,349 (96.2%) were undiagnosed. Pts who were undiagnosed had lower BMIs and BPs and were less likely to be African American or have Medicaid and were seen less by Nephrology, Cardiology or Weight management subspecialties compared with those diagnosed with hypertension (table). Additionally undiagnosed pts had fewer abnormal BPs and had a longer interval between their 1st and 3rd abnormal BP compared with those diagnosed with hypertension.

Conclusions: In this large cohort of overweight/obese adolescents with HTN, the vast majority of pts were undiagnosed and not referred to subspecialists who manage BP monitoring and treatment. Thus it is crucial that future efforts focus on improving detection and early recognition of HTN in order to reduce cardiovascular morbidity and mortality in this at-risk population.

SA-PO667
Multidisciplinary Selection of Angioplasty Indications in Atheromatous Renal Artery Stenosis Leads to an Improvement in Blood Pressure, Drug Sensitivity and Renal Function

Thomas Fournier,1 Florence Sens,2 Olivier Roussetie,2 Antoine Milton,1 Laurent Julliard,1 Nephrology, hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France;1 Radiology, hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France;1 Vascular Surgery, hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France.

Background: Angioplasty as treatment of atheromatous renal artery stenosis (ARAS) is controversial since 3 large randomised trials (CORAL, ASTRAL, STAR) failed to prove the superiority of percutaneous renal artery angioplasty and stenting (PTRAS) over medical treatment alone (MT). However, since population selection was questionable among other biases, the extrapolation of these results in clinical practice is uncertain.

Methods: ARAS cases were discussed during bi-monthly multidisciplinary meetings gathering nephrologists, radiologists and vascular surgeons from April 2013 to February 2015. For every patient, we compiled clinical, biological and radiological data. We then recorded blood pressure (BP), renal function and treatment evolution after a one-year follow-up.

Results: During 23 months, 52 cases were discussed. Mean age was 69 years. Two-thirds of patients had at least 3 cardiovascular risk factors. Mean BP was 161±77 mmHg, despite the use of 2.5±1.1 anti-hypertensive drugs. CDK-EPI was 53mL/min/1.73m², 31% of patients had a history of pulmonary edema. Collective decisions were PTRAS for 21 patients (40%), MT for 28 patients (54%) and surgery for 3 patients (6%). PTRAS group showed a significant improvement at 1 year for clinic BP: 147±25 vs 130±15 mmHg (P<0.001), SCR: 1.1±1 vs 0.9±0.7 mg/dL (P<0.001), and were seen less by Nephrology, Cardiology or Weight management subspecialties. In the MT group, clinic BP: 148±27 vs 149±25 mmHg (P=0.76), SCR: 1.1±1 vs 1.1±1 mg/dL (P=0.12), and 3/4 patients were seen more by nephrologist.

Conclusions: Since the ARAS staging is controversial, the multidisciplinary approach proposed in this study is easy to implement and can result in significant reductions in blood pressure and improvement in renal function over one year.

SA-PO670
Comparison of Control Rates Among Recommended Drug Selection Strategies for Initial Therapy of Hypertension

Kamal A. Ghareeb,1 Stephen T. Turner,1 Arlene B. Shulman,2 Phyllis Daley-Soo,1 Paul J. Martin,1 Richard M. Cooper,1 Julie A. Johnson,1 Julie A. Johnson,1 Gary L. Schwartz,3 Antoine Millon,3 Florence Sens,2 Olivier Roussetie,2 Antoine Milton,1 Laurent Julliard,1 Nephrology,/Hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France;1 Radiology, Hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France;1 Vascular Surgery, Hôpital E. Herriot, Hospices Civils de Lyon, Lyon, France.

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Conclusions: In this large cohort of overweight/obese adolescents with hypertension (HTN), the vast majority of pts were undiagnosed and not referred to subspecialists who manage BP monitoring and treatment. Thus it is crucial that future efforts focus on improving detection and early recognition of HTN in order to reduce cardiovascular morbidity and mortality in this at-risk population.

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kidney failure. HIV stage A (HR=0.3, p<10^-4) had a protective effect. Multivariate analysis revealed that age (HR=1.05, p=0.002) and CDC stage A (HR=0.35, p=0.01) were risk and protecting factors, respectively.

**Conclusions:** The prevalence of CKD in this very large cohort of people living with HIV-2 seems to be comparable to what is known in literature for people living with HIV-1. HIV-2 infection parameters determine most of the kidney risk. The role of ARV exposition remains to be taken into account.

**Funding:** Government Support - Non-U.S.

**SA-PO671**

**Effect of Nephropathy on the Frequency of Cardiac Dysautonomia in HIV Patients**


1 Dept of Nephrology, Allama Iqbal Medical College/Jinnah Hospital, Lahore, Pakistan; 2 HIV Clinic, Jinnah Hospital, Lahore, Pakistan.

**Background:** Dysfunction of autonomic nervous system including Cardiac Dysautonomia (CD) is seen in a variety of conditions like diabetes mellitus, adrenal insufficiency and renal failure. CD is well documented in patients with renal dysfunction. Prevalence of renal dysfunction (HIV Nephropathy) is high in our population of HIV positive patients, but the effect of HIV nephropathy on the frequency of CD has not been previously studied. We conducted this study to determine the effect of HIV nephropathy on the frequency of CD.

**Methods:** This cross sectional study was conducted at HIV clinic in collaboration with the Department of Nephrology Jinnah Hospital Lahore. A total of 47 HIV positive patients were enrolled; 13 (28%) with nephropathy and 34 (72%) without nephropathy. Patients underwent 5 tests for cardiac autonomic dysfunction including resting tachycardia, abnormal heart rate response to deep breathing, abnormal Valsalva ratio, abnormal 30:15 ratio and postural hypotension. Patients with 2 or more abnormal tests were considered positive for CD.

**Results:** Of 47 patients, 39(83%) were male, 5(11%) female and 3(6%) were transgender with median age of 31 years (range 19-56 years). The median CD4 count was 339 (range 39-797) and 96% (n=45) patients were on highly active anti-retroviral therapy (HAART). The median duration of HIV was 12 months (range 1-56) and median duration of HAART was 11 months (range 0-49). CD was seen in 42 (89%) patients. Seventeen (36.2%) patients had 2, 18(38.3%) had 3, 6 (12.8%) had 4 and 1 (2%) had 5 abnormal tests. The frequency of CD was comparable among patients with and without nephropathy [92% (12 out of 13) vs 88% (30 out of 34), respectively; p=0.01]. The presence of CD had no correlation with CD4 count, degree of renal impairment, treatment regimen and duration on HAART.

**Conclusions:** There was high frequency of CD in our population of HIV patients and it was independent of presence or absence of nephropathy, CD4 count and duration of anti-retroviral therapy.

**SA-PO672**

**Gloermerul Filtration Rate Estimating Equations Using Beta-Trace Protein and Beta-2 Microglobulin in Chronic Kidney Disease**


**Background:** Beta-trace protein (BTP) and beta-2 microglobulin (B2M), like cystatin C (Cys), are novel serum filtration markers that have stronger associations with adverse outcomes than serum creatinine (Cr). However, comparisons of BTP and B2M to Cr have been replaced by relatively accurate equations derived from large epidemiological studies. Nonetheless, equations including Modification Diet in Renal disease-4 and 6 variables (MDRD-4, -6) and Chronic Kidney Disease-Epidemiology Consortium (CKD-EPI) are known to have wide variations in predicting GFR among patients with relatively good kidney function. As renal clearance of any solute is dependent on its presence in the plasma and not whole blood, we suspect that varying hemoglobin/hematocrit (Hct) may play an important role in the actual clearance of solutes. We aim to determine if adding the plasma factor PF (1 - Hct/100) to MDRD-4, -6, or CKD-EPI equations can improve the accuracy of determining actual GFR.

**Methods:** This is a retrospective pilot study where the most recent 200 existing 24-hour urine collections have been replaced by relatively accurate equations derived from large epidemiological studies. Nonetheless, equations including Modification Diet in Renal disease-4 and 6 variables (MDRD-4, -6) and Chronic Kidney Disease-Epidemiology Consortium (CKD-EPI) are known to have wide variations in predicting GFR among patients with relatively good kidney function. As renal clearance of any solute is dependent on its presence in the plasma and not whole blood, we suspect that varying hemoglobin/hematocrit (Hct) may play an important role in the actual clearance of solutes. We aim to determine if adding the plasma factor PF (1 - Hct/100) to MDRD-4, -6, or CKD-EPI equations can improve the accuracy of determining actual GFR.

**Results:** Of 162 samples of the total dataset. *p<0.001 for difference of 1-P from CKD-EPI Cr-Cys equation

<table>
<thead>
<tr>
<th>Description</th>
<th>IQR(95%CI)</th>
<th>1-P(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTP age, sex</td>
<td>15.0(14.1, 15.9)</td>
<td>23.6(21.3, 26.1)</td>
</tr>
<tr>
<td>BTP+B2M*</td>
<td>12.1(11.4, 13.0)</td>
<td>15.5(13.3, 17.7)</td>
</tr>
<tr>
<td>CKD-EPI Cr age, sex, race</td>
<td>11.6(10.9, 12.4)</td>
<td>16.4(14.2, 18.6)</td>
</tr>
<tr>
<td>CKD-EPI Cys age, sex</td>
<td>11.4(10.6, 12.4)</td>
<td>16.9(14.9, 19.1)</td>
</tr>
<tr>
<td>CKD-EPI Cr-Cys age, sex, race</td>
<td>9.3 (8.7, 10.1)</td>
<td>11.3 (9.5, 13.2)</td>
</tr>
<tr>
<td>Average of CKD-EPI Cr-Cys + BTP-B2M</td>
<td>10.2 (9.5, 11.0)</td>
<td>9.6 (8.0, 11.4)</td>
</tr>
</tbody>
</table>

The table shows the coefficients included in each equation and the performance of the equations in the validation dataset compared to the CKD-EPI Cr-Cys equation.
Results: 90 out 200 samples met inclusion criteria. Albeit small, when each of the aforementioned equation was adjusted for PF, R² variation improved. MDRD-4: unadjusted R² = 0.836 to adjusted R² = 0.853, MDRD-6, R² = 0.811 to 0.813, CKD-epi, R² = 0.746 to 0.747. Conclusions: Adding PF to MDRD-4, MDRD-6, and CKD-EPI equations reduced variations when correlated to 24-hour urine collections. Of interest, PF appears to improve MDRD (derived for CKD patients where anemia is prevalent) variations better than CKD-EPI. Large-scale reevaluation of eGFR estimates with consideration for PF is warranted.

SA-PO674
Interest of Cystatin C in the Evaluation of Glomerular Filtration Rate in Type 2 Cardio-Renal Syndrome
Delphine Kervella,1,2 Sundrine Lemoine,2 Florence Sensi,1,3 Eric Pouliquen,1,3 Laurence Dubourg,2,3 Fisum Guerbe-egziabher,1,3 Laurens Juillard,1,3 Nephrology, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; Renal Function, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; Univ Claude Bernard Lyon 1, Lyon, France.

Background: In patients suffering from type 2 cardio-renal syndrome (CRS2), glomerular filtration rate (GFR) is overestimated with creatinine based formulae, leading to the misclassification of these patients in chronic kidney disease stages. As cystatin C is less dependent from muscle mass than creatinine, the aim of this study was to determine if estimation of GFR based on cystatin C offers a better evaluation of renal function than creatinine-based estimations in patients with CRS2.

Methods: GFR measured by Inulin clearance (measured GFR, mGFR) in 50 patients with CRS2 was compared to estimations of GFR (eGFR) with CKD EPI ( Chronic Kidney Disease Epidemiology Collaboration) formulae based on creatinine (CKD EPI, cystatin (CKD EPI(cyst)), and cystatin and creatinine (CKD EPI(cyst,cr)). We calculated absolute bias (eGFR-mGFR) and accuracy 30% for each formula.

Results: Mean mGFR is 26.5±11.5 mL/min/1.73 m². eGFR are 35±1.5 and 35±14.5 mL/min/1.73 m² with CKD EPI, CKD EPI(cyst) and CKD EPI(cyst,cr) respectively. These values of GFR are significantly different from mGFR. Mean absolute bias are 15.4, 5.7 and 8.8 mL/min/1.73 m² and accuracies 30% are 30%, 68% and 48% respectively. The accuracy of CKD EPI(cyst) is significantly higher than the accuracy of CKD EPI.

Conclusions: Glomerular filtration rate is strongly overestimated with creatinine-based formulae, leading to the misclassification of these patients in chronic kidney disease stages. As cystatin C is less dependent from muscle mass than creatinine, the aim of this study was to determine if estimation of GFR based on cystatin C offers a better evaluation of renal function than creatinine-based estimations in patients with CRS2. CKD EPI formula based on cystatin C offers a better evaluation of GFR in this population. This high prevalence of malnutrition in this population can explain these results.

SA-PO675
Cystatin C in Capillary Blood: A New Tool for Instant Estimation of Glomerular Filtration Rate
Maurice Laville,1 Solene Pelletier,2 Denis Fouque,1 Nephrologie, Univ de Lyon, Pierre Benite, France; Nephrologie, Hospices Civils de Lyon, Pierre Benite, France.

Background: Serum creatinine is the most used endogenous marker to estimate glomerular filtration rate (eGFR) in clinical practice. A handheld device (SatSensor®, Nova Biomedicals) allows to measure creatinine level in capillary blood. The aim of the study was to assess the accuracy of GFR values (eGFR) estimated from capillary blood creatinine level (CBG), as compared to GFR values simultaneously measured by a gold standard method (mGFR) in patients with CKD.

Methods: The study included 79 adult patients (36 men, 43 women) who underwent renal function tests. The consent form contained information on the procedure and on the later use of the information for research. Inulin clearance was performed using a continuous infusion of inulin, and urine collections by periods of 30 min. Blood tests were done in the middle of each period of urine collection. Measurements of polycarboxylan concentration were performed using an enzymatic method. Inulin clearance was calculated in each period to obtain the average, and normalized to 1.73 m² body surface area. A drop of capillary blood was collected from a finger simultaneous to the first and the last blood sampling for inulin measurement. The drops were deposited on a test strip including enzyme reagents and inserted into the SatSensor® device. Reading was done at 30 sec. eGFR was calculated from CBCr with the CKD-EPI equation and the average of the 2 values was taken as eGFR. To assess the performance of CBCr-derived eGFR, the mean absolute bias (eGFR - mGFR) and the correlation coefficient (R2) were calculated.

Results: Mean age was 54±17 years, and mean BMI was 25.± 5 kg/m². Mean value of mGFR was 61±27 ml/min/1.73 m². Mean bias was -5.2 ml/min/1.73 m². On correlation analysis, there was no significant difference between the 2 methods (correlation coefficient 0.7, 0.7).

Conclusions: Estimation of GFR using instant measurement of capillary blood creatinine level and CKD-EPI formula provides consistent results as compared with a gold standard method for GFR measurement, and could be used for screening and self-assessment purposes.

Funding: Clinical Revenue Support

SA-PO676
Renal Function Estimated with Different Formulae and Mortality in the CKD-EPI Cohort: Results After 8 Years Follow-up
Pietro Manuel Ferrara,1 Antonio Lupo,2 Giovanni Gambaro.1 Div of Nephrology, Catholic Univ of the Sacred Heart, Rome, Italy; Div of Nephrology, Univ of Verona, Verona, Italy.

Background: Chronic kidney disease is a known risk factor for adverse outcomes. Its presence and severity is usually ascertained with formulae to estimate renal function based on serum creatinine and/or cystatin C. We analyzed whether renal function estimated with different formulae has a different association with mortality.

Methods: The CKD-EPI cohort is a sample of the Italian population enrolled in 2006-07, with follow-up data available up to 2014. CKD stages were defined as GFR < 90, 60-90, 45-60, < 45 mL/min based on the following formulae: Cockcroft-Gault (CG), Cockcroft-Gault normalized to body surface area (nCG), abbreviated MDRD (MDRD, 6-variables MDRD (MDRD-6), CKD-EPI calculated with serum creatinine (EPI-Cr), with serum cystatin C (EPI-Cys), and with both serum creatinine and cystatin C (EPI-CrCys). CKD stage was then included in a Cox proportional hazards model together with age, body mass index, sex, high blood pressure, diabetes, dyslipidemia, previous cardiovascular disease, smoking status and albuminuria. Harrell's c statistics with 95% confidence intervals (CI) were then calculated and compared for each formula.

Results: The final sample included 2,916 participants, all Caucasians, 47.4% males, with an average age at enrollment of 59.9±11.4 years. Participants contributed a total of 22,514 person-years of follow-up (median follow-up 7.9 years) during which 198 death events occurred. Overall, the models were highly predictive of mortality.

The GFR-Cys model performed significantly better than MDRD-6 (difference in c-statistics of 0.008, 95% CI 0.001, 0.015; p=0.034), whereas all the other models performed similarly.

Conclusions: Our study suggests that CKD defined with the CKD-EPI cystatin C formula shows a better prediction of mortality after accounting for a large number of potential risk factors.

SA-PO677
Do the BIS Equations Better Predict Death in Older Women?
Muna T. Canales,1,2 Terri L. Blackwell,1 Areef Ishani,1,3 Brent C. Taylor,1 Allison Hart,2 Rebecca Beryl,2 Kristine E. Ensrud,4,5 Malcom-Randall VFCM, Univ of Florida, California Pacific Medical Center, Minneapolis VA Health Care System; Univ of Minnesota, Hennepin County Medical Center, Minneapolis, MN.

Background: KDIGO 2012 guidelines recommend use of the CKD-EPI equations to estimate GFR except when there are alternate equations that may perform better for certain populations such as older adults. The BIS equations were specifically developed in an aged population, but their performance when compared to the CKD-EPI equations to predict mortality in older adults is unclear.

Methods: We conducted a prospective study of 1289 community-dwelling elderly women (≥72 years old) enrolled in the Study of Osteoporotic Fractures (SOF) who had both serum cystatin-C(cysc) and creatinine(SCr) measured at Year 10(1992-1994). We defined CKD stages as GFR ≥90, 89-60, 59-45 and <45 mL/min based on the following formulae: Cockcroft-Gault (CG), Cockcroft-Gault normalized to body surface area (nCG), abbreviated MDRD (MDRD), 6-variables MDRD (MDRD-6), CKD-EPI calculated with serum creatinine (EPI-Cr), with serum cystatin C (EPI-Cys), and with both serum creatinine and cystatin C (EPI-CrCys). CKD stage was then included in a Cox proportional hazards model together with age, body mass index, sex, high blood pressure, diabetes, dyslipidemia, previous cardiovascular disease, smoking status and albuminuria. Harrell’s c statistics with 95% confidence intervals (CI) were then calculated and compared for each formula.

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SA-PO678

Canine Chronic Kidney Disease: New Protein Biomarkers and Treatment with Human Umbilical Cord Mesenchymal Stem Cells


**Background:** There are few strategies to prevent the progression of renal disease in humans or animals. In canine chronic kidney disease (cCKD), as in human CKD, proteinuria correlates with CKD progression, although there are no established urinary protein biomarkers. cCKD has become more common, dogs routinely being euthanized upon diagnosis. Treatment of cCKD is suboptimal because of lack of validated biomarkers for discrimination of mortality risk when compared to CKD-EPI equations.

**Methods:** We evaluated huMSC phenotypes with flow cytometry and immunocytochemistry. We compared human umbilical cord MSC (huMSC) administration to dogs with cCKD stages 1-4 (n=10/stage) and control dogs (n=10).

**Results:** huMSC administration slowed the progression of cCKD.

**Conclusions:** Human umbilical cord MSC (huMSC) administration slows its progression.

SA-PO680

Beta-Trace Protein as Renal Marker in Older Adults – Results from the Berlin Initiative Study

Johanna Schuchardt, Olga Jakob, Jan Bartel, Markus van der Giet, Mirjam Schuchardt, Christine A. White, Elke Schaefer.

**Background:** It has been shown that GFR estimation based on b-Trace Protein (BTP), a relatively novel biomarker, is reliable and might serve as an alternative in kidney transplant recipients. Whether BTP-based GFR equations can be applied in older adults is not known.

**Methods:** BTP has been measured by immunonephelometry with N-Latex BTP Assay on a BN ProSpec system. The Berlin Initiative Study (mean age: 78.5 years) who underwent iohexol clearance measurement (mean mGFR: 60.3 mL/min/1.73m2) for the 3 GFR-estimating equations, Incidence, Prevalence, Special Populations

Poster/Saturday

**Results:** The mean age was 79.5±4.6 years; 89% were white. Mean BMI was 27.5 kg/m2. Mean follow-up time was 9.4 years. %eGFR<60 was: CKD-EPI 33%, BIS2 48%, and CKD-EPI, 24% and BIS1 49%. When compared to eGFR<75 and after adjustment for age, race, BMI, HTN & DM, eGFR<45 by BIS2 was associated with a 2.1-fold greater risk of death (95% CI 1.5-3.0) vs 1.9-fold for eGFR<45 by CKD-EPI, (95%(CI 1.5-2.5); BSI eGFR<45 was associated with a 1.6-fold greater risk of death (95% CI 1.1-2.1) vs 1.8-fold for eGFR <45 by CKD-EPI, (95% CI 1.4; p trend <0.001 across categories for each equation). In category-based NRI analyses neither of the BIS definitions materially changed discrimination of mortality risk when compared to CKD-EPI equations.

**Conclusions:** In this cohort of older community-dwelling women, the BIS equations identified a greater proportion of participants as having CKD. With respect to mortality risk prediction, the BIS equations did not perform better than current CKD-EPI equations recommended by KDIGO 2012.

Funding: Other NIH Support - NIA, Veterans Administration Support
SA-PO682

Chronic Kidney Disease: Long Term Prevalence Trends and Influence of Modifiable Risk Factors

Stein L. Hallan,1 Marius Altern Øvrehus,2 Solfird Romundstad,1 Dena E. Ritik,1 Arnulf Langhammer,1 Joachim H. Ix.1 UCSD, La Jolla, CA; *Faculty of Medicine, NTNU, Trondheim, Norway.

Background: Prevalence of chronic kidney disease (CKD) is high worldwide, and it has been increasing in the US. However, less strict treatment goals for hypertension have recently been suggested despite increasing prevalence of obesity and diabetes. We aimed to determine whether CKD prevalence is increasing in Norway, evaluating the influence of changing prevalence of CKD risk factors on CKD prevalence, and compared findings to corresponding US data.

Methods: We included general population based participants from the Nord-Trøndelag Health Studies (HUNT), Norway: 65237 from HUNT2 (1994-96) and and 50586 from HUNT3 (2006-08). eGFR and u-ACR based on fresh blood and 3 urine samples were used to diagnose CKD. Thorough quality-control and comparisons of methods over time excluded analytical drift. We used attendance weights used to avoid responder bias.

Results: Total CKD prevalence remained stable in Norway 1996-2007 (11.3%-11.1%, p=0.42) but increased in subjects >75 years (36.6%-39.3%, p=0.014). eGFR <60 ml/min/1.73m2 increased (4.5%-4.8%, p=0.033) while albuminuria >30mg/g decreased (7.9%-7.4%, p=0.034). The most important contributors were a strong blood pressure decline during this 10 years period, more physical activity and lower cholesterol; without these improvements 2.8, 0.7 and 0.6 percentage-point higher CKD prevalence would have been expected, respectively. In contrast, the prevalence of diabetes and obesity increased moderately, but diabetics received more intensive preventive therapy, and the proportion of diabetic patients with CKD decreased substantially (33.4%-28.6%, p=0.002). In contrast, published US data indicate a stronger increase in obesity and diabetes, and physical activity was low and not improving. Access to effective care was also suboptimal for a substantial group of the population.

Conclusions: In contrast to the US where CKD prevalence has been increasing, it remained stable over a 10 year period in Norway, likely due to substantial improvements in blood pressure, lipids and physical activity despite modestly increasing diabetes and obesity.

Funding: NIDDK Support

SA-PO683

Natural Progression of Chronic Kidney Disease in Optimally Managed Patients on the Maximum Conservative Management Pathway


Background: The natural progression of advanced chronic kidney disease (CKD)/end-stage renal disease (ESRD) managed in a specialist palliative care nephrology clinic setting is unknown.

Methods: We conducted an observational study of all patients with advanced CKD undergoing predialysis counselling between 2009-2014 in a single UK center. All patients who opted for conservative management were followed up prospectively in a specialist conservative care clinic and their clinical phenotype and renal outcomes recorded. Change underlined represents presenting author.

Conclusions: Currently available eGFR equations that were developed for adult kidney transplant recipients are not applicable in non-transplanted elderly patients. Further research is necessary to evaluate whether BTP is a useful renal marker for older adults.

Funding: Private Foundation Support
Fall in eGFR in ml/min/year was 3.9 (1.8-8). Neither baseline eGFR (p=0.13) nor presence of diabetes (p=0.72) affected this rate of decline. Time to death from eGFR 10ml/min was 276 days.

Conclusions: In this first longitudinal study of conservatively treated patients with advanced CKD, variable rate of decline of eGFR ranging between 1.8-8ml/year led to death of 55% of the cohort within the median follow up period of 15 months. Reassuringly the majority of patients died at their preferred place of terminal care (home/hospice) and were registered as deaths due to ESRD. Over 50% of patient’s eGFR decline was less than 4 ml/min per year which could translate into a life expectancy of >1 year without dialysis in these exceedingly frail individuals. Prospective study is ongoing to determine the quality of life of these patients treated conservatively.

SA-PO684

Estimating County-Level Prevalence of Chronic Kidney Disease (CKD) in the United States

Jain Excell Hussain, Jennifer L. Bragg-Gresham, Hal Morgenstern, Yi Li, Neil R. Powe, Delphine S. Tuot, Deborah Rolka, Sharon Saydah, Rajiv Saran, Univers of Michigan, Ann Arbor, MI; 2 Unv of California, San Francisco, CA; 3 Centers for Disease Control and Prevention, Atlanta, GA.

Background: The prevalence of adult CKD in the US, estimated from 2005-2012 national survey data, is about 13%; however, those surveys are not designed to provide estimates for small regions. Applying a Bayesian multi-level model (BMLM), we estimated adult CKD prevalence in US counties using national and state surveys.

Methods: Data on self-reported CKD and risk-factors were obtained from (i) the National Health and Nutrition Examination Survey (NHANES 2005-2012; n=20,831), and (ii) the Behavior Risk Factor Surveillance System (BRFSS 2011; n=506,467); NHANES also provided CKD laboratory data. CKD was defined as estimated glomerular filtration rate 15-60 ml/min/1.73m2 or urinary albumin-to-creatinine ratio >30mg/g. As BRFSS does not include laboratory data, CKD for each person in the BRFSS was multiply imputed using a logistic regression model trained on NHANES data. A BMLM that effectively borrows information from neighboring counties was then fit to each imputed dataset to produce 10 sets of county-level estimates of CKD prevalence. These estimates were combined to obtain a final prevalence estimate for each county.

Results: Estimated county-level prevalence of CKD ranged from 12.3 to 27.8% (median: 18.8%) in 2011 (see map).

The standard deviation of these estimates ranged from 0.8 to 7%, and the coefficient of variation ranged from 5 to 32% of the estimate, suggesting good statistical precision.

Conclusions: We believe this is the first attempt to estimate CKD prevalence in U.S. counties. Our approach yields estimates with improved statistical precision for small counties, and is being used to study geographic variation in CKD burden across the U.S.

Funding: Other U.S. Government Support

SA-PO685

Overall CKD Prevalence in the U.S. Has Stabilized in Recent Years

Daniel P. Murphy, Charles E. McCulloch, Feng Lin, Tanushree Banerjee, Jennifer L. Bragg-Gresham, Mark Eberhardt, Meda E. Pavkov, Rajiv Saran, Neil R. Powe, Chi-yuan Hsu, UCSF [Drs. CY Hsu and NR Powe are Co-Senior Authors]; 2 Univ of Michigan; 3 CDC.

Background: ESRD incidence rates in the U.S. have stabilized recently. We sought to better understand trends in CKD prevalence since 2003-2004.

Methods: We examined data on adults from the National Health and Nutrition Examination Surveys from 1988 through 2012. We determined prevalence of stage 3-4 CKD (CKD-EPI equation eGFR 15-59 ml/min/1.73m2) overall and by age, sex, race, and diabetes strata. We examined crude prevalence and adjusted prevalence for age, sex, race, and diabetes mellitus (diagnosed and undiagnosed). Restricted cubic splines were used to model trends. The years 2003-4 (last years with published literature) were compared to 2011-12 (most recent years of available data).

Results: Consistent with the published literature, we saw a rise in CKD prevalence from the late 1990s to the early 2000s. But since around 2003-4, adjusted and unadjusted prevalence of CKD have stabilized (Figure). This temporal trend was observed across age (p for interaction=0.11), sex (p=0.61) and racial-ethnic subgroups (p=0.07; although the trend in non-Hispanic blacks appeared to differ); and did not differ by diabetes status (p=0.17). There was no difference in overall stage 3-4 CKD prevalence comparing 2003-4 and 2011-12 (p=0.25). Similar trends were seen with an expanded definition of CKD to include persons with higher eGFRe but albuminuria or used the MDRD equation.

Conclusion: Over the last decade in the U.S., there has been stabilization in the overall prevalence of stage 3-4 CKD, with a possible exception in blacks. This is contrast to what has been reported by prior studies analyzing older data but consistent with the observed stabilization of overall ESRD incidence. Efforts should be continued to implement reno-protective measures, especially in blacks.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

SA-PO686

Global Prevalence of Chronic Kidney Disease Categories 3-5 – A Systematic Review


Background: Chronic kidney disease (CKD) has become a leading contributor to the global burden of disease. We performed a systematic review of published studies to estimate the global prevalence of CKD categories 3-5 defined by estimated glomerular filtration rate (eGFR) less than 60 ml/min/m2.

Methods: PubMed, EMBASE and Scopus were searched for studies published in English from 2003 to 2013 reporting prevalence of CKD categories 3-5 in the general population. Studies were included if they (1) sampled from the general adult population, (2) assessed CKD using CKD-EPI or MDRD Study equations, (3) not on renal replacement therapy.

Results: A total of 13,081 studies were considered, of which 566 studies from 54 countries assessed prevalence of CKD, and 284 studies were in unsellected general population. The global prevalence of CKD accounting for clustering among all adults aged 20 years or older are shown in table below

<table>
<thead>
<tr>
<th>CKD Category (C)</th>
<th>Countries</th>
<th>Studies</th>
<th>CKD Prevalence (95% CI)</th>
<th>Expected Number of Individuals with CKD (Millions) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 3 to 5 (eGFR &lt;60 ml/min/1.73m2)</td>
<td>41</td>
<td>264</td>
<td>7.0 (5.2 to 9.3)</td>
<td>335.0 (249.0 to 446.0)</td>
</tr>
<tr>
<td>C 3 to 5 (20 to 65 yrs)</td>
<td>29</td>
<td>66</td>
<td>3.9 (2.1 to 7.2)</td>
<td>154.4 (80.0 to 289.0)</td>
</tr>
<tr>
<td>C 3 to 5 (65 + yrs)</td>
<td>25</td>
<td>58</td>
<td>28.9 (19.3 to 41.1)</td>
<td>229.6 (154.4 to 328.0)</td>
</tr>
<tr>
<td>C 3 only (eGFR 30-59 ml/min/1.73m2)</td>
<td>27</td>
<td>86</td>
<td>6.2 (4.2 to 9.3)</td>
<td>332.8 (220.9 to 446.0)</td>
</tr>
<tr>
<td>C 4 only (eGFR 15-29 ml/min/1.73m2)</td>
<td>18</td>
<td>50</td>
<td>0.3 (0.2 to 0.4)</td>
<td>14.4 (11.5 to 17.2)</td>
</tr>
<tr>
<td>C 5 only (eGFR&lt;15 ml/min/1.73m2)</td>
<td>15</td>
<td>29</td>
<td>0.1 (0.1 to 0.2)</td>
<td>5.2 (3.8 to 7.2)</td>
</tr>
</tbody>
</table>
Prevalence of Chronic Kidney Disease in Diabetes and Glomerulonephritis in China

Luxia Zhang, Jinwei Wang, Ming Hui Zhao. Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.

Background: Diabetes is the leading cause of end stage kidney disease worldwide, while glomerulonephritis is thought to be the predominant cause in developing countries. However, the surging prevalence of diabetes in developing countries such as China may have substantial impact on the spectrum of chronic kidney disease.

Methods: A national in-patient database involving 19.5 million patient-records was used. Diagnoses of chronic kidney disease with diabetes (DM-CKD) as well as with glomerulonephritis (GN-CKD) were extracted from International Classification of Diseases-10 codes of the discharge diagnoses. Furthermore, a general population-based, national representative sample of 47,204 participants was used. Identification of DM-CKD and GN-CKD was based on laboratory tests and the questionnaire inquiring about medical history. Then the prevalence of DM-CKD and GN-CKD was compared among both hospitalized population and general population.

Results: Among 19.5 million hospitalized patients, 1.19% and 0.79% were identified as with DM-CKD and with GN-CKD, respectively. Compared with GN-CKD, DM-CKD was associated with 7.2% (95% confidence interval [CI] 6.4-8.0%) 5.4% (95%CI 4.7-6.0%) and 59% (95%CI 46-73%) increase of costs, length-of-stay and in-hospital mortality, respectively. For general population, the prevalence of GN-CKD is also exceeded by that of DM-CKD at 0.84% (95%CI 0.68-1.00%) and 1.23% (95% CI 1.06-1.41%), respectively. The estimated number of DM-CKD patients in China was 20.1 million.

Conclusions: Our study indicates that DM-CKD surpassed GN-CKD in both hospitalized population and general population, which marked a transition of kidney disease spectrum in China. Furthermore, DM-CKD is associated with substantial increased healthcare resources utilization and increased risk of in-hospital mortality.

Funding: Government Support - Non-U.S.

Prevalence of Chronic Kidney Disease on the U.S.-Mexico Border: Role of Acculturation

Jonathan Michael Starkey, Kristina Vatcheva, Susan P. Fisher-Hoch, Joseph B. McCormick. Inst for Translational Sciences, Univ of Texas Medical Branch, Galveston, TX; Univ of Texas School of Public Health, Houston, TX.

Background: Mexican-Americans are the dominant Hispanic group in the US and face significant health disparities, including end-stage renal disease, diabetes and obesity. We characterize the quantity and associations of chronic kidney disease (CKD) in Cameron County, TX where almost 90% of the population is Hispanic and is predominantly zero or first generation Mexican-American.

Methods: The Cameron County Hispanic Cohort (CCHC) is a random sample of the Hispanic population on the southernmost point along the US-Mexico border. 1,777 participants with baseline serum creatinine measurements from 2003-2014 are included in this cross-sectional study. The glomerular filtration rate (eGFR) is estimated from serum creatinine and CKD is defined as eGFR < 60 ml/min/1.73 m^2. The weighted prevalence of CKD is estimated. A multivariate model of factors associated with CKD outcome.

Results: The prevalence of CKD is 6.0% in the CCHC and estimates the prevalence in Cameron County, TX. Stratified by gender, the prevalence in men and women is 6.9% and 4.2% respectively. Multivariate analysis reveals significant associations of country of birth (OR 2.14, 95% CI [1.02, 4.46]) for those born in the US), hyperglycemia (OR 2.72, 95% CI [1.41, 5.239]) and granulocyte count (OR 1.345, 95% CI [1.038, 1.708]) with CKD status after adjusting for age, gender, diabetes status, cardiovascular disease history, hypertension, smoking history, obesity, LDL and statin use.

Conclusions: The prevalence of CKD in the CCHC is higher than previous national estimates in Hispanics or Mexican-Americans. The data suggest that acculturation, triglycerides and inflammation are associated with CKD in Hispanics living on the US-Mexico border. More research is needed in Mexican-Americans to investigate CKD in this growing minority population.

Funding: Other NIH Support - K22 LM011869-01A1, National Library of Medicine (NLM) Starkey, Jonathan M (PI)

MD000170 P20 funded from the National Center on Minority Health and Health disparities (NCMHD) McCormick, Joseph (PI), and the Centers for Clinical and Translational Science Award U1L TR000371 from the National Center for Advancing Translational Science (NCATS) Clinical and Translational Science Award (UL1TR000071)

SA-PO689

Validation of the Kidney Failure Risk Equation in Manitoba

Reid Whitlock,1,2 Paul Komenda,1,2 Claudio Rigatto,1,2 Allison Dart,1,2* Joe A. Bueti,1,2 Randy Wald,1 Navdeep Tangri,1,2,3 Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; 2Nephrology, Seven Oaks Hospital, Winnipeg, MB, Canada; 3Medicine, Univ of Manitoba, Winnipeg, MB, Canada; Nephrology, Health Science Centre, Winnipeg, MB, Canada.

Background: Patients with chronic kidney disease (CKD) are at risk for progression to kidney failure. We previously developed the Kidney Failure Risk Equation (KFRE) to predict the progression of CKD to kidney failure in patients referred to nephrologists. This study aims to validate the KFRE in an unreferred population in Manitoba, and to determine risk thresholds for clinical decision-making.

Methods: We included patients from the Diagnostic Services of Manitoba database with an eGFR < 60 ml/min/1.73 m^2 and a urinary albumin creatinine ratio measured between October 1, 2006 – March 31, 2007. Five year kidney failure risk was predicted using the 4-variable KFRE and compared with treated kidney failure events from the Manitoba Renal Program database. Sensitivity and specificity for KFRE thresholds (3% and 10% over 5 years) were then compared to eGFR thresholds (30 and 45 ml/min/1.73 m^2).

Results: 1,512 patients were included and 151 developed kidney failure over the 5-year follow-up period. The 4-variable KFRE more accurately predicted kidney failure when compared to eGFR alone (AUROC’s 0.90 [95% confidence interval (CI) 0.88-0.92] for KFRE vs. 0.78 [95% CI 0.74-0.83] for eGFR). At a risk threshold of 3% over 5 years, the KFRE had a sensitivity of 97% and a specificity of 62%.

Conclusions: The KFRE is highly accurate at predicting 5-year risk of kidney failure in a population based sample of Manitobans with CKD Stages 3 to 5. Integration of the 4-variable KFRE into laboratory information systems should be considered.

Funding: Private Foundation Support

SA-PO690

A Risk Prediction Model of End-Stage Renal Disease in Type 1 Diabetes Using Urine MCP-1 as an Alternative Biomarker of ACR

Masayuki Yamanouchi, Monika A. Niewczas, Natalia Z. Nowak, Andrzejj S. Krolewski. Genetics & Epidemiology, Joslin Diabetes Center, Boston, MA.

Background: There is a great need to develop risk prediction models to recruit patients at high risk of end-stage renal disease (ESRD) for clinical trials in patients with type 1 diabetes. We developed two models to predict progression of CKD 3 and 4 to ESRD in 5 years in patients with type 1 diabetes: “ACR model” that consists of patient’s age, eGFR, Hba1c and ACR, and “Urine MCP-1 model” that consists of the same markers but replacing ACR with urine MCP-1.

Methods: We identified 285 patients with type 1 diabetes and impaired renal function (eGFR: 15-60 ml/min/1.73 m^2) from Joslin Proteinuria Cohort that was followed for 7 to 18 years to ascertain ESRD. We focused on the events within 5 years from enrollment. For the ACR model, the Cox model identified four baseline variables: age, eGFR, ACR, and Hba1c for the final model. For the urine MCP-1 model, urine MCP-1, age, eGFR and Hba1c were identified by the Cox model. Assigned point scores corresponded to each coefficient.

Results: 5-year risk of ESRD in the study group was 40.5%. In the ACR model, the variable with highest magnitude was eGFR<30, 4 points; followed by ACR<300, 2 points; Hba1c<7.5, 1 point; and age<45 years, 1 point, while in the urine MCP-1 model, the variable with highest magnitude was eGFR<30, 2 points; followed by urine MCP-1>545, 1 point; Hba1c>7.5, 1 point; and age<45 years, 1 point. The model with urine MCP-1 performed almost equal to the model with ACR (C statistic of 0.702 (0.556-0.831) vs. 0.719 (0.574-0.845)). Although the number of patients who developed ESRD in the high risk group in the urine MCP-1 model is smaller than in the ACR model, the incident rate was not different (0.719 (0.574-0.845)). Using the risk score with urine MCP-1, we can identify a subgroup of patients at very high risk of ESRD.
SA-PO691
A Reliable Formula to Estimate 24-h Urine Sodium Excretion from Morning Fasting Urine in Patients with Chronic Kidney Disease
Se Jun Kim,1 Ho Jun Chin,2 Sejoong Kim,3 Dong Ki Kim,1 Suhngwol Kim,1 Jung Hwan Park,4 Sung Joon Shin,2 Bum Soon Choi,2 Chun Soo Lim,1 Sang Ho Lee.1
1Kyung Hee Univ Hospital, Seoul, Korea; 2Seoul National Univ Bundang Hospital, Seong-Nam, Korea; 3Seoul National Univ Hospital, Seoul, Korea; 4KonKuk Univ Hospital, Seoul, Korea; 5Dongguk Univ Ilsan Hospital, Goyang, Korea; 6Seoul St Mary’s Hospital, Seoul, Korea; 7Seoul National Univ Barama Medical Center, Seoul, Korea.

Background: Estimated 24 hour urine sodium excretion based on spot urine has been proposed to replace 24 hour urine collection in epidemiologic studies. However, estimated sodium excretion has not been verified whether it is useful in patients with chronic kidney disease (CKD) as well as in interventional study. The aim is to evaluate the estimated sodium excretion in prospective low salt diet education study (ESPECIAL) cohort.

Methods: New formula was developed from baseline data of 228 CKD patients of ESPECIAL cohort using a multivariable linear regression and compared with previous three formulas from healthy population (Kawasaki, INTERSALT, Tanaka) and one from CKD patients (Nerbas) for the prediction of 24 hour sodium excretion after ARB treatment and low salt diet education.

Results: Among previous reported formulas, the estimation by Tanaka’s formula showed the smallest bias (estimated 144.3±46.5 vs. measured 154.1±69.6 mEq/day), but weak correlation (r=0.34). We developed new formula with improved bias (estimated 154.0±39.7 mEq/day) and correlation (r=0.56). New formula also showed the best correlation (r=0.57) with smallest bias (estimated ±4 mEq/day) even after ARB treatment, which did not show significant change of measured sodium excretion [56.3±70.6 mEq/day]. Intensive low salt diet education elicited the significant decrease of measured sodium excretion (121.2±61.9 mEq/day). Intensive low salt diet education elicited the significant decrease of measured sodium excretion (121.2±61.9 mEq/day). Although new formula also showed best correlation, any of formulas did not predict the amount of the decrease of measured sodium excretion.

Conclusions: We developed more reliable formula for estimating urine sodium excretion for CKD patients. However, our data suggests estimated sodium excretion could be applied for epidemiological study rather than low salt intervention study.

SA-PO692
Evaluation of Glycated Albumin for Glycemic Monitoring in Diabetic Nephropathy
Yang Fei, Ying Fan, Yunmei Liu, Niansong Wang. Dept of Nephrology and Rheumatology, Shanghai Jiaotong Univ Affiliated the Sixth Hospital, Shanghai, China.

Background: Glycated albumin(GA) has been now widely used for the evaluation of blood glucose in diabetic nephropathy(DN) patients. However, the effect of proteinuria on GA should be taken into account, especially in patients with advanced DN.

Methods: A total of 621 diabetic nephropathy patients from year 2009 to 2014 were enrolled in the study. According to the 24 urine protein(UP) output, subjects were divided into 3 groups defined as (1) microalbuminuria: UP=30-300mg/24h, (2) moderate albuminuria: UP=300-1000mg/24h, (3) macroalbuminuria: UP>1000mg/24h.

Results: In all DN patients, the related factors of GA were fasting blood glucose(FBG), potential blood glucose(PBG), body mass index (BMI) and 24 UP. The multivariable regression equation was GA = 0.254FBG + 0.347PBG-0.341 BMI-1.306UP, (R²=0.375).

Conclusions: In diabetic nephropathy patients, blood glucose, serum albumin and 24h urinary protein output may serve as important factors for the evaluation of GA on glycemic level. GA tended to be underestimated in DN patients with macroalbuminuria. The adjGA may be a better way to objectively evaluate glycemic status in patients with advanced DN.

SA-PO693
Meredith C. Foster,1 Julie K. Bowser,2 Josef Cores,2 Roger A. Fielding,3 Lesley Inker,4 Andrew S. Levy,1 Tufts Medical Center; 1Tufts University; 2Johns Hopkins Univ; 3Tufts Univ.

Background: Established serum filtration markers are influenced by body composition (creatinine by muscle mass, cystatin C by fat mass) but limited data exist evaluating associations of these markers with body composition assessed using a gold-standard measurement approach. Our aim was to examine the association of body composition quantified using dual energy X-ray absorptiometry (DXA) with serum creatinine and cystatin C in US adults.

Methods: We conducted a cross-sectional analysis in 43782 adults age 18+ years from NHANES 1999-2002. Body composition included total lean mass and total fat mass; body mass index (BMI, kg/m^2) was included for comparison. Associations of natural-log-transformed creatinine and cystatin C with body composition measures were evaluated using multivariable linear regression, stratified by age. Analyses were weighted to account for the NHANES design with multiple imputation for missing DXA data.

Results: Lean mass was associated with higher serum creatinine in all age groups whereas higher fat mass was associated with higher creatinine in adults age 65+ (Table). Lean mass and fat mass were associated with higher serum cystatin C across all age groups; associations of lean mass with cystatin C were not significant with additional adjustment for fat mass.

Conclusions: Fat mass and lean mass are differentially associated with creatinine and cystatin C in US adults. Findings in younger adults suggest that observed associations may reflect the impact of body composition rather than kidney function on serum marker levels. Further work is needed to determine how the observed associations are influenced by GFR and body composition simultaneously and the impact of fat and lean mass on CKD prevalence estimates.

SA-PO694
Associations of the Levels of Kidney Function with Protein-Energy Wasting Syndrome Are Independent of Serum CRP and Bicarbonate
Xiaohui Chen,1 G. Wei,3 Robert E. Boucher,1 Dominique Ferranti,2 Michel Chonchol,1 Kalani L. Raphael,1 Sirini Beddhu.2 "U of Utah, "VA SLC; "UC Denver.

Background: Inflammation and metabolic acidosis are putative causative factors of protein-energy wasting (PEW) in CKD. Therefore, we examined whether serum CRP and bicarbonate levels attenuate the associations of CKD with PEW in 11,854 adult (age > 20 years) participants in the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: PEW syndrome was defined as the presence of at least one criterion in two out of three categories: serum chemistry (albumin < 3.25 g/dl or cholesterol < 100 mg/dl), body weight (BMI < 20 kg/m^2 or unintentional weight loss > 10% over 1 yr), and muscle mass (body fat % < 10% or MAMC < 10% of 50th percentile of reference population). Using eGFR 60 to 89 ml/min/1.73 m^2 as the reference, the odds of PEW in ≥ 45, 50 < 45 ml/min/1.73 m^2 groups were examined in logistic regression models using svy set in STATA 13.

Results: Mean age was 46.0 yrs, 50.3% were male, 9.5% were black. The prevalence of PEW syndrome had a U shaped association with the level of kidney function.

Compared to the reference group, both eGFR ≥ 90 and < 45 groups had nearly two-fold increased odds of PEW. This was not attenuated after adjusting for serum CRP or bicarbonate.

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73m²)</th>
<th>PEW syndrome OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>≥ 90</td>
<td>1.85 (1.41, 2.68)</td>
</tr>
<tr>
<td>45 – 59.9</td>
<td>1.11 (0.70, 1.76)</td>
</tr>
<tr>
<td>&lt;45</td>
<td>2.09 (1.05, 4.13)</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, race, education, smoking, alcohol use, MI, CHF, stroke, diabetes, lung disease and cancer

> Above > serum CRP and serum bicarbonate
Discussions About CKD Between African Americans with High CKD Risks

Methods: As part of a randomized controlled trial, we characterized CKD awareness and perceived risk of CKD among AAs with uncontrolled hypertension and CKD (eGFR 15-60 ml/min/1.73m2 or UACR ≥30mg/g). We assessed patients’ self-reported CKD awareness (“Do you have a kidney problem or chronic kidney disease?”; yes or no) and degree of perceived likelihood (“How likely do you think it is that you could develop kidney problems or kidney failure in the next 10 years?”; not likely versus slightly, moderately, or very likely response) and perceived concern of developing CKD (“How concerned are you about developing kidney problems in the next 10 years?”; not concerned versus slightly, moderately, or very concerned response). We constructed multivariable models to assess patient characteristics independently associated with patients’ CKD awareness and perceived CKD risks.

Results: Among 52 AA patients with CKD, the mean age was 58 years, 67% were female, 67% had diabetes, 15% had coronary artery disease, 40% had eGFR=60 and 60% had albuminuria alone. The majority (n=37, 71%) of patients were not aware of their CKD. Among these, 27% (n=10) considered themselves unlikely to develop CKD and 19% (n=7) were not concerned about developing CKD. CKD awareness was greater among patients with an eGFR <60 (adj. OR 2.5, 95% CI [1.9-3.2]) and patients with higher eGFR [adj. OR 0.96 (0.92-1.0)]. CKD awareness was low, with some patients unconcerned about developing CKD in the future. Strategies to improve recognition of CKD risks among AAs at high CKD risk are needed. Funding: NIDDK Support

SA-PO696

Discussions About CKD Between African Americans with High CKD Risks and Their Primary Care Physicians

Methods: In a randomized controlled trial of African American (AA) patients with uncontrolled hypertension and CKD, we analyzed audio-recorded encounters between patients and their PCs using the Roter Interaction Analysis System to characterize the occurrence of CKD discussions (e.g., discussion of kidney disease, eGFR, creatinine, or albuminuria) and patient-physician communication patterns (e.g., patient-centeredness, the degree to which the discussion focused on the patient’s psychosocial and lifestyle context) during routine primary care visits. In multivariable logistic regression models, we assessed patient visit, and communication characteristics independently associated with the presence of CKD discussions among all patients and among those with CKD (eGFR=60-<150 ml/min/1.73m2 or UACR ≥30mg/g).

Results: Among 124 patients, the mean age was 58 years, 69% were female, 48% had diabetes, 35% had CKD (mean eGFR 33). The average visit length was 22 minutes. Patients and PCPs discussed CKD in 47% of visits and discussions more frequently occurred among patients with CKD (vs. without CKD) (66% and 36% respectively, p=0.002). Discussions and PCPs discussed CKD in 47% of visits and discussions more frequently occurred among patients with CKD (vs. without CKD) (66% and 36% respectively, p=0.002). Discussions and PCPs discussed CKD in 47% of visits and discussions more frequently occurred among patients with CKD (vs. without CKD) (66% and 36% respectively, p=0.002).

Conclusions: Among AA patients with uncontrolled hypertension and CKD, awareness of CKD was low, with some patients unconcerned about developing CKD in the future. Strategies to improve recognition of CKD risks among AAs at high CKD risk are needed. Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO697

Primary Care Utilization Is Associated with Reduced Mortality Among Older Adults With CKD

Methods: We quantified the association between primary care utilization and ESRD incidence or mortality among older US adults with CKD (in 2005-2006) using Medicare claims. We assessed (in 2006) patients’ primary care utilization (no visit at least one, other care utilization [nephrology care [no visit at least one], the total number of annual evaluation and management (E & M) visits with any type of provider), and patients’ comorbid conditions and sociodemographics. We used standard and cause-specific (accurate for competing risk of death) Cox proportional hazard models overall and stratified by age (65-74, 75-84, or ≥85 years) to estimate hazard ratios (HRs) for ESRD or mortality.

Results: Among 106,765 patients, 79% (70% had at least one primary care visit in 2006, and 21% had at least one nephrologist visit. The median number of ambulatory & E & M visits was 10. Compared to patients with no primary care visits, patients with at least one visit were younger (78 vs. 80 mean years, p<0.001), less likely African American (10 vs. 14%, p<0.001), and had a greater prevalence of diabetes (46 vs. 42%, p<0.001), hypertension (88 vs. 78%, p<0.001), or coronary artery disease (74 vs. 72%, p=0.001). Over 4 years of follow-up, 4,264 patients developed ESRD and 45,059 died. Primary care utilization was not associated with ESRD incidence. However, compared to patients with no primary care visits, patients with at least one visit had a lower risk of death (HR [95%CI]: 0.73 (0.72-0.75)) overall and in age stratified models.

Conclusions: Primary care utilization was not associated with lower ESRD risk, but it was associated with a lower risk of death among older adults with CKD. Efforts to improve the engagement of primary care providers in the care of patients with CKD represent an important strategy to improve the health of this high risk population. Funding: NIDDK Support

SA-PO698

Routine Use of Health Care Among High-Risk African Americans at Risk of CKD

Methods: We quantified the prevalence of RHC (physical exam ~1 year prior use) among AA Jackson Heart Study (JHS) baseline participants (from 2000-2004) with hypertension (HTN) or diabetes. We identified demographic, attitudinal (e.g., perceived discrimination, anger and hostility, stress, trust in health providers) and educational (i.e., CKD awareness) factors independently associated with RHC use among high-risk AA's at risk of CKD incidence or progression.

Results: Of 5301 JHS participants, 1152 met inclusion criteria. Most (n=909, 79%) reported RHC use. Rates of RHC were similar in those with and without CKD (22% vs. 23%). Participants not using RHC (vs. using) were more likely to be <55 years of age (45 vs. 42%, p<0.001), male (43% vs. 30%), without HTN (9% vs. 5%), tobacco users (38% vs. 29%), and uninsured (14% vs. 9%), all p<0.05. In multivariable models, not using RHC was associated with age <55 (OR 1.75 [95% CI 1.25-2.5], male sex (OR 1.55 [1.12-2.16]), - HS diploma (OR 1.63 [1.12-2.34]), no HTN (OR 2.14 [1.34-3.4]), lower provider trust (OR 3.27, [1.61-6.65]) and less anger and hostility (OR 1.53, [1.1-2.1]).

Conclusions: Among high-risk AA's in the JHS, younger participants and males were less likely to use RHC. Those with low trust were also less likely to use RHC. Efforts to address health risks among high-risk AA's should target those using less RHC and consider attitudinal barriers to RHC.

SA-PO699

Development of a Question Prompt Sheet for Patients with Chronic Kidney Disease

Background: Patients with chronic kidney disease (CKD) commonly have unmet information needs. Greater patient participation in healthcare discussions can address these needs, and is associated with improved health outcomes. A question prompt sheet (QPS), a list of questions to prompt discussion, has been shown to increase patient participation in other chronic disease discussions; however, no QPS has been developed for CKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Funding: NIDDK Support
Methods: We conducted a 2-phase cross-sectional study involving semi-structured telephone interviews with 1800 patients with stage 5 CKD who were asked questions concerning the use of CKD-QPS targeted to patients with moderate CKD. Patients with an estimated glomerular filtration rate <60ml/min/1.73m², on dialysis, or with a transplant were recruited from a single VA nephrology clinic. Phase 1 interviews included 17 open-ended questions assessing patients’ CKD information needs. Responses were qualitatively analyzed to identify an initial 67-items QPS. Phase 2 participants reviewed the pre-nailed QPS to rate the importance of asking each question on a 5-point Likert scale, provide open-ended feedback, and rate their willingness to use a CKD-QPS. Question items responses were analyzed to refine and reduce QPS questions. In total of 76 participants completed interviews (phase 1: n=32, phase 2: n=44). Most were male (96%), non-Hispanic white (68%), and mean age was 66 years. Patients desired more information about CKD, particularly regarding self-care techniques, dialysis/ transplant, and CKD complications. The final QPS tool included 37-questions divided into 10 CKD subtopics (e.g., CKD definitions, causes, impact, monitoring, labs, self-care, treatment, dialysis, transplant, managing comorbid conditions). Most patients (91%) reported being ‘completely’ or ‘very’ willing to use a CKD-QPS in future doctor visits.

Conclusions: CKD patients have unmet information needs and wish to use a CKD-QPS. Further research is needed to assess whether our CKD-QPS effectively addresses patients’ information needs, enhances doctor-patient communication, and improves health outcomes.

Funding: Veterans Administration Support

SA-PO700 Medication Burden and Safety in Veterans with Chronic Kidney Disease

SA-PO701 I illicit Drug Use and Chronic Kidney Disease in an Urban Population

SA-PO702 A Tailored, Interactive Mobile Health Communication Application for Patients with Chronic Kidney Disease: Development and Feasibility Assessment

SA-PO703 Evaluation of Clinical Pharmacy Services in the Management of Kidney Disease

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

Underline represents presenting author.

788A
SA-PO704
Views and Practice Patterns of Dialysis Medical Directors Towards End-of-Life Decision Making for Patients with End-Stage Renal Disease
Enrica Fung,1 Nathan Samuel Slesnick,2 Manjula Kurella Tamura,1,3 Brigitte Schiller.1 1Stanford Univ, Palo Alto, CA; 2Satellite Healthcare, San Jose, CA; 3Geriatric Research and Education Clinical Center, Veterans Affairs, Palo Alto, CA.

Background: Nephrologists frequently engage in end-of-life decision making for patients with end-stage renal disease (ESRD). Patients with ESRD report infrequent end-of-life discussions and nephrology trainees report feeling unprepared for end-of-life decision making, but the views of dialysis medical directors have not been studied. Our objective is to understand dialysis medical directors’ views and practice patterns on end-of-life decision making for patients with ESRD.

Methods: We administered questionnaires to dialysis medical directors during medical director meetings of three different dialysis organizations in 2013. Survey questions corresponded to recommendations from the Renal Physicians Association clinical practice guidelines on initiation and withdrawal of dialysis.

Results: There were 121 medical director respondents from 28 states. The majority of respondents felt “very prepared” (66%) or “somewhat prepared” (29%) to participate in end-of-life decisions and most (80%) endorsed a model of shared decision-making. If asked to do so, 70% of the respondents provided prognostic information “often” or “nearly always”. For patients with a poor prognosis, 36% of respondents would offer a time-limited trial of dialysis “often” or “nearly always”, while 56% of respondents would suggest withdrawal from dialysis “often” or “nearly always” for those with a poor prognosis currently receiving dialysis therapy. Patient resistance and fear of taking away hope were the most commonly cited barriers to end-of-life discussions.

Conclusions: Views and reported practice patterns of medical directors are consistent with clinical practice guidelines for end-of-life decision making for patients with ESRD but inconsistent with patient perceptions.

Funding: NIDDK Support

SA-PO705
Emergency Department Utilization Among United States ESRD Patients
Brendon P. Loyvasik, Rebecca H. Zhang, Taylor A. Melanson, Stephen O. Pustan, Rachel E. Patzer. Emory Univ, Atlanta, GA.

Background: Single center studies suggest that ESRD patients have a high rate of emergency department (ED) utilization, with 0.9-2.4 ED visits/patient-year. Prior studies show that ESRD is a stronger risk factor for ED use than heart failure, lung disease, or cancer. However, ED utilization among a national ESRD patient population has not been examined.

Methods: We examined a cohort of 788,162 incident adult ESRD patients in the United States Renal Data System from 2005-2011. ED utilization was identified using CPT codes 99281-5 (Severity Levels 1-5) and 99291 (Critical Care) by American College of Emergency Physicians guidelines. ED and hospital admission, diagnosis, and procedures were obtained from the USRDS and Medicare Physician/Supplier and Inpatient databases for 2011.

Results: In the first year of ESRD diagnosis, 1,143,372 ED visits were observed for 480,176 unique ESRD patients. 77% of ESRD patients used the ED within the first ESRD year at an average of 2.69 ED visits/patient-year. The national range was 1 to 172 ED visits per year with median 2 visits (interquartile range 1-4 visits) and 95th percentile 8 visits.

Conclusions: Patients with ESRD over 100 times in their first ESRD year. Nearly half (46.0%) of ED visits were coded as Critical Care emergencies. 15.4% of ESRD patients used the ED over 100 times in their first ESRD year. 1,143,372 ED visits were observed for 480,176 unique ESRD patients. 77% of ESRD patients used the ED within the first ESRD year at an average of 2.69 ED visits/patient-year. The national range was 1 to 172 ED visits per year with median 2 visits (interquartile range 1-4 visits) and 95th percentile 8 visits.

Funding: NIDDK Support

SA-PO706
Impact of Evidence-Based Clinical Care on Major Adverse Clinical Events in Patients with Clinically Significant Proteinuria: A Population-Based Retrospective Cohort Study
Julius Oluoch Okel1, Bilal Qarni,2 Timothy Olusegun Olanrewaju,2 Aminu K. Bello.1 1Univ of Alberta; 2Univ of Ilorin, Nigeria.

Background: Proteinuria is an important prognostic marker for cardiovascular (CV) and renal events. Most studies of quality of care (QoC) in chronic kidney disease (CKD) have focused on other markers for risk stratification and outcomes. We hypothesized that in proteinuric CKD, markers of good quality care will be associated with lower risk of adverse clinical outcomes (all-cause mortality, all-cause hospitalization, CV and renal outcomes).

Methods: We used a population-based cohort of patients with significant proteinuria (albumin-creatinine ratio (ACR) ≥60 mg/mmol, protein-creatinine ratio (PCR) ≥100 mg/mmol or protein 3+ on dipstick) to evaluate current patterns of evidence-based care and association with outcomes. Markers of good quality care were defined as nephrology referral, relevant laboratory testing and appropriate medication use (ACEI/ARBs; statins).

Results: Of the 71, 660 with at least 1 or 2 proteinuria measurements, 16,204 (22.6%) had significant proteinuria. At follow-up, receipt of good quality care (1) timely referral, (2)HbA1c testing, (3)use of ACEI/ARBs and (4) use of statins) was associated with reduced risk of mortality: 0.67 (0.59-0.75), 0.52 (0.46-0.59), 0.68 (0.62-0.74), and 0.63 (0.57-0.69), and all-cause hospitalization: 0.85 (0.79-0.93), 0.65 (0.59-0.72), 0.93 (0.87-0.99), and 0.82 (0.77-0.88) respectively. There were no statistically significant associations with the risk of CV and renal events.

Conclusions: This study examined the link between evidence-based treatment and clinical outcomes in an especially high-risk population with CKD. Good quality care impacts mortality risk and hospitalization risk, and reduced risk of hospitalization. The impact of QoC on renal and cardiovascular events is less clear. The findings would justify future interventions to increase uptake of such treatments in patients with proteinuric CKD.

Funding: NHLBI, NHLBI, NHLBI

SA-PO707
APOL1 Risk Alleles and Risks of Cardiovascular Disease in Children with Focal Segmental Glomerulosclerosis (FSGS) (FSGS) Robert Woroniecki,1 Derek Ng,2 Sophie Limou,1 Cheryl Ann Winkler,1 Kimberly J. Reidy,3 Mark Mitsnefes,4 Craig S. Wong,1 Bradley Warady,1 Susan L. Furth,4 Jeffrey B. Kopp,4 Frederick J. Kaskel.1 1Stony Brook Children’s Hospital, Stony Brook, NY; 2Johns Hopkins Bloomberg School of Public Health, Baltimore, NY; 3NCI, NIH, FNL, Frederick, MD; 4Emory, Children’s Hospital at Montefiore, Bronx, NY; 5Cincinnati Children’s Hospital, Cincinnati, OH; 6Univ of New Mexico, Albuquerque, NM; 7Children’s Mercy Hospital, Kansas City, MO; 6Univ of Pennsylvania, Philadelphia, PA; 4NIDDK, NIH, Bethesda, MD.

Background: APOL1 renal risk alleles are a major cause of glomerular disease in African Americans (AA). It is controversial as to whether individuals with high risk (HR) APOL1 genotypes (2 risk alleles) are at risk for athereosclerotic heart disease, and association with left ventricular hypertrophy (LVH) has not been explored. It is unclear whether children with focal segmental glomerulosclerosis (FSGS) and HR APOL1 are at increased cardiovascular risk.

Methods: Self-identified AA children with FSGS in CKiD study cohort were genotyped for APOL1 renal risk variants: G1 (rs73855319, S342G) and G2 (rs71785313, NY388-389 deletion), and compared to non-AA children with FSGS, none with HR.

Results: Of the 71, 660 with at least 1 or 2 proteinuria measurements, 16,204 (22.6%) had significant proteinuria. At follow-up, receipt of good quality care (1) timely referral, (2)HbA1c testing, (3)use of ACEI/ARBs and (4) use of statins) was associated with reduced risk of mortality: 0.67 (0.59-0.75), 0.52 (0.46-0.59), 0.68 (0.62-0.74), and 0.63 (0.57-0.69), and all-cause hospitalization: 0.85 (0.79-0.93), 0.65 (0.59-0.72), 0.93 (0.87-0.99), and 0.82 (0.77-0.88) respectively. There were no statistically significant associations with the risk of CV and renal events.

Conclusions: This study examined the link between evidence-based treatment and clinical outcomes in an especially high-risk population with CKD. Good quality care impacts mortality risk and hospitalization risk, and reduced risk of hospitalization. The impact of QoC on renal and cardiovascular events is less clear. The findings would justify future interventions to increase uptake of such treatments in patients with proteinuric CKD.

Funding: NHLBI, NHLBI, NHLBI

SA-PO708
Trends in Burden of Out-of-Pocket Expenses in United States Adults with Kidney Disease from 2002-2011
Mukonso N. Ozrie,1 Kinfe Gebreziabher Bishu,2 Clara E. Dismuke,3 Leonard Egede.2 1Nephrology, MUSC; 2Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.

Background: High out-of-pocket (OOP) burden negatively impacts healthcare access and outcomes. Studies examining high OOP burden in the general population exists however no studies has examined OOP healthcare burden in people with kidney disease (KD). This study examined trends in high OOP healthcare in people with KD while concurrently evaluating the impact of insurance status and income category on high OOP burden.

Methods: We analyzed 2,966 adults aged 18-64 years with kidney disease using the Medical Expenditure Panel Survey-MEPS. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute and unspecified renal failure; 158 - chronic renal failure; 159 - acute and unspecified renal failure; 157 - acute and unspecified renal failure; 158 - chronic renal failure; 160 - calculus or urinary tract and; 161 -...
Buffalo, Buffalo, NY; Impact of Timely AV Fistula Placement on Resource Utilization After Ritika Sharma, Candace D. Grant, Ronak Patel, Monika Wadhwani, Vladimir Disease in Patients with Chronic Kidney Disease Health Disparities and Increased Risk of Developing End Stage Renal however people with kidney disease in the US still experience high OOP burden. Policies of people with high OOP fell by 10 percentage points from 2002/2003 to 2010/2010. The proportion of poor/near poor people and uninsured with high OOP was as high as 52% and 30% respectively in 2002/2003 but fell to about 25% and 27% respectively in 2010/2011. 

Conclusions: Trends in high OOP burden in people with KD has decreased over time however people with kidney disease in the US still experience high OOP burden. Policies to reduce high OOP in people with KD could significantly impact KD outcomes.

SA-PO709 Health Disparities and Increased Risk of Developing End Stage Renal Disease in Patients with Chronic Kidney Disease Alejandro Pevey, Ritika Sharma, Candace D. Grant, Ronak Patel, Monika Wadhawan, Vladimir Liberman, Shanza Mujeeb, Saira Sharif, Shayan Shirazian, Nobuyuki (Bill) Miyawaki, Joseph Mattana. Medicine, Winthrop-Univ Hospital, Mineola, NY.

Background: Health disparities occur in groups of people that experience suboptimal health care based on their social, economic, and/or environmental disadvantage. Identifying how these disparities affect the risk of chronic kidney disease (CKD) progression to end stage renal disease (ESRD) can hopefully lead to a reduction in these health inequities and improve health outcomes for all CKD patients. We examined health disparities and the risk of ESRD using patient-specific and community-specific variables. 

Methods: We studied a cross-section of 623 patients with stage 3 and 4 CKD and estimated their 2- and 5-year risk of ESRD using the method of Tangri et al. (JAMA 2011; 305:1553–1559). The U.S. Census Bureau Community Survey was used to obtain patient zip code-specific data including percent foreign born, percent below the poverty level, median household income, and percentage graduating high school. We did a multivariable generalized linear analysis on the outcome variables of the 2 and 5 year risk of ESRD.

Results: Lower household income was associated with a higher risk of ESRD at 2 and 5 years (p<0.05). There was a trend towards a higher risk of ESRD amongst patients from zip codes with higher poverty rates and lower education levels. Being single, including by divorce and separation but not by being widowed, was associated with a significantly higher risk of ESRD. We also found that patients on Medicaid and patients with private insurance or self pay had a significantly higher risk of ESRD compared to those on Medicare.

Conclusions: Our findings suggest that there are substantial health disparities related to CKD and the risk of ESRD. Some of these disparities are patient-specific but others appear to be related to factors associated with the community where they reside. This suggests that evaluation of patient-specific as well as community-specific variables might help to better individualize CKD care and improve our ability to identify and treat the patient at increased risk of developing ESRD.

SA-PO710 Impact of Timely AV Fistula Placement on Resource Utilization After Initiation of Dialysis Edwin J. Anand,1 Kabir Jalal,1 Laura L. Argauer,1 Brian M. Murray,1 Pradeep Arora,2 Rocco C. Venuto,1 1Medicine, SUNY at Buffalo, Buffalo, NY; 2Computer Task Group, Buffalo, NY. Computer Task Group, Buffalo, NY. Computer Task Group, Buffalo, NY. Medicine, VA Medical Center, Buffalo, NY.

Background: Maintenance dialysis is ideally initiated in the outpatient setting with a permanent access. This requires advance planning and of care between nephrologists, and access surgeons. The costs associated with ‘crash’ initiation of dialysis is anticipated to be high. In this observational study, we studied the hospitalization rates and costs of care in the 12 months following dialysis initiation between patients who started dialysis in an ideal manner versus sub-optimally.

Methods: Claims and laboratory data from a large, regional insurance company covering half a million patients between January 2001 and May 2014 were reviewed. 422 patients were started on dialysis in the above period. 257 patients (61%) had a crash start of dialysis. 86 patients (20%) had a fistula prior to dialysis. Compared to patients who did not crash, patients who crashed were older (p<0.0001), had a higher hospitalization rate in the one year period (p=0.0088). Multivariate analysis confirmed that patients who crashed had a significantly higher hospitalization rate in the one year following dialysis (p=0.0067). Patients with a fistula in place prior to dialysis experienced fewer hospitalizations (p=0.0377). Cost in the first year was also higher in patients who had a ‘crash’ without a fistula (p=0.0181). The cost advantage of having a fistula decreased with increasing age (p=0.0402).

Conclusions: Dialysis ‘crash’ results in increased morbidity and resource utilization. Coordination of care and timely access creation should reduce hospitalization and costs.

SA-PO711 DASH Diet Accordant Foods in the Homes of Urban African Americans at Risk for CKD Deidra C. Crews,1 Yang Liu,2 Edgar R. Miller,1 Patti Ephraim,1 Jessica M. Ameling,1 Kimberly Gadzune1, Lisa A. Cooper,1 L. Ebony Boulware.1,2 Johns Hopkins U., Baltimore, MD; 1Duke U., Baltimore, MD.

Background: The Dietary Approaches to Stop Hypertension (DASH) diet is recommended for the treatment of hypertension, especially among African Americans (AAs). Many barriers may hinder urban AAs from following the DASH diet, putting them at increased risk of poor health outcomes, including CKD.

Methods: In a randomized trial of urban AAs with uncontrolled hypertension, we assessed (via interview and home inspection) the presence of DASH diet accordant foods and full-sized kitchen appliances needed to prepare DASH meals. We examined factors associated with having DASH diet accordant foods or needed appliances using logistic models adjusted for age, sex, food insecurity (skipping meals due to lack of money), income, literacy, diabetes, obesity, CKD (eGFR<60 or albuminuria) and comorbid disease (Charlson Index).

Results: Among 159 participants, mean age was 57 yrs and 74% were female. Only 14.5% had 5 of the DASH food categories in their homes (fruits, vegetables, low fat dairy, whole grains, plant proteins). Over 80% had full-sized ovens and refrigerators.

DASH Accordant Foods in Home N (% ) Participants
- Fresh or frozen vegetables 131 (82%)
- Fresh or frozen fruits 93 (58%)
- Low fat dairy 48 (30%)
- Whole grains 102 (64%)
- Plant proteins 129 (81%)

Participants with CKD (vs without) had lower odds of having fresh fruits (adjusted odds ratio, 95% confidence interval: 0.40, 0.18-0.86). Younger age (yr increments) and annual income <$30K (vs ≥$30K) were associated with lower odds of having whole grains (0.96, 0.93-0.99 and 0.28, 0.11-0.72, respectively). Younger age was associated with lower odds of having plant proteins (0.94, 0.90-0.99). Persons with low literacy (<3rd grade level versus higher) had lower odds of having an oven (0.15, 0.04-0.52) and lower odds of a full-sized refrigerator in their homes (0.12, 0.02-0.59).

Conclusions: The homes of urban AAs at high risk for CKD were often lacking either foods or needed appliances required for DASH meals. The lack of these items was associated with CKD, younger age, low income and/or low literacy. Interventions to improve DASH adherence in this high-risk group should consider these factors.

Funding: NIDDK Support, Other NIH Support - NHLBI


Background: Chronic Kidney Disease (CKD) is under-recognized and suboptimally managed especially in primary care setting. We aimed to evaluate the impact of interactive workshops and web-based tools in improving CKD management among internal medicine residents.

Methods: A pre-test assessed knowledge in areas of CKD diagnosis, anemia (A), bone-mineral disease (B), control of BP (C) and degree of proteinuria (D). Interactive workshop offered a CDA of CKD lasting 90-minutes was conducted over 5 weeks along with access to self-developed online CKD management resource (www.nephromania.com). Post-test was conducted at workshop completion and 12 weeks later. Assessment for post-intervention CKD care improvement was done through chart review.

Results: Among 98 participating residents, 25% utilized the online resource and 62% found it very helpful with majority bookmarking it on smart phones. KDOQI guidelines awareness, recognition of CKD diagnosis and complications were respectively 22%, 70% and 75% on pre-test, 98%, 93% and 90% on immediate post-test (P<0.001), declining to 80%, 77% and 74% at 12-weeks. Aggregate scores are shown in Figure 1A. Practice patterns measured through chart-review (n=94) to assess compliance with CKD guidelines over next 3 months failed to show change (figure1B).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 790A
Conclusions: Our study showed effectiveness of targeted interactive workshops to improve recognition of CKD and its complications. Intelectualizing the taught concepts by residents did not translate to improved patient care. Declining retention of core concepts at 12-week testing indicates the need for ongoing reinforcement sessions. Continued education including online resources utilization is warranted as opposed to annual core-lectures provided by most training programs.

SA-PO713
Evaluating Progress of Healthy People 2020 Chronic Kidney Disease Objectives: Are We There Yet? Aseel Ryskulova,1 Lawrence Agodoa,2 Paul W. Eggers,2 Kevin C. Abbott.2 1NCHS, CDC, 2NIDDK, NIH.

Background: Chronic Kidney Disease (CKD) is a significant public health problem in the U.S. and a major source of disability, poor quality of life, and premature death for those afflicted. CKD and End-Stage Renal Disease (ESRD), the final stage of the CKD, exact a high economic price. In 2012 ESRD costs exceeded $49 billion dollars including 34 billion (about 20%) of total Medicare expenditures. An estimated 11.5% of adults ages 20 or older had physiological evidence of CKD determined from data collected through the 2001-06 National Health and Nutrition Examination Survey (NHANES). Each year in the United States, more than 115,000 people are diagnosed with ESRD.

Methods: Reflecting the importance of CKD, 24 CKD objectives area were included in the Healthy People 2020 (HP2020) national health goals to reduce new cases of CKD and related complications, disability, death, and economic costs. CKD objectives are focused on improving cardiovascular care in patients with CKD; increasing the proportion of patients with CKD and diabetes who received recommended evaluation and treatment; reducing death rate and percentage of U.S. population with CKD; and increasing CKD awareness in persons with impaired renal function. All CKD objectives are measurable, having at least one data point from national data systems including the NHANES, National Death Index, and U.S. Renal Data System.

Results: In 2015, 14 objectives had met their target (n=9) or showed improvement (n=5). Six objectives showed little or no significant change. Two objectives: increase the proportion of persons with diabetes and CKD who received recommended medical treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and increase the proportion of patients receiving a kidney transplant within 3 years of ESRD, moved away from the target. The remaining 2 objectives were not evaluated as they were informational with no target set. Disparities persisted by sex, race/ethnicity, and SES status.

Conclusions: The presentation will cover the most recent national and state data for selected CKD objectives and provide an overview of the HP2020 and data search using the HP2020 website.

SA-PO714
Tele-nephrology for the Remote Management of Chronic Kidney Disease (CKD): A Retrospective Cohort Study Rajeev Rohatgi,1 Judy K. Tan,2 Anita Mehrrot,1 Medicine, James J. Peters VAMC, Bronx, NY; 2Medicine, Icahn School of Medicine, New York, NY.

Background: Veterans with CKD who live in the Hudson Valley Veterans Affair Medical Center (HVVMC) catchment area travel to the Bronx VAMC for nephrology care. Analysis of the no-show and cancellation frequencies for these renal appointments exceeded 50%, likely due to the distance between HVVMC and the Bronx (60 miles).

Methods: We hypothesized that patients managed via a tele-nephrology service, where patients visit their local VA and are evaluated remotely via videoconference by a Bronx VA nephrologist, would exhibit comparable clinical outcomes and visit compliance as patients visit following enrollment. We transcribed audio recordings, and quantified the frequency of diet discussions among African Americans (AAs) at increased CKD risk.

Results: In a randomized trial of urban AAs with uncontrolled hypertension, we audio-recorded patients’ routine visits with their primary care physicians (PCPs) at the first visit following enrollment. We transcribed audio recordings, and quantified the frequency of diet discussions among African Americans about diet during visits. We marked transcripts for discussions of dietary modification (e.g. sodium, weight, etc). We assessed patterns of patient-physician communication, including patient centeredness, during each encounter using the Roter Interaction System. We marked indicators independently associated with discussions of diet using logistic regression.

Results: Among 127 participants, mean age was 58 years and 70% were female. Average CPV visit lasted 25 minutes. Diet was discussed in 73% of visits, but only included discussion of the Dietary Approaches to Stop Hypertension (DASH) diet in 12%, weight/obesity in 36%, and cholesterol in 39% of visits. Independent predictors of diet discussions (odds ratio, 95% confidence interval) were patient centeredness score ratio (7.5, 1.3-41.9), and less than one year of education, and clinic location in New York City (OR = 0.5, 95% CI = 0.2-1.0) (for each minute increment). Patient age, gender, literacy, comorbid disease burden, obesity, diabetes nor CKD status predicted discussions.

Conclusions: Discussions of diet in primary care were frequent, and they were more likely to occur when visits were longer, were centered on patient priorities, and were attended by patients with incomes ≤$10k. Diet discussions focused on various topics, but infrequently included discussion of dietary modifications. Improvements in the content of diet discussions among African Americans at risk for CKD may be needed.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO716

Background: Tele-Nephrology: a feasible way to improve access for patients with kidney disease who reside in underserved areas.

Methods: A retrospective and descriptive study design was used to evaluate the effect of the Tele-Nephrology clinic intervention. Multiple clinical indicators were included in the analysis: blood pressure control, stabilization of the renal function and electrolyte/metabolic control. 101 patients that were evaluated in the clinic between 2013-2015 were included and the indicators were collected retrospectively.

Results: 101 patients were included, 95% male (n=96) and 5% female (n=5). The mean age was 65.5 years. 50 patients had Chronic Kidney Disease (CKD) stage III (49.5%), 14 patients had CKD stage IV (13%), 8 patients had CKD stage V (7.9%). A one-way analysis of variance analysis (ANOVA) between subjects was conducted and showed that the effect
of the Tele-Nephrology clinic intervention reducing blood pressure was statistically significant (systolic blood pressure P-value <0.0001). Renal function stabilized but the creatinine changes over time were not statistically significant (P-value: 0.50).

Subgroup analysis of individuals with eGFR < 30 ml/min or on dialysis reduced the differences in age and SPPB between groups, but demonstrated no significant difference to change in SPPB over time. HRQOL did not change significantly between groups. Proportion of individuals with improved PA over 1-year was 36% and 38% in EC and CG, respectively (p=0.82).

Conclusions: In this study, an exercise counseling clinic had no significant effect physical function as measured by SPPB at 1-year, suggesting that exercise counseling alone is inadequate to improve physical function in CKD.

SA-PO718

Ideal and Actual Support of Renal Replacement Therapy Modality Selection Patients with Chronic Kidney Disease: A Nationwide Survey in Japan
Shiho Kosaka,1 Shinichi Nishi,2 Yugo Shibagaki,3 Junichi Hoshino,4 Kazuo Takahashi,5 Yukiko Katagiri,6 Chiika Murayama,7 Yuko Funaki.7 1Sophia Univ; Tokyo, Japan; 2Kobe Univ Graduate School of Medicine, Kobe, Japan; 3St. Marianna Univ Hospital, Kawasaki, Japan; 4Toranomon Hospital, Tokyo, Japan; 5Fujita Health Univ School of Medicine, Toyoake, Japan.

Background: Optimal renal replacement therapy (RRT) selection supports for chronic kidney disease (CKD) patients are essential to improve post-treatment outcomes. We aimed to investigate how and when modality selection supports for patients with CKD are used by nephrologists in Japan, through a nationwide questionnaire survey of nephrologists.

Methods: A questionnaire was mailed to 1903 board-certified nephrologists of Japanese Society of Nephrology. Questionnaireitems targeting support for modality selection examined the following points: establishment of an RRT modality selection (RRT-MS) clinic, ideal and actual disease stage at which RRT-MS explanation is discussed, timing of RRT initiation, and type of specialist discussing RRT-MS with patients.

Results: The valid response rate was 12.3% (234/1903). Ninety-four out of 234 responding nephrologists (40.9%) had clinics dedicated to RRT-MS. Modality selection was most frequently discussed at CKD stage 4 (53.0%), stage 3b (22.8%), and stage 3a (13.4%). Nephrologists considered stage 3b (32.5%), stage 3a (19.5%), most ideal for discussing RRT-MS, a significant difference was therefore found between ideal and actual timing of RRT-MS discussion. Timing (by eGFR) of access placement of hemodialysis (HD) and peritoneal dialysis (PD) was significantly earlier in patients of RRT-MS clinics than in those of conventional clinics (HD, 12.3/14.1; PD, 12.6/14.9 ml/min/1.73 m²). Regarding types of specialists, nurses most frequently supported patients in RRT-MS (67.1%), however, this may be partly explained by the fact that nephrologists are required to commit more specialiststo supporting patients for RRT-MS.

Conclusions: A gap between ideal and actual timing of discussion of RRT-MSwith patients in Japan was identified. To promote appropriate timing of RRT-MS among CKD patients, early and multidisciplinary support systems should be structured.

Funding: Government Support - Non-U.S.

SA-PO719

Primary Care Physicians’ Perceived Barriers and Facilitators to Care of Older Adults with Kidney Failure Not on Dialysis
Helen Tam-Tham, Brenda Hemmelgarn, Chandra Mary Thomas, Karen Fruetel, Robert R. Quinn, Kathryn M. King-Shier. Univ of Calgary, AB, Canada.

Background: Primary care physicians are important care providers for older adults with kidney failure, but how they perceive and practice conservative (non-dialysis) care has not been studied. We undertook a qualitative study to describe barriers, facilitators, and possible enhancements of conservative care in the community for these older adults.

Methods: Semi-structured telephone interviews were conducted with primary care physicians from southern Alberta, Canada. Participants were identified by a snowball sampling strategy and purposively sampled based on sex, age, and rural/urban location of clinical practice. All participants managed at least 1 patient ≥75 years with kidney failure (eGFR <15ml/min/1.73m² for at least 3 months, not on dialysis) over the past year. Transcripts were analyzed thematically by conventional content analysis.

Results: Twenty-seven primary care physicians participated in this study (55.6% of participants were male, 55.6% of participants were aged 40 to 60 years, and 51.9% of participants practiced in the primary care setting for greater than 20 years). Perceived barriers to conservative care included: managing expectations of kidney failure for patients and their families, optimizing medical management of conservative care, and negotiating provider roles and responsibilities of co-management. Facilitators for care included: establishing patient and their family expectations of care early, preserving continuity of care, and utilizing a multidisciplinary team approach. Primary care physicians also identified suggestions for enhancement of conservative care in the community, including direct telephone access by primary care physicians to conservative care clinicians, treatment decision aids for patients and their families, and a conservative care clinical pathway for primary care providers.

Conclusions: We found important barriers and facilitators to conservative care by primary care physicians in the community. Further investigation of potential strategies that remove barriers and enable facilitators is required to improve the quality of conservative care in the community.

Funding: Government Support - Non-U.S.
Background: Awareness of chronic kidney disease (CKD) is low, even among patients with advanced disease. Increasing awareness to 11.7% is a Healthy People 2020 goal. The National Health and Nutrition Examination Survey (NHANES) measures CKD awareness using the question “Have you ever been told by a doctor or other health professional that you had weak or failing kidneys (excluding kidney stones, bladder infections, or incontinence)?” The framing of this question may influence responses. We sought to compare its sensitivity/ specificity to different questions as well as to awareness of other chronic conditions.

Methods: We administered a questionnaire to 220 English, Spanish and Cantonese-speaking adults who received primary care in a public healthcare delivery system. We obtained demographic data, screened for health literacy and ascertained patient awareness about chronic health conditions, including CKD, diabetes, hypertension and hyperlipidemia. CKD awareness was measured using the NHANES question and additional ones, asking if patients had been told about “kidney disease”, “protein in the urine”, “kidney problem”, or “kidney damage”. Health conditions were verified by medical record review.

Results: In our diverse study population (9.6% White, 40.5% Black, 36.4% Hispanic, 12.0% Asian), mean age was 58, mean eGFR was 47 ml/min/1.73m² and 47% had low health literacy. Sensitivities of each CKD awareness question were: 26.7% for “kidney damage”, 28.0% for “kidney disease”, 33.5% weak or failing kidneys” (NAHINES), 36.2% for “protein in the urine” and 40.6% for “kidney problem”. Specificities ranged from 88.2% to 97.7%. Combining all 5 questions yielded a sensitivity of 61.1% and a specificity of 79.6%. This was comparable to awareness of hyperlipidemia (68.8%) but was lower than awareness for hypertension and diabetes (89.6% and 94.3% respectively). Sensitivities were lower in patients with low health literacy.

Conclusions: CKD awareness is low compared to other chronic diseases. Nevertheless, by using more sensitive combinations of questions to ascertain CKD awareness, we have likely reached the Healthy People 2020 goal.

Funding: NIDDK Support

SA-PO721

The Effects of Age and Symptoms on Recommendations to Initiate Dialysis


Background: Recommendations to initiate dialysis vary by country. Age and symptom burden influence nephrologists’ recommendations to initiate dialysis, but the extent of this influence differed substantially between nephrologists in different countries.

Methods: We assessed the association of community health indicators with late nephrology referral in patients reaching end-stage renal disease in the U.S. We assessed the association of community health indicators with late nephrology referral in patients reaching end-stage renal disease in the U.S. and 47% had low health literacy. Sensitivities of each CKD awareness question were: 26.7% for “kidney damage”, 28.0% for “kidney disease”, 33.5% weak or failing kidneys” (NAHINES), 36.2% for “protein in the urine” and 40.6% for “kidney problem”. Specificities ranged from 88.2% to 97.7%. Combining all 5 questions yielded a sensitivity of 61.1% and a specificity of 79.6%. This was comparable to awareness of hyperlipidemia (68.8%) but was lower than awareness for hypertension and diabetes (89.6% and 94.3% respectively). Sensitivities were lower in patients with low health literacy.

Conclusions: CKD awareness is low compared to other chronic diseases. Nevertheless, by using more sensitive combinations of questions to ascertain CKD awareness, we have likely reached the Healthy People 2020 goal.

Funding: NIDDK Support

SA-PO722

The Association of Community Health Indicators with Late Nephrology Referral in Patients Reaching End-Stage Renal Disease in the U.S.

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Background: Late nephrology referral in patients reaching end-stage renal disease (ESRD) is associated with inadequate preparation for dialysis and poorer clinical outcomes after renal replacement therapy (RRT). Previous studies have focused on individual-level factors to identify patients at higher risk of late nephrology referral. Environmental and socioeconomic conditions of communities in which patients live may also impact nephrology referral patterns.

Methods: We assessed the association of community health indicators with late nephrology referral in 587,574 patients reaching ESRD, using the data from United States Renal Data System (USRDS) from 2005-2012. An overall community health risk score was calculated using 35 community-level factors based on 1) health outcomes, 2) health behaviors, 3) access and quality of care, 4) socioeconomic factors, and 5) physical environment, using County Health Rankings data from University of Wisconsin Population Health Institute. Late nephrology referral was defined as the first encounter with a nephrologist occurring < 6 months before RRT initiation. Multilevel logistic regression models adjusted for individual characteristics, including demographics, cause of ESRD, body mass index, comorbidities, and insurance and employment status.

Results: Late nephrology referral was associated with inadequate preparation for dialysis and poorer clinical outcomes after renal replacement therapy (RRT). Previous studies have focused on individual-level factors to identify patients at higher risk of late nephrology referral. Environmental and socioeconomic conditions of communities in which patients live may also impact nephrology referral patterns.

Conclusions: For patients at a given eGFR, other characteristics such as age and symptom burden influence nephrologists’ recommendations to initiate dialysis but the extent of this influence differed substantially between nephrologists in different countries. Further research is required to understand the effect of these differences on patients and health systems.

SA-PO722
Results: The prevalence of late nephrology referral was 47.8%. A significant dose-response relationship of community risk score with late nephrology referral was found, with an adjusted odds ratio of 1.52 (95% CI: 1.36-1.71) for the highest versus lowest risk communities.

Figure 1. Adjusted odds ratio for late nephrology referral, by overall community risk level.

Conclusions: Higher community risk is significantly associated with late nephrology referral, independent of individual-level factors. Community risk may be an important consideration for developing interventions to improve access to pre-ESRD nephrology care.

SA-PO723
Assessment of Quality of Care Received by Patients with Predialytic Chronic Kidney Disease Seen at a Philippine General Medicine Out-Patient Clinic – Experience at a Government Training Hospital Rizza Ann B. Lao, Section of Nephrology, Univ of the Philippines-Philippine General Hospital, Manila, Philippines.

Background: In a country with limited access to dialysis and transplantation such as the Philippines, it is imperative to recognize patients with early stage CKD and aggressively intervene in a timely fashion to prevent ESRD and death. The objective of this study is to evaluate the quality of care (QoC) of patients with predialytic CKD seen at a general medicine clinic.

Methods: This was a retrospective study which reviewed the medical records of 276 patients with CKD Stages 3-4 who have at least 1 year of consulat. Patients who were admitted for critical illness, and are on dialysis were excluded. For each QoC parameter, percentage of patients who received the appropriate care were reported. For the QoC correlates, Mann-Whitney U Test, Kruskal-Wallis Test or regression analysis was done.

Results: The mean QoC score for this study is 58.36% (± 23.7%) and the average annual GFR decline is 3.92 mL/min/1.73m².

Conclusions: Understanding of RRT options was poor among CKDopps participants in the US. Though the responses may not necessarily reflect information that was actually provided by their nephrology clinic teams, our results indicate that current educational strategies fall to adequately communicate key messages on RRT.

Funding: Pharmaceutical Company Support - Amgen, Kyowa Hakko Kirin, AbbVie, Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support), Hecal AG, DGIN, Shire, WiNe Institute, Società Italiana di Nefrologia (SIN), Japanese Society for Peritoneal Dialysis, Fresenius Medical Care, Keryx, Private Foundation Support

SA-PO725
Statin Prescribing Among U.S. Ambulatory Outpatient Visits for Patients with CKD William A. Janes,1 Talar Markosian,1 David J. Leehey,2 Benjamin Ling,1 Nicholas Burge,1 Vinod K. Bansal,1 Julia Koval,1 Ivan Pacold,1 Kevin Stroup,2 Holly J. Kramer,1 Loyola Univ Chicago;2 Hines VA Medical Center.

Background: Approximately 1 in 3 adults with CKD is at high risk of developing cardiovascular disease (CVD). Recent lipid management guidelines agree that statins should be used for CVD prevention via lipid lowering. However, lack of congruent recommendations for statin use in adults with CKD may lead to low utilization of statins in this population at high risk for CVD.

Methods: Outpatient visit data during years 2006 to 2010 were obtained from the National Ambulatory Medical Care Survey to determine the frequency of statin prescriptions among outpatient visits for adults ≥50 years with non-dialysis stage 1-5 CKD based on ICD-9 codes. Drug type (particular statin or other cholesterol lowering drugs type) was determined by the generic code recorded in the survey data. The analysis accounted for the complex survey design and utilized the sampling weight, cluster and strata statements so that results are generalizable to US outpatient ambulatory visits during years 2006-2010.

Results: A total of 2262 visits were included with patients being 48% white, 54% male and mean age of 69.6 years. 52% visits were covered by Medicare. Overall, 43% and 31.5% of visits for non-dialysis CKD stage 3-5 and stages 1-2, respectively, included a statin prescription with simvastatin being the most commonly prescribed statin. Table 1 shows the prevalence of statin prescription in all patients with non-dialysis dependent CKD by provider type for the outpatient visit.

<table>
<thead>
<tr>
<th>Provider Type</th>
<th>% Visits (standard error) with Statin Prescription for Adults age ≥50 years with non-dialysis CKD by prescriber type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Medicine/Family Practice</td>
<td>35.6 (0.05)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>46.8 (0.10)</td>
</tr>
<tr>
<td>Nephrology</td>
<td>45.4 (0.13)</td>
</tr>
<tr>
<td>Advanced Nurse Practitioner</td>
<td>40.6 (0.16)</td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>7.7 (0.04)</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: These results suggest that the rate of prescription of statins in CKD patients with non-CKD attributed to nephropathy differs by the provider charge for the patient with CKD. Lack of CVD preventive care may impact overall CVD risk in patients with diabetes and CKD-dependent CKD.

SA-PO726

Patients’ Knowledge of Their Chronic Kidney Disease Stage and Education About Kidney Failure Prevention – The CKD-REIN Cohort

Benedicte Stengel,1 Celine Lange,2 Brianzong,3 Luc Frimat,1 Denis Fouque,1 Maurice Laville,4 Christian Jacquelinet,2,4,5 Michael R. Robinson,6,7 Ziad Massy,8,9 Christian Combe,2,9 1Inserm U1018-CESP USV; Villejuif; 2Agence Biomedecine; 3CHU Nancy; 4CHU Lyon; 5Arbor Research Collaborative for Health, Ann Arbor; 6A’Paré - APHP; 7CHU Bordeaux, France.

Background: Patient knowledge about their CKD stage and how to prevent kidney failure is important to reduce ERSD risk through better adherence to treatment and lifestyle changes. We report primary findings about CKD knowledge among patients seen by nephrologists in France.

Methods: We used baseline data from the CKD-REIN study, a prospective cohort of patients with CKD stage 3 and 4 in a national sample of 40 nephrology clinics. Information was collected from patient interview and self-administered questionnaire. Comparisons between stages were adjusted for age and gender.

Results: Median age was 68[60-76] and 56% were men. About 80% reported knowledge that their kidney function was low. Patients were more likely to know their creatinine level (~40%) than GFR or CKD stage. For each question, knowledge increased slightly from that their kidney function was low. Patients were more likely to know their creatinine level (~40%) than GFR or CKD stage. For each question, knowledge increased slightly from stage 3 to stage 4. Education about how to prevent kidney failure was uncommon (~10%) in Rural and Remote First Nations.

Conclusions: Most CKD patients seen by nephrologists are aware that they have low kidney function, but their knowledge of disease severity is low. Very few received education about prevention of kidney failure. While the precise impact of these gaps in knowledge on CKD outcomes requires further investigation, the findings highlight the need to more effectively educate CKD patients about its potentially serious consequences.

Funding: Pharmaceutical Company Support - Amgen, Baxter, Fresenius, GSK, Lilly, MSD, Sanofi, Government Support - Non-U.S.

SA-PO727

The Cost-Effectiveness of Primary Screening for Chronic Kidney Disease in Rural and Remote First Nations

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Background: Chronic Kidney Disease (CKD) is a risk factor for cardiovascular disease, early mortality, and kidney failure. We have shown that the burden of CKD in First Nations (FN) populations in Manitoba is similar to that in diabetic and hypertensive populations. The cost-effectiveness of screening for CKD and subsequent treatment in FN or other high-risk indigenous populations has not yet been described.

Methods: We constructed a Markov model comparing screening in adult FN (age 18+) for CKD both proteinuria and estimated glomerular filtration rate (eGFR) to usual care from the perspective of the publicly funded Canadian health care payer. Patients were assigned an initial risk classification based on urine albumin-to-creatinine ratio and eGFR using the Kidney Disease Improving Global Outcomes (KDIGO) heat map. We obtained screening tests results on 1346 adult participants from the First Nations Community Based Screening to Improve Kidney Health and Decrease Dialysis (FINISHED) initiative. Our analysis was further stratified into communities accessible by road and communities accessed by air travel. Our primary outcome of interest was the incremental cost per quality-adjusted life-year (QALY).

Results: Overall crude prevalence of CKD in FN was 26.7%. Screening for CKD was associated with an ICER of $33,500/QALY in comparison to usual care. Restricting the model to screening in the remotest air access communities (prevalence of CKD 36.0%), this ratio fell to an ICER of $16,180/QALY. In less remote road access communities (CKD prevalence 18.4%), an ICER was $63,780/QALY. Primary model drivers included the cost of dialysis, assumed treatment effectiveness, and rates of progression towards kidney failure.

Conclusions: Targeted screening for CKD in rural and remote First Nations is likely cost-effective (≤ $50,000/QALY). These findings may be translatable to other high-risk indigenous groups with elevated rates of CKD and kidney failure and warrant further research.

SA-PO728

Getting a Diagnosis of Chronic Kidney Disease: Despite Fears, Patients Want to Know Early

Julie A. Wright Nunes,3 Meghan Roney,2 Eve Kerr,1 Akinlolu O. Ojo,1 Angela Fagerlin.1,2,4 1Internal Medicine, Univ of Michigan, Ann Arbor; 2Center for Bioethics and Social Sciences in Medicine, Univ of Michigan, Ann Arbor; 3Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI.

Background: Little is known about patient perspectives related to getting a diagnosis of chronic kidney disease (CKD). This information could help providers optimize diagnosis messaging at the point of care.

Methods: Using root/cause analysis and quality function deployment we conducted semi-structured patient interviews. Adult patients with established non-diagnosis CKD were interviewed between January-October 2014. Interviews were audiotaped and transcribed. Content analysis was done with Dedoose, a qualitative software package.

Results: 49 patients completed interviews. Mean (SD) age was 63 (14) years, 50% were male, 80% were Caucasian and 84% had CKD Stage 3-5. Key themes emerged from a total of 786 statements: 1) Reaction to diagnosis (160 statements) 2) Barriers to accepting diagnosis (61 statements) and 3) Expectations of diagnosis communication (122 statements). 45% of patients felt fearful after getting a CKD diagnosis - most often related to perceived threats of future dialysis and death. Barriers to diagnosis acceptance included disbelief because of lack of symptoms and lack of prior familiarity with CKD. Despite fear and denial the majority of patients (63%) desired early diagnosis communication by their providers, i.e. at earliest stages of identification. Consistent terminology and disease explanations by providers across the care continuum were perceived as critical to effective communication and diagnosis delivery, yet patients expressed frustration at inconsistent terminology/explanations.

Conclusions: Our findings emphasize that patients learning of a CKD diagnosis can experience fear, but they also prefer early communication of diagnosis. More work is needed to set uniform diagnosis terminology for patients with CKD across the care continuum.

Funding: NIDDK Support

SA-PO729

The Impact of Chronic Kidney Disease on Household Income: Does Health Affect Wealth?

Rachael L. Morton,1,2 Alan Cass,3 Borislava N. Mihaylova.2 1Univ Sydney, Australia; 2Charles Darwin Univ, Australia; 3Univ Oxford, United Kingdom; 4On behalf of SHARP Collaborators.

Background: The impact of progressive chronic kidney disease (CKD) on household income is unclear. We sought to determine whether CKD severity and non-fatal adverse events were associated with a fall into poverty.

Methods: Prospective cohort study among participants with moderate-to-severe CKD randomized into the Study of Heart and Renal Protection (SHARP) with information on household income at study entry and study end (median follow-up 5 years). Household income recorded as: High (> twice the participating country median); Medium-high (> the median, but < twice the median); Medium-low (< the median, but > half the median); and Low (< half the median income, i.e. poverty). Logistic regression models with sociodemographic factors, smoking, prior diseases, severity of CKD, income category at entry and incident non-fatal events (myocardial infarction, stroke, incident cancer, initiation of dialysis, kidney transplantation) were used to determine a fall into poverty, defined as a move into the lowest household income category.

Results: 2914 SHARP participants were included in the analysis; 933 of these were in poverty at screening and a further 436 (22% of the remaining) moved into poverty by study end. In addition to black ethnicity, low educational attainment, single adult household and low income category at baseline, CKD severity was a significant predictor of a fall into poverty.

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

Underline represents presenting author.
Conclusions: Patients in advanced stages of CKD are at an increased risk of falling into financial hardship. Kidney transplantation may have a role in reducing the risks of household poverty due to CKD.

Funding: Government Support - Non-U.S.

SA-PO730

Healthcare Expenditures for Non-Diabetes Dialyzed Kidney Disease Compared to Other Chronic Diseases

Christina Small,1 Holly J. Kramer,1 Karen A. Griffin,1 David J. Leehey,1 Vinod K. Bansal,2 Kavitha Vellanki,1 Talar Markossian.1 1Loyola Univ Chicago; 2Hines VA Medical Center.

Background: There is a paucity of literature comparing the expenditures of kidney disease with other common costly chronic diseases in the United States. Our study compares the U.S. healthcare expenditures of non-dialysis dependent kidney diseases to several other chronic conditions.

Methods: This study used the 2012 Medical Conditions and Consolidated Data files from the Medical Expenditure Panel Survey administered by the Agency for Healthcare Research and Quality. Analyses included adults age ≥ 21 years with one of the following conditions: kidney disease, stroke, cancer, or a combination of the three (multichronic). Non-dialysis dependent kidney disease included any ICD9 code for kidney related conditions while chronic kidney disease (CKD) included only ICD9 code “585.” Analyses of calculated healthcare expenditures accounted for the complex survey design and incorporated the sampling weights so that estimates represent healthcare expenditures for the 2012 adult U.S. population (~313.4 million). Out of pocket healthcare expenditure burden was defined as the ratio of out of pocket healthcare expenditure to total person-level income for the year 2012.

Results: The mean age for non-dialysis dependent kidney disease and CKD was 56.5 and 65.9 years, respectively. Table 1 shows the median total and out of pocket healthcare expenditures and mean out of pocket healthcare expenditure burden for kidney disease, CKD and other chronic conditions.

<table>
<thead>
<tr>
<th>Chronic Condition</th>
<th>Median Out of Pocket Expenditures, $ (range)</th>
<th>Median Total Expenditures $ (range)</th>
<th>Mean Out of Pocket Expenditures Burden %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>3862 (34,913,955)</td>
<td>22,919 (1,782,189,893)</td>
<td>9.5</td>
</tr>
<tr>
<td>Any kidney disease</td>
<td>795 (0.02,034)</td>
<td>6,351 (0,262,189)</td>
<td>5.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>760 (0.54,698)</td>
<td>8,528 (0,147,533)</td>
<td>5.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>790 (0.79,313)</td>
<td>7,606 (0,212,886)</td>
<td>5.2</td>
</tr>
<tr>
<td>Multiple Chronic Conditions</td>
<td>824 (2.5,711)</td>
<td>16,323 (992-276,047)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Conclusions: Healthcare expenditures including out of pocket costs are higher for non-dialysis dependent CKD compared to other chronic medical conditions. Policy efforts should focus on reducing the healthcare cost burden for patients with kidney disease.

SA-PO731

Smartphone-Based Self-Management System for Chronic Kidney Disease: Results from a Single Centre Prospective Trial

Stephanie W. Ong,1 Sarbjit Vaniita Jassal,1 Akib Uddin,2 Kelly Min,3 Joseph A. Calazano,3 Alexander G. Londe,4 Nephrology, Univ Health Network, Toronto, ON, Canada; Pharmacy, Univ Health Network, Toronto, ON, Canada; Centre of Global Ehealth Innovation, Univ Health Network, Toronto, ON, Canada.

Background: Following user-centric design principles we developed a smartphone-based self-management support system for patients with advanced CKD. The patient interface focuses on 4 behavioral elements over which they have direct control: monitoring BP at home, self-assessment of symptoms, managing medications and tracking laboratory results. The main objectives of this 6-month prospective study were to determine acceptability,measured by system adoption and adherence, and assess effectiveness by using pre and post changes in BP,medications, labs and self-management behaviors.

Methods: We tested the mobile app system in 10 renal clinics at a single academic renal center in Toronto. The 47 enrolled patients were instructed at a regular clinic visit on the use of the mobile app. The clinical team independently received information on the mobile app system’s operation.

Results: 61% of participants were non-smartphone owners. All had more than one chronic condition and on average were on 10 to 15 medications. Most were over the age of 50 with the greatest representation in the age group 55-64.~80% of the users achieved more than the recommended 80% adherence rate to mobile app use.27% with normal clinic BP readings were discovered to have ‘masked’ hypertension on home BP monitoring. By the end of the study the SBP fell by 6.8 ± 20.4 mm Hg (p=0.05) and DBP by 0.9 ± 9.1 mm Hg. Out of 250 medication reviews,49% required intervention from the clinical team, such as altering drug dosing. Due to the short study duration and infrequency of lab testing, there were no changes in pre and post laboratory test results. On exit, patients and clinicians felt the mobile app helped engage and empower patients in their CKD care.

Conclusions: The mobile app was acceptable and suggests improvements in BP management and medication error prevention. This provides early evidence to supporting innovative use of mobile technology in CKD management and strongly supporting its use in a larger clinical.

SA-PO732

Potentially Preventable Hospitalization Among Patients with Chronic Kidney Disease and High Inpatient Use

Paul E. Ronksley, Braden J. Manns, Marcello Tonelli, James Wick, Brenda Hemmelgarn, Univ of Calgary, Calgary, AB, Canada.

Background: While prior studies have observed high rates of hospitalization among patients with chronic kidney disease (CKD), little attention has been given to those with high inpatient use. We explored clinical characteristics, patterns of hospital use, and potentially preventable acute care encounters among hospitalized patients with CKD.

Methods: We identified all adults (≥18 years) with an eGFR<60 mL/min/1.73m2 in Alberta, Canada between Jan 1 and Dec 31, 2009, excluding those with prior kidney failure. Patients with CKD were linked to administrative data to capture clinical characteristics and frequency of hospital encounters, and followed until death or end of study (Dec 31, 2012). Patients with 1 or more hospital encounters were categorized into 3 groups: persistent high use (upper 5% of inpatient use (‘3 encounters/yr) in 2 or more years), episodic high use (upper 5% in 1 year only), or non-high use (lower 95% in all years). Within each group we described patient characteristics and calculated the proportion of potentially preventable hospitalizations as defined by 4 CKD-specific ambulatory care sensitive conditions (ACSC); heart failure, hyperkalemia, volume overload, malignant hypertension.

Results: During a median follow-up of 3 years, 57007 patients had 118671 hospitalizations of which 1.7% of patients were persistent high users of hospital services, 12.3% episodic high users, and 86.0% non-high users. Persistent high users were often younger, male, First Nations, living in rural areas, and had higher levels of comorbidity compared to episodic and non-high use groups. Overall, 24804 (20.9%) CKD-related ACSC encounters were observed in the cohort. The proportion of ACSC encounters were higher in persistent high users (29.1%) compared to episodic (27.3%) and non-high users (17.3%) (p<0.01). The majority of the encounters were attributed to heart failure and hyperkalemia in all groups.

Conclusions: A substantial proportion of hospitalizations among patients with CKD and high inpatient use are ACSC-related. These findings suggest opportunities to reduce inpatient use and cost by focusing on strategies to improve community-based care for this subset of patients.

SA-PO733

Effect of Increased Blood Pressure Variability on Neurocognition in Children with Chronic Kidney Disease

Marc Lande,1 Susan R. Mendley,2 Matthew Matheson,3 S. Shinmar,4 Arlene C. Gerson,5 Joshua A. Samuels,6 Bradley Warady,2 Susan L. Furth,2 Stephen R. Hooper,1 Univ of Rochester; 1CKD Investigators.

Background: Increased blood pressure variability (BPV) is associated with lower neurocognitive test (NCT) performance in adults. We previously studied children with chronic kidney disease (CKD), who are at risk for cognitive dysfunction and increased BPV. However, little is known about the impact of increased BPV on cognition in children with CKD.

Methods: Children 6-18 years enrolled in the prospective NIH-sponsored Chronic Kidney Disease in Children (CKiD) study had NCT including WASI Matrix Reasoning, parent BRIEF, CPT-II, Digit Span, and Verbal Fluency. Casual BP visit-to-visit BPV was assessed by SD (BPV-SD) and average real variability (ARV), and 24-hour ambulatory BP monitoring by SD of wake and sleep periods. For unadjusted analyses, test scores of the subjects with BPV in the upper tertile were compared to that of subjects in the lower tertile. Multiple linear regressions were used to evaluate the relation between BPV and NCT scores, adjusting for BP index, sex, age, maternal education, race, BMI %tile, estimated GFR, % of life with CKD, nphritic proteinuria, and low birth weight.

Results: Depending on the task, 121-511 subjects had both BP and NCT results available. In unadjusted analysis, subjects with increased visit-to-visit systolic BPV scored lower on Verbal Category Switching (3rd vs 1st tertile of BPV-SD, 8.4 ± 2.7 vs 9.8 ± 3.0, p = 0.004; of ARV, 8.6 ± 3.0 vs 9.7 ± 2.5, p = 0.009). There was no effect of increased visit-to-visit BPV or ambulatory BPV on any other task. In adjusted analyses, increased visit-to-visit systolic BPV remained significantly associated with lower Verbal Category Switching scores for BPV-SD (β=–0.28, 95% CI:–1.34, –0.15) and there was a trend for ARV (β = 5.7, 95%CI:–1.16, 0.03).

Conclusions: Increased visit-to-visit systolic BPV was independently associated with decreased Verbal Category Switching scores in children with CKD. These results suggest that children with chronic kidney disease (CKD), who may have difficulties with set shifting that are related, in part, to increased BPV. Further study is needed to determine the significance of this isolated result.

Funding: Other NIH Support - NHLBI
SA-PO734

Rapid Post-Transplant Improvement of HRQOL in Older Kidney Recipients

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Background: It is widely accepted that health-related quality of life (HRQOL) is significantly compromised in patients with ESRD. In adults, kidney transplantation (KTx) is known to improve HRQOL. In older recipients there is a lack of studies measuring the effect of KTx on HRQOL. The aim of this study was to measure HRQOL longitudinally in enlisted patients >65 years of age, from pre-transplant and until 6 months after KTx.

Methods: Patients >65 years listed for transplantation at our centre were asked to complete the SF36 questionnaire at enlisting and thereafter every 6 months until KTx. Post transplant, the patients received a new SF36 form 10 after weeks and 6 months.

Results: A total of 180 patients have been included from Jan 2013. Mean age at enlisting was 70.6 years (65.0-81.8) and 68% were male. By the end of May 2015, 100 patients were transplanted and 59 of them had completed both pre- and post-transplant questionnaires. Mean time from completing the first pre-tx questionnaire to transplantation was five months. When comparing the scores for the last SF36 pre-tx with 6 months post-tx, there was a statistically significant increase of the mean scores for GH (53-71), PF (66-74), BP (64-78), VT (53-71) and MH (79-85). There was also a tendency towards improved scores for RP and RE, while the SF score was unchanged.

Conclusions: Our preliminary findings indicate that older patients report a significant improved HRQOL measured by SF36 already 10 weeks after KTx and the status remains stable after 6 months. Longer follow-up is warranted.

Funding: Government Support - Non-U.S.

SA-PO735

L-Carnitine Improves Cognitive and Renal Functions in a Rat Model of Chronic Kidney Disease

Zaber Anis Armaly,1 Adel Rafik Jabbour,1 Na proliferation and kidney function. The Prevalence of Cognitive Impairment in Chinese Peritoneal Dialysis Patients

Chi-hon Leung, Cheuk-Chun Szeto. Dept of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong.

Background: Cognitive impairment is common amongst patients with chronic kidney disease and may be associated with excessive morbidity in dialysis patients. This study determines the prevalence and risk factors of cognitive impairment in Chinese peritoneal dialysis (PD) patients.

Methods: We studied 178 prevalence PD patients (103 males). Cognitive impairment was screened by the 10-item Abbreviated Mental Test (AMT) questionnaire. We also determined patients’ comorbidity load, dialysis adequacy, residual renal function, nutritional status, and degree of frailty.

Results: The mean age was 60.7 ± 11.7 years; vintage of dialysis 42.5 ± 44.1 months. Average AMT score was 9.3 ± 1.3. The AMT score is closely associated with age (r = -0.53), and inversely associated with years on dialysis (r = -0.42) and residual renal function (r = -0.38), but not by decline in GFR. The only domains that discriminated for GFR associated influence were effects- and burden of kidney disease and social support. Multivariable linear regression analyses were employed including the following explanatory variables: GFR, age, sex, comorbidity and the interaction between sex and age. Significant associations were found between decline in GFR and endurance (6-MWT; p=0.039), strength (IQS; p=0.035), balance (FR; p=0.024) and fine motor skills (PUT; p=0.015) as well as by the patients’ perceived domains in the KDQOL-SF™-domains of effects- (p=0.023) and burden (p=0.016) of kidney disease and social support (p=0.006) after having taken the explanatory variables into account. There were significant associations between the KDQOL-SF™-domains role physical and emotional well-being and 6-MWT (p=0.018; p=0.018, respectively) and IQS (p=0.005; p=0.045, respectively), but these were dependent on age, sex and comorbidity but not driven by GFR.

Conclusions: Physical functions comprising endurance, strength, balance and fine motor skills were impaired relatively early in the course of KTx (3b-5), seemed to progress with declining GFR and could be detected by easy to perform physical function tests. The relationship between self perceived physical functioning and well being, respectively, with measured endurance and strength, respectively, were driven by age, sex and comorbidity but not by decline in GFR. The only domains that discriminated for GFR associated influence were effects- and burden of kidney disease and social support.

SA-PO737

The Prevalence of Cognitive Impairment in Chinese Peritoneal Dialysis Patients

Chun Szeto.

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Background: Physical functions are impaired in dialysis patients. It is unclear which functions are affected and how they decline in the course of KTx. This study investigated the effects of declining GFR (KTx 3-5) on measured physical functions, self perceived physical functioning and well being.

Methods: In this cross sectional analysis 101 patients (40 women, 61 men; mean age: 67±13 years, median GFR: 21 (9-41) ml/min/1.73m²) were tested with 6 Minutes Walk (6-MWT), Isometric Quadriceps Strength (IQS), Functional Reach (FR) and Picking-up (PUT). Self perceived physical functioning and well being were assessed by KDQOL-SF™. GFR was measured with iohexol clearance and comorbidity by Davies’ index. Multivariable linear regression analyses were employed including the following explanatory variables: GFR, age, sex, comorbidity and the interaction between sex and age.

Conclusions: Administration of L-Carnitine in a rat model of CKD, significantly improves cognitive and renal functions in a rat model of chronic kidney disease (CKD) has reached epidemic proportions. L-Carnitine, considered as the “gatekeeper” responsible for mitochondrial function, has reached epidemic proportions. L-Carnitine, considered as the “gatekeeper” responsible for mitochondrial function, has reached epidemic proportions. L-Carnitine, considered as the “gatekeeper” responsible for mitochondrial function, has reached epidemic proportions.

Conclusions: Our preliminary findings indicate that older patients report a significant improved HRQOL measured by SF36 already 10 weeks after KTx and the status remains stable after 6 months. Longer follow-up is warranted.

Funding: Government Support - Non-U.S.
Neurocognitive Functioning and Association with Clinical Outcomes in Adults with End-Stage Kidney Disease: The COGNITIVE-HD Study

**Background:** Cognitive impairment and neurocognitive disorder have been associated with increased mortality in the general population. Whether dialysis patients have specific patterns of cognitive dysfunction, or whether cognitive function is associated with activities of daily living and durability of dialysis treatment remain poorly understood.

**Methods:** The COGNITIVE-HD study will provide detailed neuropsychological assessments of cognitive function among hemodialysis patients to characterize age- and education-adjusted prevalence and patterns of cognitive impairment and the associations with physical and social functioning and clinical outcomes including cardiovascular events at 12 months. The COGNITIVE-HD study is a prospective, longitudinal, population study of 751 adults conducted in 20 dialysis centers in Italy. A detailed battery of comprehensive testing for executive function, visuospatial function, language, learning and memory, personality traits, and complex attention has been carried out by a trained psychologist at baseline to assess for presence of cognitive impairment and to evaluate the pattern of cognitive deficits, and any association between cognitive impairment and activities of daily living.

**Results:** Preliminary analyses have been conducted on the Mini Mental State Examination (MMSE) evaluation of cognitive function among 702 participants (mean age 68.2 years, 60% men). 50% had normal cognitive function (MMSE score 27-30), 22% had mild cognitive impairment (score 26-24), 19% were cognitively impaired (score <25), and 22% had mild cognitive impairment (score 26-24). 198 patients (28%) had MMSE results below 23.

**Conclusions:** The COGNITIVE-HD study will provide detailed neuropsychological assessments of cognitive function among hemodialysis patients to characterize age- and education-adjusted prevalence and patterns of cognitive impairment and the associations with physical and social functioning and clinical outcomes including cardiovascular events at 12 months. The COGNITIVE-HD study is a prospective, longitudinal, population study of 751 adults conducted in 20 dialysis centers in Italy. A detailed battery of comprehensive testing for executive function, visuospatial function, language, learning and memory, personality traits, and complex attention has been carried out by a trained psychologist at baseline to assess for presence of cognitive impairment and to evaluate the pattern of cognitive deficits, and any association between cognitive impairment and activities of daily living.

**Conclusions:** Among older men, those with primarily mild-moderate CKD and HTN do not have lower cognitive function compared to hypertensive controls after accounting for common cognitive risk factors. However, across a range of GFR, lower renal function is associated with worse performance in specific domains of cognitive function.

**Funding:** NIDDK Support, Veterans Administration Support

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Neurocognitive Functioning and Psychiatric Disorder in Children with Chronic Kidney Disease from the KNOW-Ped CKD Cohort Study (Korean Cohort Study for Outcome in Patients with Pediatric Chronic Kidney Disease)

**Background:** Depressive symptoms are common in patients with chronic kidney disease. The KNOW-Ped CKD cohort study is a cross-sectional study comparing children with end-stage kidney disease to healthy children. The study aimed to examine the prevalence of depressive symptoms and associated factors in children with chronic kidney disease.

**Methods:** A total of 322 children (M:F 218:104) enrolled from seven major pediatric nephrology centers of Korea from July 2010 to December 2013 were the subject of this study. Neurocognitive function and psychiatric status of pediatric CKD patients were evaluated using the Wechsler intelligence scale for children, Child Behavior Checklist, ADHD Rating Scale-IV, State-Trait Anxiety Inventory, Child Depression Inventory and Parental Bonding inventory-Korean version.

**Results:** Verbal, performance and full scale IQ were lower in younger age and congenital anomalies of the kidney and urinary tract as a cause of CKD. More than 10 percent of school-age children with CKD presented significant emotional distress including somatization (15%), attention problems (15%) and anxiety (12%). Impact of progression of CKD on their neurocognitive function and psychiatric status will be investigated in KNOW-PedCKD cohort study in Korea.

**Conclusions:** In young patients with CKD and those with multiple congenital problems in addition to CKD suffer from low intelligence and psychiatric disorder. Pediatric CKD patients with low intelligence and psychiatric disorder need close attention and developmental training techniques. Acknowledgement. This work was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (2013E3301600, 2013E33081601).

**Funding:** Government Support - Non-U.S.
Vitamin D Deficiency Is Significantly Associated with Depression in Chronic Kidney Disease Patients

**Background:** Recent studies have reported significant associations between vitamin D deficiency and depression in the general population. Although both vitamin D deficiency and depression are common features in chronic kidney disease (CKD) patients, the association between these two prevalent factors in this patient population remains poorly elucidated. Therefore, the association between vitamin D deficiency and depression in CKD patients was investigated.

**Methods:** The data from the Korean National Health and Nutrition Examination Survey between 2010 and 2012 were used. A total of 495 patients with estimated glomerular filtration rate ≤60 mL/min/1.73 m² were enrolled. Vitamin D deficiency was defined as 25-hydroxyvitamin D3 [25(OH)D3] levels £10 ng/mL. Patients were dichotomized by the presence of vitamin D deficiency. Depression was determined by the EuroQOL-5D (EQ5D) questionnaire. Independent association between vitamin D deficiency and depression was evaluated by multivariate logistic regression analysis.

**Results:** The mean age was 71.2 ± 9.3 years, and 257 patients (51.9%) were female. The median 25(OH)D3 levels were 17.9 (13.9-22.7) ng/mL. The prevalence of depression in CKD patients was higher compared to the general population (14.3% vs. 11.1%, P = 0.031). In addition, the prevalence of depression was significantly higher in patients with vitamin D deficiency than those without vitamin D deficiency (27.9% vs. 13.3%, P = 0.022). Multivariate logistic regression analysis showed that vitamin D deficiency was a significantly independent predictor of depression after adjusting for age, sex, alcohol, body mass index, hypertension, diabetes mellitus, anemia, suicidal idea, EQ5D index, and serum parathyroid hormone levels (odds ratio=6.27, 95% confidence interval=1.57-25.05, P=0.009).

**Conclusions:** Depression was highly prevalent in CKD patients. Vitamin D deficiency was a significantly independent predictor of depression in CKD patients. Therefore, determining vitamin D levels might be helpful to predict depression in these patients.

**SA-PO747**

Comparison of Prevalence and Predictors of Fatigue in Advanced Chronic Kidney Disease and Cancer Patients

**Background:** Although >50% of patients with advanced CKD report fatigue, its presence, predictors and consequences are under-appreciated by renal providers. We compared the symptom burden among CKD/ESRD patients to those with advanced hepatobiliary cancer (CA).

**Methods:** In 237 patients with advanced kidney disease (35% CKD stage 4-5, 65% ESRD) and 606 with advanced CA, patient-reported symptoms and health-related quality of life (HRQOL) were assessed using validated fatigue, pain, sleep quality, depression and HRQOL questionnaires. Chi-square and ANOVA were used to test between group differences and linear regression was employed to test predictors of fatigue.

**Results:** In unadjusted analyses, CKD patients reported statistically (but not clinically) less fatigue, similar poor sleep quality, and significantly lower prevalence of depression and pain as compared to CA patients. Lower levels of fatigue were strongly associated with higher HRQOL in both groups (r=0.80, P<0.001 in CKD; r=0.67, P<0.001 in CA). Depression was significantly associated with higher levels of fatigue for both groups (r=0.01 for both). Poor sleep quality was associated with higher fatigue in both groups (r= -0.40, P<0.001 in CKD; r= -0.27, P<0.001 in CA). Similarly, in both groups, more pain was associated with higher fatigue (r=0.41, P<0.001 for MOS SF-36 pain score in CKD; r= -0.48, P<0.001 for BPI in CA). Using linear regression, and including those factors significantly associated with fatigue, 29% of the variance in CKD and 31% in CA cohort was explained by depression, sleep and pain.

**Conclusions:** Patients with advanced CKD experienced similar levels of fatigue and poor sleep quality as those with advanced CA. Sleep, depression, and pain were significant predictors of fatigue in these chronically ill patients.

**SA-PO746**

Validation of a Patient-Perceived Symptom Score for Chronic Kidney Disease

**Background:** Chronic Kidney Disease (CKD) is associated with a range of symptoms, even at relatively early stages. There is increasing recognition of the importance of the patient symptom experience for clinical management and quality of life, but validated symptom scores are lacking. We have refined and validated an existing draft CKD symptom questionnaire listing 11 common renal symptoms plus lines for additional symptoms not included in the list.

**Methods:** Validation was undertaken in 4 phases. In Phase 1, 219 patients with CKD stages 1-5 not requiring renal replacement completed the draft questionnaire to identify the most prevalent symptoms in this population. Phase 2 explored cognitive validity via semi-structured interviews with 11 patients, after which the draft questionnaire was refined. Phase 3 was a focus group with 5 patients, to review and further refine the updated questionnaire. Phase 4 was content validity testing: the questionnaire was sent to 16 external expert clinicians for assessment of relevance, clarity and comprehensiveness.

**Funding:** NIDDK Support, Other NIH Support - National Cancer Institute K07CA118157; R21CA127046; and R01CA176899, Private Foundation Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Results: Phase 1 identified 13 common symptoms, and Phases 2 and 3 confirmed symptom selection and refined the wording used to describe them. The symptom descriptions finalised were: itching, sleep disturbance/insomnia, loss of appetite, feeling tired, pain in bones/joints, poor concentration/mental alertness, loss of libido/erectile dysfunction, loss of muscle strength/power, shortness of breath, cramp/muscle stiffness, restless legs/ difficulty keeping legs still, need to urinate more often, feeling cold. In Phase 4, 14 of 16 experts responded (87.5%). 10 of the 13 symptoms had “excellent” or “good” evaluation scores, and the content validity index of the whole questionnaire was 0.81, falling within the recommended threshold.

Conclusions: This work has provided a new, validated symptom score for the early-pre-dialysis CKD population, which can be used as a patient reported outcome measure in both clinical management and research.

Funding: Private Foundation Support

SA-PO747
Impact of Psychosocial Factors in Advanced Chronic Kidney Disease on Wait-Listing for Transplantation Santjeek Ajinkya, James L. Pasha, Jason Roy, Boyang Chai, Michael J. Fischer, L. Lee Hamm, Peter D. Hart, Chi Tong, Mark A. Brown, 1
1 Royal Adelaide Hospital.

Background: Transplantation (Tx) is generally regarded as the best option for renal replacement therapy. However, few patients with CKD are listed for Tx when eligible. We examined the association between psychosocial factors in patients with advanced CKD and wait-listing for kidney Tx.

Methods: The study population includes 803 individuals with an eGFR of less than or equal to 20ml/min/1.73m2 (advanced CKD) in the Chronic Renal Insufficiency Cohort study. The primary predictors were health related quality of life (HRQOL) and depressive symptoms assessed within 24 months prior to reaching the eGFR inclusion criteria using the Kidney Disease QOL (KDQOL)-36 survey and the Beck Depression Inventory (BDI), respectively. The primary composite outcome was wait-listing or transplantation (WLT). Cox proportional hazards models were used to examine the association between low HRQOL (1 SD below the cohort mean) and BDI (11) with WLT.

Results: Of the 803 subjects, 380 (47%) were wait-listed including 120 that proceeded to Tx. Compared to individuals who were not on WLT, those in the WLT group were more likely to be younger, male, have no history of cardiovascular disease, and have proteinuria > 300mg/day (p <0.01). After adjustment for demographic and clinical variables, a low Mental Component Summary (MCS) score was associated with a lower likelihood of WLT (Table). There was no association between the BDI or other QOL measures with WLT.

Predictor Adjusted Model (HR, 95% CI)
BDI ≥ 11 0.88 (0.69-1.2)
KDQOL (≥ 1 SD below the cohort mean) 0.83 (0.56-0.9)
-Mental Component Summary
-Physical Component Summary 0.92 (0.69-1.24)
-Symptoms/Problems 0.97 (0.71-1.32)
-Burden of Kidney Disease 0.82 (0.61-1.09)
-Effect of Kidney Disease on Daily Life 0.94 (0.69-1.28)

Conclusions: Lower MCS scores were associated with lower likelihood of WLT. Further work is needed to evaluate the impact of poor mental QOL in advanced CKD and how it might influence wait-listing.

Funding: NIDDK Support

SA-PO748
Perspectives on Pregnancy in Women with Chronic Kidney Disease Allison Tong,1 Mark A. Brown,1 Wolfgang C. Winkelmayr,2 Jonathan C. Craig,2 Shilpa Jawedasla,1 The Unv of Sydney;3 St. George Hospital;4 Baylor College of Medicine; Royal Adelaide Hospital.

Background: Women with chronic kidney disease (CKD) often have difficulty achieving pregnancy, and are at increased risk of adverse pregnancy outcomes. Given the medical, ethical and emotional complexities of pregnancy in CKD, the clinical approach should involve explicit consideration of women’s values; of which there are sparse data. We aimed to describe the beliefs, values, and experiences of pregnancy in women with CKD, to inform pre-pregnancy counseling and pregnancy care.

Methods: Semi-structured interviews were conducted with 41 women aged 22-56 years with advanced chronic kidney disease, from two renal units in Australia. Transcripts were analyzed thematically.

Results: Six themes were identified: bodily failure (conscious of fragility, noxious self, critical timing, suspended in limbo); devasting loss (denied motherhood, disempowerment by medical catastrophizing, resolving grief, barriers to parenthood alternatives, social isolation); intransigent guilt (disappointing partners, fear of genetic transmission, respecting families and kidney donor, the outcomes of their offspring, and genetic transmission). Communicating the medical risks of pregnancy to women with chronic kidney disease must be carefully balanced with their values of autonomy, hope, security and family. Informed and shared decision making that is sensitive to women’s priorities as identified in this study can contribute to improved pregnancy, health and psychosocial outcomes in this vulnerable population.

Conclusions: Decisions surrounding pregnancy in the context of chronic kidney disease require women to confront uncertainties about their own survival, disease progression, social support, their family and kidney donor, the outcomes of their offspring, and genetic transmission. Communicating the medical risks of pregnancy to women with chronic kidney disease must be carefully balanced with their values of autonomy, hope, security and family. Informed and shared decision making that is sensitive to women’s priorities as identified in this study can contribute to improved pregnancy, health and psychosocial outcomes in this vulnerable population.

Funding: Private Foundation Support

SA-PO750
Dual Agonist of Nuclear Hormone Receptor Farnesoid X Receptor and G Protein Coupled Receptor TGR5 Exhibits Caloric Restriction Mimetic Effects in Aging Mice Xiaoxin Wang,1 Evgenia Dobrilinskikh,1 Yuhuan Luo,1 Luciano Adorini,2 Moshe Levi,3 Univ of Colorado Denver; 1Intercept Pharmaceutical Company.

Background: Previous studies have shown that caloric restriction (CR) in mice and in rats prevent age-related proteinuria and glomerulosclerosis. We have observed an age-related decrease in renal nuclear hormone receptor farnesoid X receptor (FXR, NR1H4), and G protein-coupled receptor TGR5 (GPR11 or GPR131) expression. In contrast, renal FXR and TGR5 expression are increased by CR in the aging mice. FXR and TGR5 expression are also increased in the long-lived Ames dwarf mouse. The purpose of the present study was to determine if activation of FXR and TGR5 in the kidneys of ad lib fed aging mice have similar effects to CR.

Methods: We studied 5 month old ad lib fed, 24 month old ad lib fed, 22 months old ad lib fed mice treated with the dual FXR/TGR5 agonist INT-767 for 2 months, and compared them to lifelong 24 month old CR mice.

Results: Treatment of 22 month old ad lib fed aging mice with FXR/TGR5 dual agonist INT-767 for 2 months decreases albuminuria, TGF-β expression and fibroconnectin accumulation in aging mice. INT-767 stimulates mitochondrial biogenesis, increases mitochondrial DNA content, and mitochondrial transcription factors NR1-1 and Tfam in the aging kidney. INT-767 also increases the expression of SIRT1, PGC-1α, and ERRα mRNA, as well as PGC-1α and SIRT3 protein abundance. INT-767 activation of the mitochondrial NAD-dependent deacetylase SIRT3 restores its targets MCAD and acetyl-LDH to normal levels, which are important for regulation of mitochondrial fatty acid β-oxidation as well as mitochondrial redox status. Furthermore, INT-767 increased expression of NAMPT and Nk1, enzymes involved in synthesis of sirtuins substrate NAD.

Conclusions: Our results therefore indicate that activation of FXR and TGR5 in the aging kidney reverses most of the age-related changes and the effects of FXR and TGR5 are similar to beneficial effects achieved by lifelong CR.

Funding: NIDDK Support

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

Underline represents presenting author.

800A
SA-PO751
ESRD in Nonagenarians in the United States, 1995 Through 2010
Donal J. Sexton, Scott Reule, Robert N. Foley. Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Patients in their 90’s are increasingly being considered for maintenance dialysis, comprehensive epidemiological data could help with decision making.

Methods: We used US census data and data for patients who initiated maintenance dialysis between 1995 and 2010 (N=1,557,117) to examine trends in ESRD for those aged 90 to 99 years (N=14,289).

Results: The rate of ESRD in 1995-1996 was 0.6 per million per year in those aged 90-99 years respectively. Standardized incidence rates (SIRs) rose between 1995 and 2010 both overall (SIR 2.8) and individually in males (2.89), females (2.7) white (3.1) African American (1.93) and other races (2.43). Median survival was 10.7 months. “Unspecified renal failure” was the most common reported cause of ESRD (62.6%), followed by “diabetes mellitus type 2” (15.8%), “ATN without recovery” 3.4%, “GN (not histologically examined)” 3.18%, “renal artery stenosis” 2.44% and other 12.4%. Causes of death included: Cardiac deaths 42.4%, Infection 12.07%, Withdrawal of dialysis/ Uremia 10.16%, Stroke/Intracranial Hemorrhage 3%, Cachexia 2.99%, Cancer 2.45%, Other 12.03% and Unknown 14.89 %. Mortality fell over time, AHR (95% CI) 0.79 (0.72, 0.87) in 2009-2010 vs 1995-1996. Factors associated with a higher likelihood of death included: ischemic heart disease (AHR 1.13), AV graft (AHR 1.36 vs AV fistula), or venous catheter for hemodialysis vascular access (AHR 1.7 vs AV fistula), shorter pre-dialysis nephrology care (AHR 1.37), higher eGFR at dialysis initiation (AHR 1.13), serum albumin < 3.5 g/dl (AHR 1.34), cerebrovascular disease (AHR 1.21), peripheral vascular disease (AHR 1.14), cancer (AHR 1.08), inability to ambulate (1.43) or transfer (1.59), “ATN without recovery” as primary cause of ESRD (AHR 1.11 vs “renal failure not specified”).

Conclusions: ESRD in nonagenarians has risen over the period of observation in the United States. Rising prevalence may be attributable not only to rising incidence but to falling mortality also.

SA-PO752
Impact of Geriatric Multi-Morbidity Versus Medical Multi-Morbidity on Quality of Life in Older CKD Patients
Donal J. Sexton, Mi-kyung Song, Frank Moore, Kyung Liu, Kieran Reid, Jamie Giffuni, Jamie Giffuni, Robert N. Foley. Medicine, Univ of Minnesota, Minneapolis, MN.

Background: Geriatric conditions are constellations of signs and symptoms not always linked to a disease, such as cognitive impairment and fatigue; geriatric conditions are associated with worse quality of life (QoL). Older adults with CKD are likely to have geriatric multi-morbidity (GM), defined as ≥2 geriatric conditions. Medical multi-morbidity (MM) is also common in this population and affects QoL. We compared the impact of GM to MM on QoL in older CKD patients.

Methods: We used baseline data from an ongoing trial of exercise in persons ≥55 years with stage 3b-4 CKD. For GM, persons were defined with 1) cognitive impairment if Montreal Cognitive Assessment (26-2) 2) poor physical function if Short Physical Performance Battery ≤ 7; 3) dizziness as reported by Memorial Symptom Assessment Scale; 4) fatigue if reported ≥ “good bit of time” to feeling worn out on Short Form-36 (SF-36); and 5) chronic pain if ≥ “moderate” pain on SF-36. For MM, hypertension, diabetes, CAD, and cancer were self-reported. Major depression was defined as Beck Depression Inventory ≤ 15. QoL was measured with the SF-36. Linear regression adjusting for age, sex, race, site, BMI, and eGFR was utilized.

Results: Of 72 persons (31% women, mean age 68.6±7.8 years, mean eGFR 33±9.8 ml/min/1.73m³), 49% (35) had GM and 76% (55) had MM. GM was associated with lower scores in all SF-36 subdomains (all p<0.05). MM was associated with lower scores in two SF-36 subdomains (both p<0.05).

Conclusions: In older adults with CKD, geriatric multi-morbidity is common and likely affects QoL.

| Standardized βs of the associations of geriatric multi-morbidity and medical multi-morbidity with SF-36 |
|---------------------------------------------------------------|---------------------------------------------------------------|
| SF-36 subdomain | Geriatric multi-morbidity | P value | Medical multi-morbidity | P value |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Physical functioning | -0.519 | <0.001 | -0.185 | 0.09 |
| Role-physical | -0.489 | <0.001 | -0.060 | 0.61 |
| Bodily pain | -0.650 | <0.001 | -0.025 | 0.81 |
| General health | -0.451 | <0.001 | -0.259 | 0.02 |
| Vitality | -0.524 | <0.001 | -0.136 | 0.25 |
| Social functioning | -0.503 | <0.001 | -0.077 | 0.49 |
| Role-emotional | -0.289 | 0.02 | -0.257 | 0.05 |
| Mental health | -0.353 | 0.07 | -0.106 | 0.41 |

Funding: Private Foundation Support

SA-PO753
A Survey of Provider Knowledge, Attitude, and Practices Surrounding Conservative Management for Patients with Advanced Chronic Kidney Disease
Sanah Parvez, Khaled Abdel-Kader, V. Shane Pankratz, Mi-kyung Song, Mark L. Unruh. 1 Div of Nephrology, Univ of New Mexico; 2 Div of Nephrology, Vanderbilt Univ; 3 Adult and Geriatric Health Div; School of Nursing, Univ of North Carolina.

Background: Despite the potential benefits of conservative management (CM), discussing CM as a viable treatment option rarely occurs. Several factors might contribute to this but no studies in the U.S. have described them. The purpose of this survey was to describe nephrologist’s (NEPHs) and primary care providers’ (PCPs) knowledge, attitudes, and practices of CM for patients with advanced CKD.

Methods: We developed a survey based on the relevant literature to include items assessing knowledge, attitudes, and self-reported practices of CM for patients with advanced CKD. We then conducted a web-based cross sectional survey between April and May 2015. We used the American Medical Association’s Physician Masterfile to identify NEPH and PCPs practicing in the U.S.

Results: 431 (67.6% NEPHs, 32.4% PCPs) providers completed the survey. The respondents were, on average, white, predominantly male, and in their 30s and 40s. A majority of both PCP (83.5%) and NEPH respondents (78.2%) reported that they were likely to discuss CM with their older advanced CKD patients. Self-reported number of patients managed conservatively was at least >11 patients for 30.6% NEPHs and 49.2% of PCPs. As shown in the figure where a higher percent demonstrates a lower barrier, the major barriers to CM discussions identified by NEPHs and PCPs significantly differed.

There were significant differences in knowledge across the groups with PCPs reporting significantly more uncertainty about survival rates with CM.

Conclusions: Both NEPH and PCP are comfortable with discussing CM with their patients. PCPs have less certainty regarding patient selection for CM and report feeling less informed about outcomes of CM.

Funding: Pharmaceutical Company Support - DCI Inc

SA-PO754
Which Therapeutic Project for Elderly Reaching ESRD? Patient’s Characteristics and Outcomes
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Background: The KDIGO guidelines recommend referral for planning RRT in people at risk of kidney failure. Treatment without dialysis in ESRD patient is another therapeutic option especially in elderly. The objective of our study is to describe the therapeutic projects declared by nephrologist and associated patient’s characteristics and outcomes in a prospective design.

Methods: 573 patients over 75 y/o (82±5 y/o) with eGFR below 20 (14 ± 4) were included by nephrologists in 2009 and followed 4 yrs (Moranne et al 2012). At baseline, we recorded social, clinical characteristics and therapeutic project declared by nephrologist. The first project was considered at the second visit as Postponed decision about dialysis (STAB), decision to start Dialysis when required (DIAL), Non-dialysis made by nephrologist (NDne) or at patient’s request (NDpt). During follow-up, we evaluated the dialysis start and death before dialysis and compared patient’s characteristics and incidence of these events according to the therapeutic projects.

Results: The therapeutic project was STAB in 234 patients (41%), DIAL in 216 pts (38%), NDne in 66 (12%) and NDpt in 55 (10%). Patients were older in ND group, with more women for NDpt and more comorbidities for NDne (dementia, active malignancy,
Specific Prognosis Factors of Death and Dialysis Start for Elderly Patients Reaching ESRD in the Prospective PSPA Cohort Study

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Background: The death before dialysis start is high in elderly patients reaching ESRD and the treatment without dialysis is another option. We need to better predict the outcomes of this specific population and identify prognosis factors to improve strategies of care. The objective of our study is the identification of prognosis factors of dialysis start or death before dialysis in a multicenter prospective cohort of elderly reaching ESRD.

Methods: 573 patients over 75 y/o (82.5 y/o) were included by nephrologist in 2009-10 (Moranne et al 2012). At baseline, we recorded social and clinical characteristics, laboratory test and medications. Information about death or dialysis status is available for all patients after 4 years follow-up. Prognosis factors for dialysis start or death before dialysis were quantified with subdistribution hazard ratios using proportional hazard regression models constructed according to Fine and Gray to take account competing risks.

Results: After 4 years follow-up, 274 patients (48%) started dialysis and 223 (39%) died. Compared to patients without dialysis, those independently associated with higher risk of death prior to dialysis are: higher age, male, diabetes, lower eGFR, behavioural disorder, less mobility, cerebrovascular disease, cardiac heart failure, active malignancy and anemia. The variables associated to higher probability of dialysis start are: lower age, male, lower eGFR, high blood pressure, hyperphosphatemia, higher proteinuria, chronic respiratory disease, cerebrovascular disease and less behavioural disorder or active malignancy.

Conclusions: We observed a higher probability of dialysis start than death before dialysis in this population of elderly included by nephrologists. We identified specific prognosis factors that could discriminate the risk of starting dialysis or died before dialysis to help organisation of the CKD 5 care in elderly patients.

Funding: Pharmaceutical Company Support - Roche, Baxter, Amgen, Fresenius, MSD, Shire

Saint-Etienne, France; Nephrology, CHU Pontchaillon, Rennes, France.

SA-PO756

Attitudes, Experiences and Perspectives of Elderly Kidney Transplant Recipients: Thematic Synthesis of Qualitative Research

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1 Nephrology, Hospital Albert Einstein, São Paulo, Brazil.

Background: Kidney transplantation offers improved survival and quality of life in an increasing number of elderly patients with end-stage kidney disease. However, elderly kidney transplant recipients may face unique challenges due to a higher burden of comorbidity, greater cumulative risk of immunosuppression-related complications, and increasing frailty. We aimed to describe the perspectives of elderly kidney transplant recipients.

Methods: Electronic databases were searched to April 2015. Thematic synthesis was used to analyze the findings.

Results: 41 studies involving more than 120 kidney transplant recipients aged 60 yrs and over were included (29 studies did not specify number of patients aged ≥ 60 y/o). We identified 6 themes. Regaining strength and vitality meant valuing the marked physical and psychosocial improvements in daily functioning and life participation. Extending life was the willingness to accept an organ, including an extended criteria kidney, to prolong survival. Debt of gratitude entailed a need to be consciously appreciative towards their donors knowing they were unable to repay their sacrifice. Moral responsibility of maintaining health motivated adherence to medication and lifestyle recommendations out of an ethical duty to protect their gift and prolong graft survival. Disillusionment with transplant reflected disappontment and exasperation at having to contend with side effects and adverse events such as cancer, and residual physical limitations. Finality of treatment options reflected an acute awareness that their current transplant may be their last and some would not return to dialysis if the transplant failed.

Conclusions: Kidney transplantation reverses deterioration of functioning and well-being that patients experienced whilst on dialysis. However, elderly transplant recipients may have anxieties about debilitating adverse events, comorbidities, and a sense of vulnerability that the current transplant may be their last. Addressing these concerns in the care of elderly kidney transplant recipients may improve treatment outcomes in this growing population.

SA-PO757

Indoxyl Sulfate, a Representative Uremic Toxic, Suppresses Myogenic Differentiation: Implication in Uremic Sarcopenia

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Background: Sarcopenia (or muscle wasting) is a common feature of the uremic phenotype and retards the process of tissue repair and recovery in uremic patients. Disturbed skeletal myotube differentiation and contribute to sarcopenia in uremic patients. The expressions of myogenic differentiation markers and related signaling proteins were determined by Western blotting.

Results: We first investigated the non-lethal concentration of IS by MTT assay, and found IS level less than 1 mM with significant cellular toxicity as compared with control group. In order to development the protocol, we confirmed myotubes were visibly formed throughout 4 days of differentiation first. IS significantly attenuated the number of myotubes and the percentage of mature myotubes. Furthermore, IS significantly and dose-dependently decreased the expression of MyoD, Myogenin and myosin heavy chain, which is the representative markers of slow and fast myofiber phenotype, both in translational and transcriptional level. The molecular signals of myotube differentiation were also disturbed by IS treatment.

Conclusions: These findings suggest that IS, a uremic toxic, dysregulates myotube differentiation in C2C12 cells. This is the first time to provide additional evidence that IS might contribute to the development of sarcopenia in uremic patients. Further explore would give the light to provide potential therapeutics in uremic sarcopenia.

Funding: Other NIH Support - MOST in Taiwan
Methods: This was a retrospective observational study. Clinical and social demographic data were collected from clinical records. The Kidney Disease Quality of Life and Beck depression inventory were used to assess quality of life and depression symptoms. Results: 104 patients were included. 68.3% were men, 71.2% married, 91.3% Caucasian and 44.2% were in productive life period. A relation between quality of life score and time of dialysis was observed (p = 0.0118, CI -0.023; 0.0003). Patients younger than 65 y.o. showed more favorable results, such as general health perceptions, emotional well-being, energy/fatigue, pain and dialysis staff encouragement. Patients between 65 to 75 y.o. showed lower energy/fatigue index (11.98; CI: 9.92; -1.10) and a reduction of 18.97-points (CI: -33.97; -3.98) for emotional well-being. A 15.04-point (CI: -27.21; -2.87) depression correlated with time in hemodialysis (p = 0.0007; CI 0.14%; 0.55%). For each month an increase of 0.35% on depression symptoms was found.

Conclusions: For younger patients younger than 65 years hemodialysis treatment represents a rehabilitation possibility. Patients over 75 years had significant increase on social support and social interaction. Patients 65 to 75 y.o. had worse perception of quality of life.

SA-PO760
Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults: The Cardiovascular Health Study

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Background: Fibroblast growth factor 23 (FGF23) may inhibit 25-hydroxyvitamin-D-1α-hydroxylase (CYP27B1) in monocytes. We hypothesized that higher circulating FGF23 would lead to an increase in serious infection risk because FGF23 decreases the intracrine production of 1,25-dihydroxyvitamin D (1,25(OH)2D), which consequently reduces production of cathelicidins.

Methods: Plasma C-terminal FGF23 concentrations were measured in 3141 Cardiovascular Health Study participants. Cox proportional-hazards models were used to examine the association between FGF23 levels and the first infection-related hospitalization (multivariable models adjusted for demographics, co-existing illnesses, body mass index, tobacco use, albumin, estimated glomerular filtration rate, urine albumin creatinine ratio, C-reactive protein, and IL-6). We tested whether associations differed by the presence of chronic kidney disease (CKD) (eGFR < 60 vs 230 vs >60 ml/min/1.73m2 [vs 832]).

Results: Participants were 78±5 years, 60% females, and the median serum FGF23 level was 70 [IQR 53, 99] pg/mL. During a median follow-up of 15.7 years, 1162 (37%) had an infection-related hospitalization. In the adjusted models, participants in the highest quartile of FGF23 (compared to the lowest) had a higher risk of infection (hazard ratio [HR] 1:33; 95% confidence interval [95% CI], 1:10-1:60). The association was stronger for those participants with CKD (HR 1:27, 95% CI 1:11-1:46 per doubling of FGF23) than in those without CKD (HR 1:07, 95% CI 0:98-1:17 per doubling of FGF23; p-value for interaction: 0.06). The addition of serum calcium, phosphorus, vitamin D and PTH into the statistical models did not attenuate these associations.

Conclusions: In ambulatory elders, higher serum FGF23 levels were independently associated with the risk of first infection-related hospitalization. This association appeared stronger in the setting of CKD.

SA-PO761
Characteristic of the Elderly Patients in the Chronic Renal Insufficiency Standards Implementation Study (CRISIS) Cohort Compared To Their Younger Cohort A Descriptive Analysis

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Background: CKD in the Elderly is associated with high mortality and slower rate of progression to ESRD. Identifying the characteristics of this phenotype and modifying their risk may reduce the burden of death but this can be challenging due to the heterogeneity of the disease in this group.

Methods: The CRISIS cohort of 2706 participants was divided into four groups based on their age. Descriptive statistical analysis was performed using SPSS and in between group significance was calculated using one way ANOVA or Chi-Square test.

Results: Essential characteristics of the cohort are shown in the table below.

Conclusions: The group aged ≥75 years had the highest incidence of death and accumulation of co-morbidities. We aim to develop a risk prediction model to identify the characteristics of this phenotype, which may help in modifying their risk.

SA-PO762
Muscle Strength Rather Than Muscle Mass Is More Important in Evaluating Physical Function in Elderly Patients with Predialysis Chronic Kidney Disease

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Background: Recently, physical function has been reported to be strongly associated with prognosis of patients with chronic kidney disease (CKD). Sarcoptosis, which is well described in CKD patients on dialysis especially of the elderly and is known to be associated with reduced physical function, but whether this is the case in elderly predialysis CKD is undetermined.

Methods: We enrolled consecutive 85 elderly patients (age over 60) with predialysis CKD (estimated GFR<eGFR < 60 ml/min/1.73m2) at outpatient nephrology clinic at St Marianna University Hospital. We evaluated kidney functional parameters, muscle mass by bioimpedance, muscle strength by dynamometer (hand grip, knee extension) and 4-meter walking speed in those participants.

Results: Average age was 74 years old, 76% were men, 33% had diabetes mellitus (DM) and average eGFR was 28.6ml/min/1.73m2. Patients were divided into those with eGFR<30 or ≥30. After adjustment for age, gender and history of DM, hand grip strength (-4.36, 95%CI:-0.85–7.85), knee extension strength (-5.62, 95%CI:-2.28–8.97) and 4-meter walking speed (>0.12, 95%CI:-0.02–0.22) were significantly reduced in those with eGFR<30. However, there was no difference in muscle mass (-0.23, 95%CI:-0.68–0.23).

Conclusions: In conclusion, muscle strength and walking speed but not muscle mass developed along with progression of CKD. Thus, it seemed more important to check muscle strength and walking speed rather than muscle mass when evaluating physical function in elderly patients with predialysis CKD.
SA-PO767

Lower Muscle Endurance, Strength and Quality Are Associated with Greater Risk of Functional Limitations in Older Adults with CKD

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Background: Chronic kidney disease is associated with inflammation and insulin resistance, contributing to fatigue and muscle weakness. The association of muscle endurance, strength, and quality with functional limitation among persons with CKD is unknown.

Methods: We studied 186 participants with eGFR<60 at the year 3 Health ABC visit. Participants were excluded if unable to complete >90% of quadriceps isokinetic fatigue testing. Quadriceps endurance was defined by total work using isokinetic dynamometer. Quadriceps strength was measuring by isometric torque. Leg lean mass (legm) was measured using DXA. Muscle quality was defined by specific work (work/legm) and specific torque (torque/legm). Outcome was incident persistent severe lower extremity limitation (PSLL) based on 2 consecutive reports of having a lot of difficulty or inability to walk 1/4 mile or climb 10 steps without resting. We used competing risks regression.

Results: Participants had a mean age 76.2 ±53 years, eGFR of 49 ±10. None had mobility disability. There were 82 PSLL events over a median 6 years. After adjustment each 1-SD lower quadriceps isokinetic work and isometric maximal torque were associated with a 1.38 fold (95% CI 1.04, 1.85, P=0.028) and 1.43 fold (95% CI 1.01, 2.03 P=0.045) greater risk of PSLL, respectively. Leg lean mass was not associated with PSLL (P=0.12).

Conclusions: Among older adults with CKD free of mobility disability, lower muscle endurance, strength, and quality are independently associated with greater risk of severe lower extremity limitation.

Funding: NIDDK Support, Other NIH Support - NIDDK K23DK099442

Health ABC study funded by NIA

SA-PO764

Efficacy and Safety of Exercise Training in Patients with Predialysis Chronic Kidney Disease

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Background: Efficacy and safety of exercise training has not been well studied in patients with predialysis chronic kidney disease (CKD). Since we have reported in elderly patients with predialysis CKD that there was a significant reduction in muscle strength and short-term exercise did not damage kidney, we conducted a randomized controlled trial to elucidate the long-term efficacy and safety of exercise in this population.

Methods: Study design was a randomized controlled trial. Thirty six male elderly patients with CKD stage 3-4 seen at the outpatient nephrology clinic at St. Marianna University Hospital agreed to participate in the study with written informed consent. We randomly divided them into intervention (I) group and control (C) group. Patients with C group did not received exercise advice. Both groups received conventional drug therapy for CKD and were checked the daily foot steps by pedometer. Primary outcome was the change in estimated glomerular filtration rate (eGFR) and secondary outcomes were the changes in muscle strengths by dynamometer (hand grip and knee extension).

Results: There were no difference in baseline characteristics (demographic, kidney functional parameter, hemoglobin and serum albumin level) with average age of 68.7±6.8 years and eGFR of 39.0±11.6 ml/min/1.73m². Change in eGFR were not different at 12 months among both groups. Muscle strength in knee extension increased in I group (0.65±0.17kgf to 0.70±0.17kgf in knee extension) but not in C group (0.66±0.15 to 0.62±0.13kgf). This showed statistically significant difference. Change in muscle strength in hand grip also showed the difference between the groups.

Conclusions: Only the advice on exercise training could increase the physical activity and muscle strength without compromising kidney function in the elderly patients with predialysis CKD.

SA-PO765

Determinants of Impaired Cardiorespiratory Fitness in Older Adults with CKD

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Background: Chronic Kidney Disease (CKD) may be associated with impaired cardiorespiratory fitness (CRF). We examined methods of estimating CRF in CKD and identified factors associated with CRF.

Methods: We measured peak aerobic capacity (VO2peak) using a modified Graded Exercise Treadmill Test (GXT) in 71 older adults with CKD stage 3b-4 in an ongoing exercise clinical trial. GFR was estimated with the CKD-Epi equation. Linear regression was used to examine factors associated with VO2peak. Resting VO2 was measured prior to GXT in seated position. Metabolic Equivalents of Task (MET, oxygen consumption during exercise relative to rest) was estimated at peak exercise based on GXT stage and compared to actual achieved METS.

Results: Mean age was 68.4±7.7 years, with 51% African-Americans, 30% women; mean eGFR was 33±11 ml/min/1.73m² and mean Hb 12.3±1.6 g/dL. Mean VO2peak was 17.4±5.4 ml/kg/min, which was 31±17 lower than expected based on normative values (p<0.001). In a multivariate model including demographics and co-morbidity, lower hemoglobin - but not GFR - was associated with lower VO2peak (Table). Albuminuria did not correlate with VO2peak.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Standardized β</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.25</td>
<td>0.005</td>
</tr>
<tr>
<td>African-American</td>
<td>0.08</td>
<td>0.3</td>
</tr>
<tr>
<td>Male</td>
<td>0.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.01</td>
<td>0.9</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>-0.25</td>
<td>.002</td>
</tr>
<tr>
<td>Body Mass Index</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>GFR</td>
<td>0.09</td>
<td>0.3</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.19</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Estimated METS: Mean achieved METS was 5.6±1.8. Although there was low bias for estimated vs. achieved METS (mean difference, -0.45), precision and accuracy were poor, with only 35% of predicted values within 1 MET of achieved values, and nearly one third of estimated values >30% different from achieved.

Conclusions: Among older adults with CKD stage, CRF as reflected by VO2peak is markedly impaired. Lower hemoglobin, obesity, and prevalent cardiac disease are associated with worse aerobic capacity. The use of estimated METS during treadmill testing poorly estimates actual aerobic capacity.

Funding: NIDDK Support, Veterans Administration Support

SA-PO766

Access to Kidney Transplantation and Outcomes of Those Listed for Kidney Transplant in Elderly

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Background: Data suggests that patients above 70 years of age (<70 yo) with ESRD derive a benefit from kidney transplant (KT). We report our single center experience of access to transplant and outcomes for those >70 y.o. listed for KT. We used the number of evaluations in a year and rate of acceptance after evaluation as surrogate markers for KT access in elderly.

Methods: We assessed the rate of acceptance for KT and its trends over the years for those ≥70 y.o. between 2000-2014. Linear regression was used to assess trends over time. Differences in rates of listing by diabetes status and mortality among those transplanted vs waitlisted was assessed.

Results: Over 15 year period, we evaluated 612 elderly patients (pts). 25.3% of those evaluated were approved to be listed for transplant. There were 9 patients who were evaluated twice of those 5 were approved for listing the second time and two got transplanted. There was 300% increase in annual evaluation of the elderly from year 2000 to 2014 and trend towards increased acceptance rate of those evaluated (slope=-0.82, p=0.12).

Funding: NIDDK Support, Veterans Administration Support
The acceptance rate was lower in diabetics compared to non-diabetics (18.2% vs 32.0%; p=0.001). 38.0% of listed pts have been transplanted and the rate of transplant did not differ by diabetes status. Of those transplanted 59.3% had living donors. Mortality remained significantly high for transplant vs waitlisted patients. Though there has been some improvement in the acceptance rate for listing over time.

SA-PO767

P-Cystatin C Improves GFR Estimation in Older People
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Background: There is a need for validation of commonly used cystatin C and creatinine based formulas for eGFR (estimated glomerular filtration rate) in the older segment of the general population for all levels of kidney function.

Methods: Markers used for eGFR estimation were P-Cystatin C and P-Creatinine.

Measured GFR (mGFR) adjusted to body surface area was performed by a single sample iohexol clearance in 112 participants, aged 70-100 years old from the population-based cohort “Good Aging in Skåne”. The participants were selected to cover a wide range of kidney function and to obtain an even distribution regarding sex and age. The timing of the sample depended on eGFR (eGFR >50, 25-50, and >25 at 4, 7, and 24 hours respectively). Formulas of both markers (CKD EPI combined, Lund-Malmo combined, BIS2), only creatinine (CKD EPI creatinine, MDRD) and only cystatin C (CKD EPI cystatin C) were compared. The analysis included bias (median difference: mGFR-eGFR), precision (IQR: interquartile range of the differences), accuracy (P30: percentage of estimates ±30% of mGFR) as well as accuracy (P30) above and below mGFR 45.

Results: There were 57 women and 55 men. Mean age was 82 years and mean GFR 55 ml/min per 1.73m². Results are presented in the table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (95%CI)</th>
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</thead>
<tbody>
<tr>
<td>Age per 1 year increase</td>
<td>1.05 (1.03, 1.07)</td>
</tr>
<tr>
<td>Male sex vs. female</td>
<td>1.16 (0.87, 1.55)</td>
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<tr>
<td>African American vs. not</td>
<td>0.82 (0.58, 1.16)</td>
</tr>
<tr>
<td>Smoke no vs. yes</td>
<td>Ref</td>
</tr>
<tr>
<td>BMI &lt;18.5 kg/m²</td>
<td>2.22 (0.85, 5.76)</td>
</tr>
<tr>
<td>BMI 18.5-25 kg/m²</td>
<td>Ref</td>
</tr>
<tr>
<td>BMI 25-29.9 kg/m²</td>
<td>0.74 (0.52, 1.06)</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>0.87 (0.60, 1.27)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Ref</td>
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<tr>
<td>Hypertension</td>
<td>0.71 (0.45, 1.11)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.96 (0.64, 1.42)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.82 (0.44, 1.53)</td>
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<tr>
<td>CHF</td>
<td>1.76 (1.27, 2.45)</td>
</tr>
<tr>
<td>CAD</td>
<td>1.00 (0.72, 1.39)</td>
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<tr>
<td>Malignancy</td>
<td>1.20 (0.86, 1.67)</td>
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<tr>
<td>PVD</td>
<td>0.65 (0.32, 1.29)</td>
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<tr>
<td>Alcohol use</td>
<td>Ref</td>
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<td>No vs. Yes</td>
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<td>Missing</td>
<td>0.98 (0.57, 1.69)</td>
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<tr>
<td>Depression</td>
<td>0.69 (0.37, 1.30)</td>
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<tr>
<td>Albumin (g/dl) per 1 unit increase</td>
<td>0.75 (0.59, 0.96)</td>
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<tr>
<td>Potassium (meq/l) per 1 unit increase</td>
<td>0.92 (0.74, 1.13)</td>
</tr>
<tr>
<td>AVF access</td>
<td>Ref</td>
</tr>
<tr>
<td>No AVF vs. AVF</td>
<td>Ref</td>
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<tr>
<td>AVF present</td>
<td>0.35 (0.20, 0.61)</td>
</tr>
<tr>
<td>Missing</td>
<td>0.72 (0.45, 1.16)</td>
</tr>
</tbody>
</table>

SA-PO768

Factors Associated with Early Death After Dialysis Initiation Among Elderly CKD Patients
Fahad Saeed, Susana Arrigain, Jesse D. Schold, Joseph V. Nally, Sankar D. Navaneethan. Nephrology, Cleveland Clinic.

Background: There are limited studies examining prognosis for elderly CKD patients following dialysis initiation. Herein, we evaluated the factors associated with poor one year survival after dialysis initiation among elderly CKD patients at our institution.

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

Differential Significance of Prognostic Factors for 6-Month and 3-Year Mortality in Elderly Patients on Hemodialysis
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Background: As the population of elderly people has been growing, the number of older chronic kidney disease patients commencing renal replacement therapy (RRT) is increasing. The survival advantage of RRT may be counterbalanced by the burden of treatment and its negative effect on quality of life in the elderly, and old age is no longer seen as a contraindication to RRT. Therefore, it is important to evaluate survival factors in this population. We conducted this study to investigate prognostic factors for mortality in elderly patients starting hemodialysis (HD) for end-stage renal disease (ESRD).

Methods: We studied 621 CKD patients/65 years from an EMR based CKD registry linked to the USRDS data. We retrospectively analyzed factors associated with one year mortality after dialysis initiation including: age, sex, race, presence of diabetes, hypertension, BMI, stroke, CHF, COPD, malignancy, peripheral vascular disease, depression, alcohol use, smoking, presence of AVF, pre-dialysis serum albumin and potassium.

Results: In our study, 224 (36%) patients died within the first year of dialysis initiation. Results from the Cox proportional model showed that older age and CHF were associated with early deaths, while higher albumin, presence of AVF and HTN were associated with a lower hazard of early death.

Conclusions: CHF and older age in the pre-dialysis setting are associated with higher 1-year mortality after dialysis initiation. These prognostic data need to be presented to geriatric CKD patients while discussing renal replacement therapy options.

Table. Multivariable Cox model of 1 year mortality among elderly CKD patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1 year increase</td>
<td>1.05 (1.03, 1.07)</td>
</tr>
<tr>
<td>Male sex vs. female</td>
<td>1.16 (0.87, 1.55)</td>
</tr>
<tr>
<td>African American vs. not</td>
<td>0.82 (0.58, 1.16)</td>
</tr>
<tr>
<td>Smoke no vs. yes</td>
<td>Ref</td>
</tr>
<tr>
<td>BMI &lt;18.5 kg/m²</td>
<td>2.22 (0.85, 5.76)</td>
</tr>
<tr>
<td>BMI 18.5-25 kg/m²</td>
<td>Ref</td>
</tr>
<tr>
<td>BMI 25-29.9 kg/m²</td>
<td>0.74 (0.52, 1.06)</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>0.87 (0.60, 1.27)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Ref</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.71 (0.45, 1.11)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.96 (0.64, 1.42)</td>
</tr>
<tr>
<td>COPD</td>
<td>0.82 (0.44, 1.53)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.76 (1.27, 2.45)</td>
</tr>
<tr>
<td>CAD</td>
<td>1.00 (0.72, 1.39)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.20 (0.86, 1.67)</td>
</tr>
<tr>
<td>PVD</td>
<td>0.65 (0.32, 1.29)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Ref</td>
</tr>
<tr>
<td>No vs. Yes</td>
<td>0.73 (0.52, 1.04)</td>
</tr>
<tr>
<td>Missing</td>
<td>0.98 (0.57, 1.69)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.69 (0.37, 1.30)</td>
</tr>
<tr>
<td>Albumin (g/dl) per 1 unit increase</td>
<td>0.75 (0.59, 0.96)</td>
</tr>
<tr>
<td>Potassium (meq/l) per 1 unit increase</td>
<td>0.92 (0.74, 1.13)</td>
</tr>
<tr>
<td>AVF access</td>
<td>Ref</td>
</tr>
<tr>
<td>No AVF vs. AVF</td>
<td>Ref</td>
</tr>
<tr>
<td>AVF present</td>
<td>0.35 (0.20, 0.61)</td>
</tr>
<tr>
<td>Missing</td>
<td>0.72 (0.45, 1.16)</td>
</tr>
</tbody>
</table>
Methods: This is a single-center, retrospective cohort study from January 2009 to December 2014. In total, 90 ESRD patients commencing HD were enrolled. All the patients were aged 65 years or older. Six-month and 3-year survival rates and prognostic factors for mortality were evaluated.

Results: The mean follow-up period was 21.7±18.3 months. The 6-month and 3-year survival rate were 94.0% and 66.9%, respectively. Age, unplanned initiation of HD, presence of heart failure, high value of estimated GFR on starting HD, Charlson comorbidity index (CCI), and Eastern Cooperative Oncology Group Performance status (ECOG-PS) were associated with 3-year mortality, whereas only the presence of heart failure and ECOG-PS were significant predictors of 6-month mortality. There was no significant difference in 6-month mortality rate between patients aged ≥ 80 and < 80. On the other hand, 3-year mortality rate of ≥ 80 year-old patients was significantly higher than that of < 80 (≥ 80: 53.3% vs ≤ 80: 14.2%, p = 0.0004).

Conclusions: There is a variation of significance among different prognostic factors according to the duration of life after starting hemodialysis. The presence of heart failure and ECOG-PS predicted short-term mortality among elderly ESRD patients starting HD. These results might help clinical decision making when nephrologists consider commencing HD for elderly ESRRD patients.

SA-PO770
Cumulative Cardiovascular Polypharmacy Is Associated With the Risk of Geriatric Acute Kidney Injury
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Background: Polypharmacy is common in the elderly due to multiple morbidities. However, the effect of polypharmacy on renal outcomes is rarely recognized. We investigated the effect of cardiovascular polypharmacy on acute kidney injury (AKI) in elderly patients.

Methods: We used the Taiwan National Health Insurance PharmaCloud system to investigate the relationship between cumulative cardiovascular medications in the 3 months prior to admission and risk of AKI in the elderly at admission to general wards. Community-dwelling elderly patients (>60 years) were prospectively enrolled and classified according to the number of pre-admission cardiovascular medications. Cardiovascular polypharmacy was defined as use of 2 or more relevant medications.

Results: We enrolled 152 patients, 48% with AKI (based upon Kidney Disease Improving Global Outcomes [KDIGO] classification) and 64% with cardiovascular polypharmacy. The incidence of AKI was higher in patients taking more cardiovascular medications (0 drugs: 33%; 1 drug: 50%; 2 drugs: 57%; 3 or more: 60%; p = 0.04). Patients with higher KDIGO grades also took more cardiovascular medications (p = 0.04).

Conclusions: We found that elderly patients taking more cardiovascular medications had increased risk for adverse renal events. Interventions that reduce polypharmacy may be able to reduce the incidence of geriatric AKI.

SA-PO771
Low Bicarbonate Associates with Higher Mortality Independent of pH in Healthy Older Individuals: The Health, Aging, and Body Composition Study
Kalani L. Raphael,1 Rachel A. Murphy,1 Michael Shlipak,2 Suzanne Satterfield,3 Hunter K. Huston,1 Anthony Sebastian,1 Deborah Sellmeyer,1 Kushang V. Patel,3 Anne B. Newman,1 Mark J. Sarnak,2 Joachim H. Ix,3 Linda F. Fried,1 University of California San Francisco,2 University of Tennessee,3 Johns Hopkins Univ,1 Univ of Washington,1 Univ of Pittsburgh,2 Tufts Medical Center,3 Univ of California San Diego.

Background: Low serum [HCO₃⁻] associates with higher mortality in CKD. The purpose of this study is to determine if [HCO₃⁻] associates with all-cause mortality independent of systemic pH in healthy older persons.

Methods: Data were analyzed from the Health, Aging, and Body Composition Study, an observational study of black and white adults aged 70-79 years followed from 1997-2014. Arterialized venous blood gas measurements were obtained in 2,287 participants. Participants were grouped into one of 3 [HCO₃⁻] categories: <23.0 (low), 23.0-27.9 (reference group), and 28.0 mEq/L (high). Mortality hazard ratios (HR) in the low and high [HCO₃⁻] groups were compared to the reference group using Cox models adjusted for demographics, eGFR, albuminuria, COPD, smoking, and pH. Multivariate interaction terms tested whether CKD status modified the relationship between [HCO₃⁻] categories and mortality.

Results: The mean age was 76 years, 51% were female, and 38% were black. The mean pH was 7.41, mean [HCO₃⁻] was 25.1 mEq/L, 11% had low and 10% had high [HCO₃⁻]. The mean eGFR was 82.1 ml/min/1.73m²; 12% had CKD. During follow-up (mean 10.3 years), 1,326 (58%) participants died. The adjusted all-cause mortality HR was 1.24 (95% CI, 1.02-1.49) in the low [HCO₃⁻] category and 1.03 (95% CI, 0.84-1.26) in the high [HCO₃⁻] category compared to the reference group. CKD status did not modify the association between [HCO₃⁻] and mortality (p=0.74).

Conclusions: Healthy older persons with low [HCO₃⁻] have higher mortality risk than those with normal [HCO₃⁻] independent of pH and potential confounders. High [HCO₃⁻] does not associate with higher mortality. The potential health benefits of normalizing low [HCO₃⁻] in generally healthy older persons should be investigated.

Funding: Other NIH Support - National Institutes on Aging and National Institute of Nursing Research, Veterans Administration Support, Private Foundation Support

SA-PO772
Low Urinary Creatinine Excretion Is a Valid Surrogate for Frailty in Patients with Advanced Chronic Kidney Disease
Harmke Polinder-Bos,1 Hakon Nakac,1 Friedo W. Dekker,2 Stephan J.L. Bakker,3 Carlo A. Gaillard,1 Ron T. Ganssvoort,1 Internal Medicine, Univ Medical Center Groningen, Groningen, Netherlands;2 Epidemiology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Muscle wasting is a key component of frailty, which is highly prevalent in advanced stages of chronic kidney disease (CKD). Whether low urinary creatinine excretion (UCEr) is a valid surrogate for frailty in CKD patients is unknown. We studied cross-sectional associations between frailty and a low UCEr in patients with CKD stages 4 and 5 (not on dialysis).

Methods: 2748 healthy individuals of the general population were included to define low UCEr. Low UCEr was defined as height-indexed UCEr below the age- and sex-specific 5th percentile. In a CKD population including 320 and 967 participants of the resp. PREPARE-2 and NECOSAD studies, associations of frailty, the individual components that define frailty, and frailty-associated variables with low UCEr were evaluated using multivariate logistic and linear regression models. Frailty was defined as a composite construct including self-reported poor physical functioning, exhaustion, low physical activity, and underweight.

Results: In the general population with a median age of 46 years, median UCEr was 9.8 mmole/day for women and 14.3 mmole/day for men, compared to 7.0 mmole/day and 9.5 mmole/day in CKD patients, respectively. In the CKD patients with a median age of 63 years, low UCEr was found in 38%. Frailty, and the individual components that define frailty, were associated with a low UCEr, independent of comorbidities (OR frailty = 2.19 [1.28-3.77], p=0.005). Of the frailty-associated variables, lower hemoglobin and albumin levels, and higher parathyroid hormone levels were associated with low UCEr. Adjustment for GFR attenuated the associations of frailty, and the individual components that define frailty with low UCEr, except for underweight.

Conclusions: Low UCEr is a valid surrogate for frailty, independent of comorbidities. Low UCEr is strongly determined by a lower kidney function, suggesting that reduced kidney function induces changes in muscle mass and performance leading to frailty.

SA-PO773
Oral Anticoagulation and Kidney Function in Elderly
Antonios Dousou,1 Elke Schaeffer,2 Olga Jakob,1 Reinhold Kreutz,1 Natalie Ebert,2 Clinical Pharmacology, Charité;1 Nephrology, Charité;1 Clinical Epidemiology, Charité.

Background: In the past years new oral anticoagulants (NOACs) were approved expanding our pharmacological arsenal. Data on their utilization in elderly compared to vitamin K antagonists (VKA) are scarce and the impact of kidney function (KF) on NOAC use in a population with declining glomerular filtration rate (GFR) is of great interest. The present study investigates anticoagulant use and KF in people ≥ 70 years. Medication was assessed through personal interviews and coded using the Anatomical Therapeutic Chemical Classification System. For GFR estimation we used the CKD-EPI equation. Predictor analysis was conducted via logistic regression.

Results: Figure 1 illustrates the percentage of drug use for the three NOACs and phenprocoumon, the most common VKA in Germany, over the course of 4 years.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Table 1 shows the characteristics of patients for each oral anticoagulant group during the 4-year follow-up visit (01/2014-04/2015).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number (%) n = 112</th>
<th>Log rank test (Chi²) n=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>82 (73%)</td>
<td>10.56*</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>72 (64%)</td>
<td>8.18*</td>
</tr>
<tr>
<td>Weakness</td>
<td>98 (88%)</td>
<td>1.62</td>
</tr>
<tr>
<td>Nausea</td>
<td>44 (39%)</td>
<td>9.54*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (22%)</td>
<td>9.49*</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>58 (52%)</td>
<td>3.53</td>
</tr>
<tr>
<td>Constipation</td>
<td>62 (55%)</td>
<td>3.06</td>
</tr>
<tr>
<td>Mouth problems</td>
<td>38 (34%)</td>
<td>16.29**</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>68 (61%)</td>
<td>8.22*</td>
</tr>
<tr>
<td>Poor mobility</td>
<td>76 (68%)</td>
<td>12.28*</td>
</tr>
<tr>
<td>Itching</td>
<td>70 (63%)</td>
<td>3.95</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>89 (79%)</td>
<td>9.02</td>
</tr>
<tr>
<td>Restless legs</td>
<td>57 (51%)</td>
<td>8.05</td>
</tr>
<tr>
<td>Feeling anxious</td>
<td>62 (55%)</td>
<td>6.01</td>
</tr>
<tr>
<td>Feeling depressed</td>
<td>52 (46%)</td>
<td>3.13</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>68 (61%)</td>
<td>3.40</td>
</tr>
<tr>
<td>Skin Changes</td>
<td>28 (25%)</td>
<td>60.37***</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01 ***P<0.001

Conclusions: This study demonstrated high symptom burden, reduced functional status and QOL in dialysis patients. Patients with severe pain, weakness, shortness of breath, nausea, mouth problems, drowsiness, poor mobility and skin changes were more likely associated with higher mortality risk. Symptom identification and management may help predict and improve patient QOL outcomes in dialysis patients.

SA-PO775

Outcomes of Cardiopulmonary Resuscitation in Maintenance Dialysis Patients Based on CPR Characteristics
Haris Farooq Murad, Fahad Saeed. Cleveland Clinic Foundation.

Background: Cardiopulmonary resuscitation (CPR) is associated with high rates of mortality, especially in patients with end stage renal disease (ESRD). Previous studies have reported an in-hospital mortality rate of up to 75% in ESRD patients undergoing CPR. There are no large studies to date on how individual CPR characteristics relate to the long term outcomes in these patients. Herein, we aimed to answer this question.

Methods: By an EMR inquiry, we identified all the adult patients (>18years) who had undergone CPR from January 2006 to December 2014, and then selected patients who were on maintenance dialysis. We conducted a chart review of CPR characteristics and its association with the hospital discharge survival. We studied following variables: initial rhythm, duration of CPR, in-hospital versus out of hospital CPR and the use of hypothermia protocol.

Results: We studied a total of 497 ESRD who had undergone CPR. Sixty eight percent of our patients had expired in the hospital post-CPR. Pulseless electrical activity (PEA) was the most common initial rhythm (51.4%), followed by ventricular arrhythmias (19.6%) and asystole (19.2%). In-hospital mortality was the highest (76.8%) for patients with asystole. Mortality rates at the time of discharge were 73.3% for PEA and 57.7% for patients with ventricular arrhythmias respectively. Fifty six percent of patients who underwent therapeutic hypothermia died in the hospital as compared to 68.9% of those who did not undergo a cooling protocol. CPR duration of greater than 10 minutes was associated with higher in-hospital mortality (76.1%) as compared to patients who had CPR for less than 10 minutes (40.9%). Patients who had undergone out of hospital CPR (by paramedics or bystanders), 72.2% died before discharge; while 68.9% of patients who underwent CPR in the hospital expired during the same hospitalization. The average length of stay for patients who were alive at discharge was 17 days.

Conclusions: CPR in dialysis patients is associated with high mortality rates. It is possible to predict hospital discharge survival of patients with cardio-pulmonary arrest based on the CPR characteristics.
Methods: We collected data on 423 out of 440 dialysis patients from 7 dialysis facilities in the U.S. using self-reported questionnaires.

Results: Our study included 28.1% Caucasian and 66.7% African American patients. Eighty three percent of the patients felt that their QOL was an important determinant in guiding their future care plans, and 72.3% of patients reported that they need to have frequent discussions with their nephrologist. Only 35.4% of patients actually get information about their health and well-being from their nephrologists. Only 8.6% of patients had a discussion with any physician, nurse or social worker regarding end of life care during the past 12 months. Notably, 74.2% of our participants reported that they would like to have such discussions with their healthcare provider. Sixty seven percent of the patients wished to be full code. Fifty six percent of the patients preferred to die at home versus 20.4% wanted to die in a hospice facility and 13.4% in a hospital. Only 23.6% of patients knew about palliative care. Clinicians also need to have more dialogue between patients and their nephrologists regarding end of life care preferences, and it is necessary to develop policies and practices that would help address this need.

SA-PO777

“So I had No Choice”: Perceptions of Dialysis Decision-Making Among Older Adults Keren Ladin,1 Daniel E. Weiner.2 (1)Occupational Therapy, Tufts Univ, Medford, MA; (2)Section of Palliative Care and Medical Ethics, Univ of Pittsburgh Medical Center, Pittsburgh, PA; “Medicine, Tufts Univ Medical School, Boston, MA.

Background: Multiple treatments are available to older patients with advanced chronic kidney disease. However, poor communication about available treatment options may result in a mismatch between patient preferences and treatment choice.

Methods: Semi-structured in-depth interviews were conducted with a purposive sample of 11 patients aged 65 and older at two dialysis clinics in the Greater Boston area. Trained researchers conducted, audiotaped and transcribed interviews. Applying grounded theory, interviews were analyzed in an iterative process to identify emergent codes. Codes were discussed using consensus and organized into themes.

Results: Twenty-one patients participated in the interview. Mean age was 77±9 years; 50% were men, 19% African American and 58% diabetic. Median age was 28 (17, 39) months. Four major themes with associated subthemes were identified. The first, “Deciding to start dialysis” revealed that only two patients conceptualized dialysis initiation as a choice. Patients were seldom informed of conservative management, and many had unanswered concerns about trade-offs among treatment choices. The second theme, “Experience with dialysis”, included positive and negative physical, emotional, and social consequences of dialysis and logistics of care. While many reported greater than anticipated levels of pain, fatigue, and frustration over transportation costs and time, others reported substantial benefits, including increased longevity and the ability to achieve life goals. The third theme, “Patient Role”, revealed patients tied self-worth to meeting clinical goals. Finally, “End-of-life (EOL) preferences and conversations” revealed that most patients had not discussed EOL with their clinical team and or with loved ones.

Conclusions: Many older patients who received dialysis do not perceive that they had a choice when making their dialysis decision. Initiating dialysis may contradict patients’ EOL preferences, and many desire greater information and more discussions with clinicians. Older adults’ preferences and experiences with dialysis vary, underscoring the importance of patient involvement in decision-making.

SA-PO778

Improving Advance Care Planning in Elderly Outpatients with Chronic Kidney Disease: A Quality Improvement Initiative Keri K. Sugar,1,2,3,4 and Leigh M. Schell.1,2 1-section of Palliative Care and Medical Ethics, Univ of Pittsburgh Medical Center, Pittsburgh, PA; 2-Renal-Electrolyte Div, Univ of Pittsburgh Medical Center, Pittsburgh, PA.

Background: Despite a high annual mortality rate in patients with advanced chronic kidney disease (CKD), advance care planning (ACP) is underutilized. A minority of dialysis patients complete advance directives (AD). Timely ACP ensures that patients’ preferences for future care are respected and is associated with less intensive care at end of life. We sought to introduce ACP and increase documentation of AD in older outpatient CKD patients.

Methods: This quality improvement study was conducted over 15 weeks in older outpatients at the University of Pittsburgh Kidney Clinic. The intervention included training and role assignment the CKD nurse educator to introduce and encourage ACP completion. Inclusion criteria were age older than 65 years and referral to the CKD education session. The CKD nurse educator was assigned the role of asking whether each patient had AD and begin to ask their hemodialysis patients about ADs and document the discussion?

Results: Of the 110 patients who underwent CKD education over a period of 15 weeks, 52 (47.2%) were eligible. Thirty-one of 52 (59.6%) patients already had AD and 14 of 52 (26.9%) patients received AD (like Living wills, Substitute Decision Maker (SDM) and CPR forms). Only 2 patients had ADs in their charts (like Five Wishes).

Conclusions: In 3 months, a review of the patients’ charts will again look for any documented ADs. We have shown to want to discuss ADs in the past. We reviewed 215 chronic in-center hemodialysis patients at Sunnybrook Health Sciences Centre from March to April 2015 by the dialysis unit social workers for any documents related to ADs (like Living wills, Substitute Decision Maker (SDM) and CPR forms). Only 2 patients had ADs in their charts (1.0%). When this data has presented to the Nephrologists they agreed that ADs should be discussed with their patients and that this was a quality improvement issue. Will the staff nephrologists change their practice behaviour and begin to ask their hemodialysis patients about ADs and document the discussion?

SA-PO779

Trends in Inpatient Intensive Procedures in the Last Six Months of Life Among Medicare Beneficiaries Treated with Maintenance Dialysis, 2000-2011 Nwamaka Denise Eneanya,1 Susan M. Hailpern,2 Ann M. O’Harc2, Manjula Kurella Tamura,2 Ronit Katz,3 Yoshio N. Hall,4 (1)Div of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; (2)Kidney Research Inst, Univ of Washington, Seattle, WA; (3)Geriatric Research and Education Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA.

Background: Many US dialysis patients undergo intensive procedures intended to prolong life such as mechanical ventilation, cardiopulmonary resuscitation or feeding tube placement at the very end of life. Little is known about trends over time in use of intensive procedures in this population.

Methods: We examined temporal trends in receipt of inpatient intensive procedures in the last 6 months of life by age and race among 601,942 adult Medicare beneficiaries treated with maintenance dialysis who died between January 1, 2000 and December 31, 2011.

Results: From 2000 to 2011, inpatient admissions during the last six months of life increased slightly from 89% to 90%. Among those admitted, there was a marked increased in the use of intensive procedures ranging from 38% in 2000 to 44% in 2011. Intensive procedures at the end of life were more common among black vs. white patients (50% to 57% vs. 34% to 39%) and among younger vs. older patients (50% to 61% for those < 55 years vs. 27% to 26% for those 85+ years).

Conclusions: Despite a high annual mortality rate in patients with advanced chronic kidney disease. However, poor communication about available treatment options may result in a mismatch between patient preferences and treatment choice.

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

SA-PO780

Will Nephrologists Implement an Advance Directives Program in Their Patients? (Quality Improvement Program) Ali Mohammed Habeeb, Sheldon W. Tobe. Nephrology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

Background: Mortality remains high among patients on dialysis. Advanced age and multiple co-morbidities are the major predictors for increasing mortality. ADs extend patients’ autonomy and are the best tool to inform patients about their preferences for health care decisions when they become unable to make such decisions. Chronic dialysis patients have been shown to want to discuss ADs in the past.

Methods: We reviewed 215 chronic in-center hemodialysis patients at Sunnybrook Health Sciences Centre from March to April 2015 by the dialysis unit social workers for any documents related to ADs (like Living wills, Substitute Decision Maker (SDM) and CPR forms). Only 2 patients had ADs in their charts (1.0%). When this data has presented to the Nephrologists they agreed that ADs should be discussed with their patients and that this was a quality improvement issue. Will the staff nephrologists change their practice behaviour and begin to ask their hemodialysis patients about ADs and document the discussion?”

Results: As part of the process to discuss ADs, the unit’s social workers distributed a pamphlet for the patients with simple and explicit definitions and advantages of AD and also provided explanations about the contents of AD forms and documents. The Staff Nephrologists were educated about the importance and advantages of ADs in their patients and were asked to start discussing the issues with their patients. The Nephrologists will also be educated about how an AD discussion might go and how to document the results of the discussion. In 3 months, a review of the patients’ charts will again look for any documented ADs. We will also study the response of individual dialysis staff and their participation in completing and discussing the ADs. We will assess the potential barriers for not completing ADs by the dialysis unit staff and by patients and attempt to address these barriers.

Conclusions: We anticipated that the dialysis staff are now in the contemplation stage and we are aiming to observe the progression in their behavior to more advanced stages of behavior and try to find out what are the barriers that prevent the progression.

In adjusted analyses, racial differences in receipt of intensive procedures were most pronounced at older ages (black vs. white aOR [95% CI]; 1.38 [1.33-1.42] in patients < 55 years, 2.48 [2.38-2.59] in patients 85+ years).

Funding: NIDDK Support
SA-PO781

Current Practice of Advance Care Planning in New Zealand and Australian Renal Centres

Rachael L. Morton, 1 Lucy Spencer, 2 Allison Tong, 1 Carol A. Pollock, 2 Karen M. Detering, 2 Josephine M. Clayton, 1, 3 The Univ of Sydney, Australia; 2 Royal North Shore Hospital, Australia; 3 HammondCare Palliative Care Service, Australia; 3 Austin Health, Australia; On behalf of Univ of Technology Sydney Collaborators.

Background: Recent guidelines emphasise the need to improve advance care planning (ACP) for patients with chronic kidney disease (CKD). Little is known about current ACP practice in Australian/New Zealand renal centres. We aimed to describe current practice and barriers to ACP from the perspective of renal clinicians.

Methods: A cross-sectional survey was administered online to nephrology nurses, nephrology social workers and nephrologists between May 2014 and January 2015. Survivors to home haemodialysis described their experiences of care, covered the topics of experience, skills, comfort and knowledge regarding ACP, workplace policies and procedures concerning ACP, perceived barriers and facilitators to ACP, and perceived need for new CKD-specific ACP programs and materials.

Results: Survivors to home haemodialysis included 127 participants; 70 (58%) were male and 57 (45%) were female, 115 (91%) identified as Caucasian, and 8 (6%) as Asian. Participants reported higher 1 year prevalence and mortality compared to age-matched predominantly white population. Participants in dialysis vintage greater than 20 years were more likely to be aware that a dialysis guideline already existed and to have used it compared to those in dialysis vintage less than or equal to 20 years (p < .05). Nephrologists were most likely and administrators least likely to perceive them as barriers (all p < .05). Care coordination, and family bereavement support, with administrators least likely to view these needs. To better address palliative care needs, nephrologists need to lead interdisciplinary collaborations, including administrators, to implement palliative care pathways already available.

Conclusions: Current ACP practice in Australian/New Zealand renal centres is subject to health system, provider and patient related barriers. Given the volunteer effect associated with online survey, this study may underestimate the need for ACP support. Targeted interventions are needed to improve ACP in Australian and New Zealand renal centres.

Funding: Private Foundation Support

SA-PO782

Nephrology Leadership Required to Address Unmet Palliative Care Needs in Dialysis Centers

Alvin H. Moss, 1 Stacey Culp, 1 Dale Lupu, 2 Cheryl Arenella, 3 Nancy C. Armstead, 3 1 Medicine, West Virginia Univ School of Medicine, Morgantown, WV; 2 Daleview Associates, Silver Spring, VA; 3 Mid-Atlantic Renal Coalition, Richmond, VA.

Background: Because of high symptom burden, numerous comorbidities, and shortened life expectancy, dialysis patients are increasingly recognized as appropriate candidates for early and continuous palliative care.

Methods: In 2013 the Coalition for Supportive Care of Kidney Patients conducted an online survey of dialysis professionals and administrators using ESRD Network and Renal Physicians Association email lists to determine perceptions about how well patient palliative care needs are met. Differences among disciplines were assessed by chi-squared testing and one-way ANOVA.

Results: The 487 respondents included 41 nephrologists, 152 nurses/physician assistants, 199 social workers, and 95 dialysis center administrators. There was a significant difference by discipline in reported unmet palliative care needs for symptom management, care coordination, and family bereavement support, with administrators least likely to view each need as unmet (all p < .02). In rating possible barriers to providing high quality palliative care in their centers, mean scores differed by discipline for 7 items, and nephrologists were most likely and administrators least likely to perceive them as barriers (all p < .05). “Guidelines to help with decision-making in seriously ill patients” was selected as the top priority for change by each discipline (37% overall, p = 47 by discipline). Nephrologists were most likely to be aware that a dialysis guideline already existed and to have used it (43.9% vs 3.3% RN/PA vs 10.6% MSW vs 8.5% administrator, p < .001).

Conclusions: Nephrologists report more unmet palliative care needs, barriers, and resources than the administrators who oversee dialysis centers. Because the respondents were self-selected, a study limitation, the results likely underestimate unmet palliative care needs.

To better address palliative care needs, nephrologists need to lead interdisciplinary collaborations, including administrators, to implement palliative care pathways already established in evidence-based clinical practice guidelines.

SA-PO783

Hospice and Race for End-Of-Life Care in U.S. Dialysis Patients

Robert N. Foley, 1 Scott Reule, 1 Donal J. Sexton, 1 1 Div of Nephrology, Univ of Minnesota, Minneapolis, MN; 2 Div of Medicine, National Univ of Ireland, Galway.

Background: While hospice use is increasingly used for end-of-life care in dialysis patients, we hypothesized that important racial disparities may be present.

Methods: To address this hypothesis, we examined USRDS files to characterize end-of-life care for deaths occurring between 2006 and 2011.

Results: During this 5-year period, the proportion of deaths in hospice increased from 14.7% to 24.2%; grouped by age at death, the following trends were observed: < 65 years-11.5% to 15.0%; 65 to 79 years-19.1% to 26.1%; 80-89 years-24.9% to 34.3%; ≥ 90 years-25.9% to 39.6%. As shown in the accompanying Table, associations of hospice use varied substantially with race: compared to whites, adjusted odds ratios of hospice use were 0.56, 0.56 and 0.57, respectively, in patients of African American, Native American and Asian race.

Conclusions: While end-of-life care in hospice settings is growing rapidly in the US, substantial, unexplained racial disparities exist.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

SA-PO784

Palliative Care Perspectives of Latinos with End-Stage Renal Disease

Lilia Cervantes, 1, 2, Stuart L. Linas, 1, 2 Stacy M. Fischer, 1 1 Dept of Medicine, Univ of Colorado, Denver, CO; 2 Dept of Medicine, Denver Health and Hospital, Denver, CO.

Background: Latinos are the fastest growing minority and have a nearly 2-fold faster progression from chronic kidney disease to end-stage renal disease (ESRD). Despite the high symptom burden and mortality suffered by patients with ESRD, there is limited palliative care research and Latinos are underrepresented in existing palliative care studies. The purpose of our study is to provide the first description of the Latino palliative care perspective.

Methods: Observational descriptive survey of adult English and Spanish speaking Latinos with ESRD from a safety-net hospital and two private dialysis centers. We modified Davison’s 2010 End of Life Care Preferences and Needs Survey to include known barriers to palliative care in the Latino community. The survey was translated to 3rd grade Spanish and then back-translated to English.

Results: Participants (n=61) had a mean age of 59 years ± 12, mean Charlson Comorbidity Index of 6.5 ± 2.5, and a dialysis vintage mean of 43.3 months ±44.8. The majority (77%) spoke Spanish and reported limited understanding of hospice and palliative care. We found that 60 (98%) want to be informed about their prognosis and 55 (90%) want to be prepared and plan ahead; however, only 16 (26%) had discussed prognosis and only 10 (16%) had discussed end-of-life care with their nephrologist. The majority of participants stated that it was their doctor’s choice (68.8%) to start dialysis; however, few (14.7%) regret the decision to start dialysis. Participants reported a preference to have advance care planning conversations on a routine basis (86.8%), after starting dialysis but before becoming ill (85.2%), and while receiving dialysis (47.5%) or at home (37.7%). Participants want their family have a central role in medical decision-making (93.4%) and care giving (95%).

Conclusions: Our findings provide the first description of the palliative care perspectives of a predominantly Mexican Latino population with ESRD. By understanding the palliative care perspectives and barriers experienced by Latinos patients with ESRD, we can move toward a value-based and patient-centered model of palliative care.

Funding: Private Foundation Support

SA-PO785

Symptom Burden Amongst Latinos with End-Stage Renal Disease

Lilia Cervantes, 1, 2 Stuart L. Linas, 1, 2 Stacy M. Fischer, 1 1 Dept of Medicine, Univ of Colorado, Denver, CO; 2 Dept of Medicine, Denver Health and Hospital, Denver, CO.

Background: All patients with end-stage renal disease (ESRD) experience a high symptom burden. Although Latinos represent 19% of the US ESRD community, little research is available on their symptom burden. The purpose of our study was to provide the first description of symptom burden prevalence and severity amongst Latinos with ESRD.

Methods: Observational descriptive survey of adult English and Spanish speaking Latinos with ESRD from a safety-net hospital and two private dialysis centers. We used Davison’s ESAS-r: Renal tool which measures physical and psychological symptom distress progression from chronic kidney disease to end-stage renal disease (ESRD). Despite the first description of symptom burden prevalence and severity amongst Latinos with ESRD, there is limited palliative care research and Latinos are underrepresented in existing palliative care studies. The purpose of our study is to provide the first description of the Latino palliative care perspective.

Results: Participants (n=61) had a mean age of 59 years ± 12, mean Charlson Comorbidity Index of 6.5 ± 2.5, and a dialysis vintage mean of 43.3 months ±44.8. The majority (77%) spoke Spanish and reported limited understanding of hospice and palliative care. We found that 60 (98%) want to be informed about their prognosis and 55 (90%) want to be prepared and plan ahead; however, only 16 (26%) had discussed prognosis and only 10 (16%) had discussed end-of-life care with their nephrologist. The majority of participants stated that it was their doctor’s choice (68.8%) to start dialysis; however, few (14.7%) regret the decision to start dialysis. Participants reported a preference to have advance care planning conversations on a routine basis (86.8%), after starting dialysis but before becoming ill (85.2%), and while receiving dialysis (47.5%) or at home (37.7%). Participants want their family have a central role in medical decision-making (93.4%) and care giving (95%).

Conclusions: Our findings provide the first description of the palliative care perspectives of a predominantly Mexican Latino population with ESRD. By understanding the palliative care perspectives and barriers experienced by Latinos patients with ESRD, we can move toward a value-based and patient-centered model of palliative care.

Funding: Private Foundation Support
was experienced by 83.5% of patients and reported as moderate or severe by 67.2%. Pain was present in 85.6% and moderate or severe in 49.1%. Depression was reported by 55.7% and anxiety by 49.1% and moderate or severe in 49.2% and 39.3%, respectively. The majority (78.6%) of patients reported lack of well-being and feeling drowsy (70.5%). With respect to medication preferences, our cohort prefers Western Medicine (77.1%) over traditional curanderismo (22.9%) medicine and is agreeable (77.1%) to taking a few more medications if it meant all symptoms could be controlled. Our Latino cohort prefers (88.5%) to have their physical symptoms (e.g. pain, nausea) treated by nephrology staff.

**Conclusions:** Latinos with ESRD suffer from a debilitating symptom burden and over half of the symptoms are amenable to symptoms directed therapy. Our findings support the early identification and treatment of physical symptoms by nephrology staff.

**Funding:** Private Foundation Support

**SA-PO786**

**Care of the ‘Failing HD Patient’: Role of a Supportive Care Register Tracy Marvan, Maria Da Silva-Gane, Suresh Mathavakkannam. Renal Unit, Lister Hospital, Stevenage, Hertfordshire, United Kingdom.

**Background:** Older dialysis patients (>70) often have significant comorbidities, that worsen with duration on HD. Continuation of dialysis often occurs at the expense of frequent illness episodes. There is a progressive decline in cognitive and physical function that exacerbates dialysis. We had introduced a Supportive Care Register (SCR) in 2012 to identify ‘failing dialysis patients’ based on their physical performance scores. We attempted to understand whether being on the SCR enabled better patient care when these patients were admitted with inter-current illnesses.

**Methods:** Data was collected from Patient Administration System (PAS) and Renal IT database in a large Tertiary (non-transplanting) Renal Unit serving a catchment population of 1.2 million. Data maintained in the SCR was reviewed. Total number of HD patient admissions to the acute renal service in 2013 were obtained with analysis of demographics, length of stay (LoS) and outcomes at discharge. Patients who were admitted were checked against the SCR entries. **Results:** 287 out of the 409 total HD patients were admitted (123 F, median age 68 years, 590 episodes) with 137 of these patients being admitted more than once. The LoS was 9 days. 49 patients died in 2013 (28M; 76±16 yr; vintage 60 ml; LoS 18±12 p<0.05). 28 patients died in hospital or at home hospice following withdrawal of dialysis and institution of palliative care. 16 patients had died following severe acute illness. Five patients died at home. 18/28 patients were on the SCR and had discussions relating to ongoing and future dialysis therapy and advanced and preferred place of care planning prior to their last admission in the clinic setting. Seven patients had proceeded to discussions regarding resuscitation.

**Conclusions:** In conclusion, establishment of a SCR for dialysis patients with declining functional capacity and significant comorbidities allows for an early identification of patients at risk of physical and functional decompensation. Once identified, establishing a dialogue in the OP dialysis setting about future care needs and expectations allows for a more integrated care approach when patients decompenstate to the point of being unable to continue dialysis.

**Funding:** Government Support - Non-U.S.

**SA-PO787**

**A Descriptive Study of Home Palliative Service Utilization and Care Trajectory Among Patients Dying on Dialysis Gihad E. Nesrallah, 1 Stephanie Dixon, 2 Marnie MacKinnon, 3 Sarah E. Bota, 4 Jade S. Hayward, 5 Erin Arthur, 6 Pernia G. Blake, 7 Amit X. Garg, 8 Sara N. Davidson. 9 Nephrology Program, Humber River Hospital, Toronto, ON, Canada; 1 Inst for Clinical Evaluative Sciences, London, ON, Canada; 2 Ontario Renal Network, Toronto, ON, Canada; 3 Ottawa Health Research Inst, Ottawa, ON, Canada; 4 Faculty of Medicine, Univ of Alberta, Edmonton, AB, Canada.

**Background:** Palliative care service use and outcomes among Ontario’s dialysis recipients remain uncharacterized.

**Methods:** We conducted a descriptive, retrospective, cohort study of 5,507 patients who died while receiving or withdrawing from chronic dialysis (hemodialysis or peritoneal dialysis) in Ontario, between January 1, 2010 and December 31, 2012. Data sources included the Ontario Renal Reporting System, the Canadian Organ Replacement Register, the Home Care database, and other linked administrative health datasets. The date of death served as the index date, and we examined patterns of service use in the prior 365 days. We present selected measures of health service use and outcomes.

**Results:** Cohort characteristics at death, expressed as median (IQR) or percent of cohort included: 75 (16) yrs old, 3.0 (5) yrs on dialysis, 42% female, 65% had diabetes, 14 (4) Johns Hopkins ACG (comorbidity score). Final dialysis modality was 85% centre HD, 1% home HD, 4% PD, 10% missing. During the last year of life, 11.3% received at least one palliative care service in the home, and 17.5% withdrew from dialysis in the last 30 days of life. In the last 14 days of life, 44% of patients had an emergency department (ED) visit and 65.6% a hospital or ICU visit. ED and ICU visits were less frequent among patients who had received home palliative services in the last year of life. Place of death was ICU in 33%, and acute care hospital (without ICU) in 32%, while only 3.6% of patients died at home. Patients with home palliative care services in the last year of life had a greater frequency of death at home (15 vs. 2%) compared with those who did not.

**Conclusions:** Home palliative care services may not be used optimally by dialysis patients in Ontario. Further studies are needed to understand barriers to accessing palliative care services and to improve service planning and delivery.

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

**Underline represents presenting author.**

**810A**
Explanatory analysis showed that only SQ (OR=2.3, 95% CI 1.05, 4.97) and ALB (OR=0.22, 95% CI 0.10, 0.46) were associated with 6-month MR. Simpler models appeared to perform equally well.

Conclusions: The existing prediction model by Cohen et al. has reasonable discrimination but over-estimated the number of deaths and may require recalibration of model coefficients. The model may guide advance care planning conversations, but caution is required when applying this model in clinical decisions. A simpler model may enhance feasibility for use. Further research is needed prior to utilizing the model to predict death.

Funding: Government Support - Natl-U.S.

SA-PO790
Identifying Advanced Chronic Kidney Disease Patients with Same Survival Under Conservative Care versus Dialysis
Crisa P. Kovessy,\(^2\) 1Miklos Zsolt Molnar,\(^1\) Jennie J,\(^2\) Melissa Soocho,\(^2\) Jun Ling Lu,\(^*\) Elani Streja,\(^*\) Lawrence Agogda,\(^2\) Kevin C. Abbott,\(^2\) Paul W. Eggers,\(^2\) Kamyar Kalantar-Zadeh,\(^3\) \(^1\)Univ of Tennessee Health Science Center, Memphis, TN, USA; \(^2\)VA Medical Center, Memphis, TN, USA; \(^3\)Univ of California, Irvine, CA, USA

Background: It is unclear if dialysis offers advantages over conservative care in certain patients with advanced CKD who do not have rapidly deteriorating kidney function.

Methods: From 659,546 US veterans with CKD we identified 9,273 who transitioned to dialysis, and 6,136 who reached eGFR<15 ml/min/1.73m\(^2\), but did not start dialysis. We matched these groups for their eGFR slope and for the last eGFR prior to ESRD, and restricted analyses to patients with no rapid pre-ESRD progression (defined as a slope of <-5 to <0) and pre-ESRD eGFR of 10 to 14.9. We examined all-cause mortality using time-stratified Cox models (by 1-year increments) to account for non-proportionality of hazards.

Results: Of 1,026 veterans included in the analysis, 651 patients did not, and 375 patients did initiate dialysis. Baseline Age, gender, race, eGFR slope and last eGFR, and comorbidities were similar in the dialysis vs. no dialysis groups. Overall, 624 patients died over a median follow-up of 1.5 years. Patients on dialysis experienced lower mortality in the first year (HR, 95%CI: 0.25, 0.17-0.36, p<0.001) and in year 2 (0.67, 0.52-0.87, p<0.003). Among patients who survived at least 2 years (28% of the original cohort), the risk of death associated with dialysis was 28% higher but not statistically significant (1.28, 0.94-1.75, p=0.12) during the subsequent time period. In this latter group baseline slopes were flatter (-2.1(1.3) vs. -1.9(1.2)), but their other characteristics were similar to the overall cohort.

Conclusions: Among patients with eGFR 10-15 ml/min/1.73m\(^2\) and no rapid loss of kidney function, transition to dialysis was associated with survival advantage over a two year time period. However, in 28% of the patients conservative management was not associated with worse mortality. Better characterization of patients may benefit from conservative management warrants additional studies.

Funding: NIDDK Support, Veterans Administration Support

SA-PO791
Enteric Dialysis – Stabilization of the Gut Microbiome using Probiotics and Prebiotics (Gut-Kidney Connection)
Narayanan Ragathanathan,\(^\star\) Eli A. Friedman\(^\star\) \(^2\) Research and Development, Kibow Biotech Inc, Newtown Square, PA; \(^3\)Downstate Medical Center, State Univ of New York, Brooklyn, NY

Background: Recent scientific evidence from the human microbiome project has revealed that the trillions of gut microbiome exceed the human microbiome by a factor of 10. There are just 23,000 human genes as against the 3.3 million genes coded by the gut microbiome. This complex microbiome has a major role to play in health and diseases. Scientific evidence has shown that there is an imbalance in the ratio of this complex microbial community leads to dysbiosis as a cause for various diseases. The use of beneficial microbes – probiotics and prebiotics is generally well recognized towards digestive, gut and immune health. However, novel and niche application of probiotics and prebiotics as a dietary supplement in stabilization of Gut microbiome towards Chronic Kidney Disease (CKD) is relatively new. Many independent reviews in various scientific journals have reflected on various topics such as gut Microbiome, its dysbiosis, impact of the altered intestinal community leads to dysbiosis a cause for various diseases. The use of beneficial microbes – probiotics and prebiotics is generally well recognized towards digestive, gut and immune health. However, novel and niche application of probiotics and prebiotics as a dietary supplement in stabilization of Gut microbiome towards Chronic Kidney Disease (CKD) is relatively new. Many independent reviews in various scientific journals have reflected on various topics such as gut Microbiome, its dysbiosis, impact of the altered intestinal community leads to dysbiosis a cause for various diseases.

Methods: "Renadyl" a sybiotic dietary supplement was studied in randomized clinical trials in CKD 3 and 4 and ESRD patients. Other oral therapies for removal of uremic toxins include the use of keto acids and charcoal sorbents.

Results: Our studies using Renadyl for "Enteric Dialysis" showed reduced in levels of various uremic toxins like urea and indoxyl glucuronide. Levels of CRP also decreased with improved quality of life. This demonstrates the potential restoration of the gut microbiome dysbiosis with the use of specific strains of probiotics.

Conclusions: The use of a well-researched, clinically documented and safe probiotic / prebiotic dietary supplement formulation has the potential to safely perform continuous enteric dialysis and stabilize the gut Microbiome and its dysbiosis. Hence, the concept of “Enteric Dialysis” with continuous removal of uremic toxins may be the future key to providing an alternative HOPE for renal failure population.

Funding: NIDDK Support

SA-PO792
Charcoal Hemoperfusion in the Treatment of Pruritus in Cholestatic Liver Disease
Wongarm Kittanamongkolchai, Ziad El-Zogby, Nelson Leung, Nephrology, Mayo Clinic, Rochester, MN.

Background: Pruritus is a distressing symptom in a considerable proportion of cholestatic patients and few of them do not respond to conventional treatment. Charcoal hemoperfusion (CH) is an extracorporeal technique to eliminate albumin-bound substances that are accumulated during cholestasis by the passage of blood through a column containing activated charcoal. Several case reports have shown significant reduction of bilirubin in mechanical jaundice and neonatal hemolytic jaundice. However, the published data of CH for the treatment of resistant pruritus in cholestatic patients is scarce.

Methods: Procedure code “Charcoal hemoperfusion” was used to identify patients who received charcoal hemoperfusion at Mayo Clinic, Rochester from 1/1/2000 to 5/1/2015.

Results: Thirteen patients were identified. All patients had failed conservative treatment and 2 of them had not responded to plasmapheresis. A median of 3 (1-9) sessions for a total of 20(1-33) hours were performed. CH resulted in a significant decrease of pruritus in 9 patients (69%). 2 patients did not have significant relief and 2 patients did not pursue further treatments after having adverse reaction during the first session. Median pruritic score significantly decreased from 9/10 (9-10) to 4/10 (0-9) posttreatment (p=0.004). Duration of symptom free period ranged from 8 to 46 days (median 18 days) in 6 patients who returned for follow up. 6 patients (46%) experienced adverse reactions described in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Complications</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and rigor</td>
<td>5</td>
<td>2</td>
<td>0.12</td>
</tr>
<tr>
<td>Pain, (head, chest, back)</td>
<td>2</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Data represented in median(min-max)

Conclusions: Charcoal hemoperfusion is an effective therapy for refractory cholestatic pruritus. However, the improvement is not sustainable and the short benefit should be balanced with the invasive nature of the therapy and the relatively common adverse reactions.

SA-PO793
Strict Adherence to Medicaid InterQual® Criteria Increases Adverse Events and Health Care Utilization in Undocumented Dialysis Patients
S. Jawad Sher, Melissa D. Anderson, Ranjani N. Moorthi, Sharon M. Moc, Michael T. Eadon. Medicine, Indiana Univ, Indianapolis, IN.

Background: Current estimates suggest there are 6000 undocumented ESRD patients in the US that may be ineligible for scheduled hemodialysis. To meet emergency Medicaid requirements, hospitals have sought creative ways to treat undocumented patients. We present data from an undocumented cohort as it progressed through a succession of three periods with different discharge criteria.

Methods: This is a retrospective evaluation of a prospective cohort of 20 undocumented ESRD patients. The patients were followed over 3 consecutive periods (P1, P2, P3) each of 2 months duration. In P1, patients received weekly dialysis. In P2, patients were dialyzed based on strict emergent InterQual® Criteria. In P3, emergent criteria included long interdialytic interval as an additional justification. Adverse outcomes, utilization, and dialysis adequacy in P2 and P3 were compared to P1.

Results: The mean age of the cohort was 35.9y, 39% were female, 45% were employed, and none were US citizens. Emergent dialysis (P2&P3) was associated with increased blood pressure readings, urine output abnormalities (peak K+, mean BUN and serum bicarbonate) as compared to P1 scheduled dialysis (P < 0.05). Emergent dialysis (P2&P3) was associated with an increase in nights hospitalized and ICU days (Fig 1). Strict adherence to InterQual® Criteria (P2) was
associated with increased adverse events with a composite OR for intubation, bacteremia, NSTI/MI, ICU admit, and death of 48 (5.9-391.2) compared to P1. P2 charge estimates increased from P1 ($357,501 v $202,326 per person per year, P<0.0001).

Fig. 1 – Hospital utilization per patient per month. * = P < 0.05.

Conclusions: Strict adherence to InterQual® Criteria increases adverse events and healthcare cost per patient. We must determine better alternatives to emergent dialysis which minimize cost, while maintaining dignity, safety, and quality of life.

SA-PO794
Factors Associated with Withdrawal of Care (WOC) in Maintenance Dialysis Patients Fahad Saeed, Robert Butler, Jesse D. Schold. Nephrology, Cleveland Clinic.

Background: There is paucity of data on factors leading to WOC in dialysis patients. We studied this question by using the NIS dataset, 2005-2011.

Methods: We studied the following six major primary diagnoses: MI, cardiogenic shock, sepsis, stroke, CPR and coma. Effect of age, sex, race, hospitals' profit status and comorbidities were assessed on WOC status. We studied 836563 dialysis patients' admissions, and WOC occurred in 68152 patients.

Results: Male sex, African American and Latino races, smoking, obesity, psychosis and anemia carried lower odds of WOC. Primary diagnoses of CPR, coma, MI, cardiogenic shock, and sepsis; and co-morbidities such as CHF, dementia, HTN, CA, liver disease, paralysis, chronic lung disease, DM, weight loss were associated with higher odds of WOC. Odds of WOC were increased by approximately 6 % per year of patient age. Teaching hospitals had higher odds while private hospitals carried lower odds of WOC status.

Conclusions: Age, non-profit hospital status, coma, metastatic malignancy and weight loss are the most significant factors associated with WOC among dialysis patients. These prognostic data should be considered while treating such patients.

Odds Ratio Estimates

<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95 % CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs. Female</td>
<td>0.892</td>
<td>0.860-0.926</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Black vs. White</td>
<td>0.494</td>
<td>0.445-0.548</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hispanic vs. White</td>
<td>0.445</td>
<td>0.355-0.557</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Other vs. White</td>
<td>0.582</td>
<td>0.507-0.668</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>0.670</td>
<td>0.564-0.786</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>G-tube</td>
<td>0.785</td>
<td>0.671-0.918</td>
<td>0.0025</td>
</tr>
<tr>
<td>CPR</td>
<td>1.624</td>
<td>1.480-1.884</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gl Bleed</td>
<td>1.225</td>
<td>1.134-1.323</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cardiac shock</td>
<td>2.311</td>
<td>2.002-2.668</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MI</td>
<td>1.365</td>
<td>1.258-1.481</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Coma</td>
<td>4.850</td>
<td>4.025-5.843</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.130</td>
<td>1.964-2.311</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.544</td>
<td>1.419-1.680</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.565</td>
<td>0.498-0.642</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>0.682</td>
<td>0.593-0.784</td>
<td>&lt;.0001</td>
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<tr>
<td>Dementia</td>
<td>1.966</td>
<td>1.736-2.227</td>
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</tr>
<tr>
<td>Alcohol abuse</td>
<td>1.239</td>
<td>1.092-1.406</td>
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<tr>
<td>Anemia</td>
<td>0.874</td>
<td>0.808-0.945</td>
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<tr>
<td>CHF</td>
<td>1.225</td>
<td>1.163-1.291</td>
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<tr>
<td>DM</td>
<td>0.614</td>
<td>0.575-0.656</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>0.673</td>
<td>0.634-0.714</td>
<td>&lt;.0001</td>
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<tr>
<td>Liver disease</td>
<td>1.430</td>
<td>1.279-1.599</td>
<td>&lt;.0001</td>
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<tr>
<td>Metastatic cancer</td>
<td>3.334</td>
<td>2.988-3.719</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.777</td>
<td>0.708-0.851</td>
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<tr>
<td>Paralysis</td>
<td>1.214</td>
<td>1.096-1.346</td>
<td>0.0002</td>
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<tr>
<td>Psychosis</td>
<td>0.863</td>
<td>0.763-0.976</td>
<td>0.0191</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.323</td>
<td>2.095-2.576</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.154</td>
<td>1.819-2.551</td>
<td>&lt;.0001</td>
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<tr>
<td>Teaching hospital status</td>
<td>1.263</td>
<td>1.048-1.522</td>
<td>0.0140</td>
</tr>
</tbody>
</table>

Conclusions: Higher RDW is associated with higher mortality risk in HD patients. It is unclear whether RDW is a risk factor for mortality or an epiphenomenon of underlying biological and metabolic imbalances across RDW categories. Further studies are needed to confirm the findings generated from our study and to determine the mechanisms underlying the RDW-mortality association.

Funding: NIDDK Support

SA-PO795
Red Cell Distribution Width and Mortality in Incident Hemodialysis Patients Tania Vashistha,1 Elani Streja,1 Miklos Zsolt Molnar,2 Connie Rhee,1 Steven M. Brunelli,1 Hamid Moradi,1 Tae Hye Kim,1 Vanessa A. Ravel,1 Melissa Sooseho,1 Csaba P. Kovesdy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2UTHSC, DaVita Clinical Research.

Background: Background: Red cell distribution width (RDW) is a measure of red blood cell size and variability that is often used as an indicator of iron-deficiency anemia. Although RDW has recently been found to be associated with mortality in the general population, few studies have examined this association in hemodialysis (HD) patients.

Methods: We examined the association of RDW with all-cause mortality in a cohort of 109,675 incident HD patients from a large dialysis organization during 2007-2011 using Cox proportional hazards regression with adjustment for case-mix (demographics, comorbidities covariates) and markers of malnutrition and inflammation (MICS). RDW was divided into 5 categories:<14.5, 14.5-<15.5, 15.5-<16.5, 16.5-<17.5, and <17.5 %.

Results: The mean age (mean/SD) of the cohort was 63.1±15 years old and included 44% females, 58% diabetics, and 31% African Americans. Higher baseline RDW was linearly associated with higher all-cause mortality risk in both unadjusted and fully adjusted models.

Conclusions: Higher RDW is associated with higher mortality risk in HD patients. It is unclear whether RDW is a risk factor for mortality or an epiphenomenon of underlying biological and metabolic imbalances across RDW categories. Further studies are needed to confirm the findings generated from our study and to determine the mechanisms underlying the RDW-mortality association.

Funding: NIDDK Support

SA-PO796
Association of Pre-ESRD Hemoglobin with Early Post-ESRD Mortality Among U.S. Veterans: A Transition of Care in CKD Study Melissa Sooseho,1 Connie Rhee,2 Vanessa A. Ravel,1 Elani Streja,1 Jennie Jing,1 Danh V. Nguyen,1 Csaba P. Kovesdy,2 Kamyar Kalantar-Zadeh.1 1UC Irvine; 2UTHSC.

Background: Patients with chronic kidney disease (CKD) are often afflicted with anemia. Previous studies have shown that low hemoglobin (HGB) is associated with pre-dialysis mortality in non-dialysis dependent CKD patients, yet the association of HGB levels in the immediate period preceding dialysis (prelude) and early post-dialysis mortality remains unknown. We hypothesized that lower HGB levels are associated with higher post-transition survival in comparison to higher HGB levels.

Methods: We investigated 18,555 US veterans who initiated dialysis between 10/2007-9/2011 and had at least 1 HGB measurement during the 6 month prelude period before dialysis transition. 6 month prelude HGB was used as a continuous predictor of early post dialysis all-cause mortality occurring in the first 3 months after initiation using restricted cubic spline models and Cox proportional hazard regressions. The models were adjusted for age, gender, race, ethnicity, region and primary cause of ESRD.

Results: The analytic cohort was a mean±SD age of 68.8±11 yrs, among whom 30% were African-American, 7% Hispanic and 30% had diabetes as the cause of ESRD. The 6 month prelude HGB average was 10.9±1.6 g/dL. Prelude HGB exhibited a U-shaped association with 3-month post-ESRD all-cause mortality; patients with a 6 month prelude HGB average between 10-11.5 g/dL had better survival, whereas patients with HGB measurements <9 g/dL or >13 g/dL had higher mortality (Figure).
ESA dose was initially 3-fold greater in ESAhr than control patients and remained 2-fold greater by the end of study.

BMI 26.3 ± 11.6 years, 56% were female, and 63% were black. Median (IQR) ferritin and iron levels were 249 (2-497) ng/mL and 50 (5-78) µg/dL, respectively. Over a mean follow-up of 2.84 years, there were 582 deaths. Among subjects with levels in the highest quartile compared to the lowest quartile, both ferritin and iron were significantly associated with reduced all-cause mortality in adjusted analyses, odds ratio (OR) 0.67 (95% CI, 0.46-0.97) and OR 0.60 (95% CI, 0.42-0.85), respectively.

Conclusions: Hemoglobin during the 6 month prelude period prior to dialysis initiation exhibited a U-shaped association with all-cause mortality in the immediate interval post-dialysis with the best survival when HGB was between 9 and 11 g/dL. These results confirm the findings of earlier clinical trials, and support current therapeutic paradigms for management of pre-ESRD anemia.

Funding: NIDDK Support

SA-PO797

Higher Serum Ferritin Levels Are Associated with Better Survival in the HEMO Study

Background: Ferritin is an important indicator of total body iron stores and has been shown to prevent ox-LDL-induced oxidative injury in endothelial cells. Studies regarding the relationship between serum ferritin levels and all-cause mortality in chronic hemodialysis patients are conflicting. The purpose of this study was to determine the relationship between higher serum ferritin levels and death among participants in the Effect of Dialysis and Membrane Flux in Maintenance Hemodialysis (HEMO) trial.

Methods: We studied the association of serum ferritin and iron levels with all-cause mortality among 1799 subjects from the HEMO trial. Cox regression models adjusted for important confounding variables including demographics, comorbidities, treatment assignment, smoking, and albumin.

Results: Mean age was 58±14 years, 56% were female, and 63% were black. Median (IQR) ferritin and iron levels were 249 (2-497) ng/mL and 50 (5-78) µg/dL, respectively. Over a mean follow-up of 2.84 years, there were 582 deaths. Among subjects with levels in the highest quartile compared to the lowest quartile, both ferritin and iron were significantly associated with reduced all-cause mortality in adjusted analyses, odds ratio (OR) 0.67 (95% CI, 0.46-0.97) and OR 0.60 (95% CI, 0.42-0.85), respectively.

Conclusions: Among subjects participating in the HEMO trial higher serum ferritin and iron levels were associated with reduced mortality. We hypothesize that ferritin may play an important role in protecting the endothelium from oxidative stress-induced damage.

Funding: NIDDK Support, Veterans Administration Support

SA-PO798

Anemia in Chronic Kidney Disease Patients Could Be Linked to Indoxyl Sulfate Levels

Background: Indoxyl sulfate (IS) is a uremic toxin derived from the action of colon bacteria in dietary tryptophan. This toxin is related to many complications for chronic kidney disease (CKD) patients, including anemia. The aim of this study was to verify the relationship between IS plasma levels and anemia in hemodialysis (HD) patients.

Methods: This transversal study included 18 HD patients (50% men, 54.2 ± 11.6 yrs, BMI 26.3 ± 4.7 kg/m², time on dialysis 51 (30-52) months, all patients received the same erythropoietin dose >7700 U/treatment. Patients were categorized as of 1Q2012 and following 2011 changes to the US ESA labels and reimbursement policy.

Results: The mean of hemoglobin was 11.0 ± 1.28 g/dL and hematocrit of 34.2 ± 3.0%. The mean of IS plasma levels was 23.9 (10.3 - 100.9) mg/L and CRP 3.1 (1.3 - 8.6) mg/dL. Multivariate linear regression analysis adjusted for age, sex, time on HD, albumin, BMI, CRP revealed that serum hemoglobin (p = 0.05; p = 0.01) was independently and negatively associated with IS levels.

Conclusions: This study provided evidence that IS seems be associate with anemia in HD patients and therapeutic strategies in the clinical care to reduce uremic toxins levels may be effective to management of anemia in HD patients.

Funding: Government Support - Non-U.S.
Impact of ESAs and Iron on Survival in Hemodialysis Patients: Which Is the Best, Which Is the Worth? Jacques B. Rottembourg,1 Alain Guerin.2 1Dept of Nephrology, Hôpital de la Pitié, Paris, France; 2Hemodialysis Units, Diaverium, Paris, France.

Background: Appropriate anemia management for Hemodialysis (HD) patients (Pts) is still challenging. Intravenous (IV) iron and erythropoiesis-stimulating agents (ESAs) are the main therapies, with conflicting outcomes. In the unit, pts were treated over the last seven years, cumulative doses of ESAs (darbepoetin alfa [DA]), converted in µg per session, and IV iron (iron-sucrose [IS]), converted in mg per session, were exactly constantly reported. Survival depending on the cumulative dose of each product and both products together were calculated using the Kaplan Meier methodology.

Methods: 300 incident HD pts (67% male) mean[SD] age at start 59.16(13.6) years, were treated for 100,430 dialysis sessions [S], receiving all over 1,192,250 g of DA, and 1,794,050 mg of IS. M Hb level was 11.50±0.77 g/dL, M TSAT 37.18(5.3)% and M ferritin 562(322) µg/L. The M DA dose injected was 12.91(9.39) µg per S. The M IS dose injected was 20.91(11.57) mg per S. Expressing the separate doses of DA and IS received by the pts in three categories for each product, we obtained 9 categories of pts, depending on whether they received low, medium, or high doses of ESA and IS per S: M doses were [5.42(6), 10.86(3), 25.14(14)]µg for ESA, [12.54(5), 18.44(3), 32.31(11.9)] mg for IV iron respectively.

Results: Survival was expressed at 1000, 2000, and 3000 days (d): The better survival was obtained in the group of low ESA and low IV iron, the worst was high ESA and high IV iron. Survival is better with low ESA, whatever is the IV iron dose injected. High ESA dose, whatever IV iron dose is injected, seems to be worth.

Conclusions: Because the majority of patients on HD receives ESA and IV iron, rigorously conducted and adequately powered clinical trials studying the cumulative doses of ESA and IV iron, reflective of present-day practice, are greatly needed.

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Incidental Findings on 15 Fluorodeoxyglucose Positron Emission Tomography Along with Low Dose Computerized Tomography (FDG PET CT) Scans Among Clinically Stable Haemodialysis with Erythropoietin Hyporesponsive and/or Non-Responsive Patient Population: A Retrospective Study | Stanley Fan, Neringa Vilimiene, Muhammad M. Yaqoob.1 Kneet, Germany; 2Barts Health Cardiovascular Biological Research Unit, London, United Kingdom; 3Diaverum, Paris, France; 4Hemodialysis Units, Diaverium, Paris, France; 5Univ of Michigan, Ann Arbor, MI; 6Univ of Tokyo, Tokyo, Japan; 7Anemia Working Group of JDOPPS, Japan.

Background: The aim of this study was to identify the factors that contribute to erythropoietin hyporesponsiveness in patients on maintenance hemodialysis (MHD).

Methods: demographic data, hemoglobin, dose of erythropoietin, biochemical indicators and other related indicators of 80 MHD patients were collected and reanalyzed retrospectively. They were followed up for 12 months. Erythropoietin resistance index (ERI) was used to evaluate the response to erythropoietin in patients in MHD. The ERI was calculated by dividing the weekly weight-adjusted (kg) dose of ESA (IU) by the hemoglobin level (g/dL). Logistic regression study was used to determine the key variables which might be independently associated with erythropoietin hyporesponsiveness in MHD patients.

Results: Mean erythropoietin resistance index (ERI) for the entire study population was 16.1±7.9 µg/kg/dl. 26% patients were erythropoietin hyporesponsive. Patients were divided into two groups according to ERI: ERI<25 µg/kg/dl and ERI>25 µg/kg/dl. In ERI<25 µg/kg/dl cases, the proportion of female gender was higher, hemoglobin and 25(OH)D were significantly lower than that of patients with ERI<25 µg/kg/dl. In addition, comparing with ERI<25 µg/kg/dl patients, body mass index(BMI) and serum cholesterol were slightly lower in ERI>25 µg/kg/dl (p=0.05). Logistic regression study adjusted gender, dialysis periods, BMI, Kt/v, serum cholesterol, serum albumin, and alkaline phosphatase, indicating an independent association between 25(OH)D deficiency and the erythropoietin hyporesponsiveness(HR:4.590, 95%CI:1.277~16.503).

Conclusions: Erythropoietin hyporesponsiveness is prevalent among MHD patients. Female gender and malnutrition are associated with erythropoietin hyporesponsiveness. 25(OH)D deficiency is the main risk factor for erythropoietin hyporesponsiveness. Improving 25(OH)D deficiency and malnutrition may increase the response to erythropoietin treatment in MHD patients.
Hepcidin is a key regulator of iron metabolism and alterations in Hepcidin concentrations in Incident subjects were higher (191 ± 61) vs. Males (n=151, 140 ± 62) and in Females (n=93, 169 ± 69) vs. Males (n=151, 159 ± 71). There were no difference in age, ferritin, and PTH between male and female patients(P=0.05). The mean dosage of erythropoietin was higher in female than in male patients(14934 ± 6927U vs. 13353 ± 7554U,P=0.05). Patients were divided into 3 groups according to the tertiles of ERI and no difference was found in PTH, ferritin, and iron levels among these three groups.

Conclusions: Female hemodialysis patients are associated with higher degree of erythropoietin hyperresponsiveness. Special attention must be paid to them when treatment is made to treat anemia.

SA-PO808
Oral Vitamin C Supplementation Reduces Erythropoietin Requirement in Hemodialysis Patients with Functional Iron Deficiency

Tanjim Sultana, Maria V. DeVita, Michael F. Michelles. Medicine, Lenox Hill Hospital, New York, NY.

Background: Functional iron deficiency (FID) is a major cause of erythropoietin (Epo) hyperresponsiveness and persistent anemia in dialysis patients. Vitamin C acts as a reducing agent and enhances mobilization of the ferrous form of iron to transferrin thus increasing its bioavailability. High dose intravenous vitamin C has been shown to decrease the Epo requirement and improve hemoglobin levels in previous studies. This route has its downside regarding difficulty of use, higher cost and associations with increased oxalate levels and inflammatory markers. Use of oral vitamin C has been limited due to the concerns of low bioavailability and patients compliance to medication. This study assessed the effect of low dose oral vitamin C on Epo dose requirements in stable hemodialysis patients with functional iron deficiency.

Methods: This prospective study included 22 stable hemodialysis patients with functional iron deficiency defined as transferrin saturation (Tsat) <30 % and ferritin levels of >100 mcg/L with Epo requirement of ≥ 4000 u/HD. Patients received oral vitamin C 250 mg daily for three months. Epo dose was adjusted according to unit protocol depending on the hemoglobin level. Hemoglobin, iron and Tsat levels were recorded monthly. None of these participants received iron or renal vitamin supplementation during the study period.

Results: The mean Epo dose was reduced in fifteen patients by 867±1356U/HD (p=0.03). In seven responders there was 33 % reduction in Epo dose from their baseline line. No ill effects of oral vitamin C were observed. Despite adjustment of Epo dose, hemoglobin level was significantly increased from 10.1±0.6 mg/dl to 10.7±0.6 mg/dl (p=0.03). There were no significant change in Tsat and ferritin levels.

Conclusions: Daily low dose oral vitamin C supplementation reduced Epo dose requirements in hemodialysis patients with functional iron deficiency. Despite concerns regarding oral vitamin C absorption in dialysis patients this study indicates Vitamin C is well tolerated and effective.
Table 1. TSAT=30% is referent.

<table>
<thead>
<tr>
<th>TSAT, %</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50</td>
<td>0.56</td>
<td>0.37-0.86</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0.9</td>
<td>0.46-1.75</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 2. Ferritin < 500 ng/ml is referent.

<table>
<thead>
<tr>
<th>Ferritin, ng/ml</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1000</td>
<td>0.8</td>
<td>0.52-1.23</td>
<td>0.3</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>0.85</td>
<td>0.47-1.55</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Conclusions: TSAT 30-50% appears to be protective vs <30%. No TSAT upper limit was evident. There were no SAEs at ferritin. Fe stores across the range studied did not risk at levels, and TSAT associated with ‘risk of ID, CV and GI SAEs.


SA-PO811

Paricalcitol, Klotho and Renal Anemia in Hemodialysis Patients

Miguel Uriol Rivera,1 Sheila Cabello Pelegrín,2 Gonzalo Gómez Marqués,3 Manuel Luque-Ramírez,2 1Nephrology, Son Espases Univ Hospital, Palma de Mallorca, Islas Baleares, Spain; 2Endocrinology, Ramón y Cajal Univ Hospital, Madrid, Spain.

Background: Low Klotho levels, a protein linked to aging, is associated with an increase in the erythropoiesis process (programmed red-cell death). Chronic Kidney Disease is considered as a state of Klotho deficiency. We evaluate the association between plasma sKlotho levels with iron and hematologic parameters, and the influence of paricalcitol on these variables.

Methods: Data were obtained from the MIR-EPO study (EudraCT: 2009-015511-40). Chronic hemodialysis patients were stratified as a function of paricalcitol use (Group A) or not (Group B). Erythropoietin-stimulating agents (ESA) and iron supplementation were administered in order to maintain hemoglobin (HB) between 10.5 and 12.0 g/dl and transferrin saturation (TSAT) ≥ 20%. After a 3-month titration period, sKlotho was measured (month 3 and 6 of follow-up) by ELISA. The changes in sKlotho from month 3 to month 6 (Δ) and their associations with iron metabolism and hematologic parameters as a function of paricalcitol use were assessed.

Results: A total of 31 patients were evaluated (Group A: 23; Group B: 8). Intact parathyroid hormone (iPTH) levels and ESA doses did not change during the study. Mean sKlotho levels decreased at month 6 compared to month 3 in the whole group of patients (527 vs 474 pg/ml, P = 0.001). After adjustment for iPTH and globular sedimentation rate, mean sKlotho levels in the Group A were higher than those observed in the Group B throughout the study (537 versus 401 pg/ml, P = 0.005). A sKlotho correlated with Δ serum iron (r: 0.42, P = 0.020) in the Group A of patients. A cubic regression model showed that Δ sKlotho increased with adjustment for iron supplementation (r: -0.47, P = 0.030) in the Group A of patients. Across all patients in the Group B, a direct correlation was observed for Δ sKlotho and Δ red blood cell count was found (r: 0.73, P = 0.030).

Conclusions: Soluble Klotho is associated with iron metabolism in hemodialysis patients. Higher soluble Klotho levels may be a novel beneficial effect of paricalcitol use on renal anaemia.

Funding: Private Foundation Support
and ΔHb(β=-0.49, P=0.010) was found in the whole group of patients. Interestingly, mean hepcidin levels were higher in Group A than in Group B(992 vs 494 pg/mL, P=0.050) during the study. In the Group A, ΔHepcidin correlated with ΔHb(β=-0.55, P=0.030).

Conclusions: IL-6 and hepcidin are likely related to different iron pools (functional and storage, respectively) since no correlations between their changes were found. Paricalcitol therapy showed an unexpected increase in iron availability for erythropoesis that might be associated with changes in IL-6 and hepcidin levels.

Funding: Private Foundation Support

SA-PO813

48 Week Open Label Safety Extension Study with Ferric Citrate Demonstrates Favorable Safety Profile in Subjects Not on Intravenous Iron: A Post-Hoc Analysis


Background: Ferric citrate (FC) is an iron-based phosphate binder approved for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis. The Phase 3 pivotal trial in subjects with ESRD demonstrated FC to effectively control serum phosphorus but also significantly increased serum iron parameters. This 48-week open label extension study to the Phase 3 pivotal trial was conducted to demonstrate long-term safety of ferric citrate. The primary data have been reported previously.

Methods: Subjects from the pivotal FC RCT (NCT01191255) who completed the active control period and, if eligible, the placebo control period were eligible to enroll in the safety extension trial. 79% had a time lag between participation in the RCT and this trial. The primary outcome was safety as assessed by lab data and adverse events (AE): 168 subjects enrolled. 166 received a dose of FC. The data presented are a post-hoc analysis of 98 of the 166 subjects that did not receive IV iron for the duration of the 48-week trial. Safety data regarding changes in serum iron parameters and treatment emergent AEs by system organ class are presented.

Results: Of the 98 subjects included in this analysis, 71 subjects were randomized to FC in the previous Phase 3 trial and 27 to the AC group. Table below shows the changes in TSAT and serum ferritin over the 48 wk period. Data presented as mean (SD).

<table>
<thead>
<tr>
<th>Time (wk)</th>
<th>TSAT (%)</th>
<th>Serum ferritin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34.5 (14.1)</td>
<td>772 (378)</td>
</tr>
<tr>
<td>12</td>
<td>37.9 (16)</td>
<td>891 (458)</td>
</tr>
<tr>
<td>24</td>
<td>38.1 (15.9)</td>
<td>904 (450)</td>
</tr>
<tr>
<td>36</td>
<td>41.7 (19.1)</td>
<td>961 (517)</td>
</tr>
<tr>
<td>48</td>
<td>40.9 (19)</td>
<td>872 (417)</td>
</tr>
</tbody>
</table>

83% of subjects experienced at least one treatment emergent adverse event with the most common being gastrointestinal disorders (40%) and infections and infestations (37%).

Conclusions: Subjects receiving ferric citrate and no IV iron demonstrated serum phosphorus control over the 48 wk study period, and an increase in TSAT and serum ferritin. The increase in TSAT did not exceed 45% in subjects receiving ferric citrate and no IV iron, which might suggest that ferric citrate is absorbed but the risk of excessive iron absorption is low.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

SA-PO814

Iron Isomaltoside: A Novel Intravenous Iron Preparation for Hemodialysis

David Jackson, Christopher Brown, Grant Sugiuira, Rachel S. Ashcroft, Ashraf I. Mikhail. Nephrology, ABM Univ Health Board, United Kingdom.

Background: Diafer® (iron isomaltoside) is newly licensed in Europe for iron deficiency anaemia in CKD patients on dialysis. It is thought the controlled-release matrix minimises free iron, possibly reducing side effects. Little is known about the efficacy & safety of Diafer in clinical practice. This study aims to assess the impact of this novel formulation on anaemia parameters in prevalent hemodialysis (HD) patients previously maintained on iron sucrose.

Methods: Data was collected for 13 months; 6 month pre-switch (iron sucrose), 1 month crossover, & 6 month post-switch (iron isomaltoside). All patients received dialysis for ≥ 3 months before evaluation, excluding potential bias of iron loading doses. For both preparations, patients received intradialytic bolus doses of 100mg at frequencies dependant on individual requirements as per current practice.

Results: The percentage of patients maintaining Hb target (100-120g/L) was 71% with iron sucrose & 70% with iron isomaltoside. No adverse drug reactions were observed. No metallic tastes were reported with Diafer administration. The CRP rise during months 1-6 was imparted by 2 infections & 1 amputation.

Conclusions: Iron isomaltoside maintains Hb stability & adequate iron status in HD patients when incorporated into current practice. While these data suggest Diafer may reduce ESA & iron requirements, further analyses are necessary to validate these findings. Whether the potential to reduce labile iron with iron isomaltoside impacts on clinical outcomes is yet to be determined.

Funding: Government Support - Non-U.S.

SA-PO815

Low Iron Availability May Influence on Second Patency Rates of Vascular Access in Patients on Hemodialysis

Yukiko Hasuake, Wataru Fukao, Takeshi Nakanishi. Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.

Background: Vascular access (VA) is essential for the patients on HD. However, VA failure is often occurred even after percutaneous-transluminal angioplasty (PTA). Iron is important for normal vascular physiology, and insufficient iron availability can lead to various vascular dysfunction. The purpose of this study was to examine the factors affecting VA patency after PTA, including iron availability and oxidative stress.

Methods: Blood samples were taken from 281 HD patients at the PTA. Routine blood chemistries and factors related to iron metabolism (transferrin saturation rate (TST), ferritin), oxidative stress (advanced oxidation protein products (AOPP), 8OHdG, GSH/GSSG), and inflammation (high-sensitive CRP, interleukin-6, tumor necrosis factor-a, pentraxin-3) were measured. The end point of study was the re-vascularization or re-operation of VA during the observational period after PTA. Cox proportional hazards models for the end point was used.

Results: 133 patients (47.3%) had native arteriovenous fistula. During follow-up period, re-vascularization was performed in 34 patients and re-operation in 31 patients. The patients with VA failure had higher numbers of leukocytes and platelet, significantly lower TST, and a tendency of higher AOPP compared with the patients without VA failure. There was no significant difference in other factors between the patients with and without VA failure. The Kaplan-Meier analysis showed lower TST (≤20%) was associated with VA failure (p=0.0010, (figure 1)).
PTA. Low Iron availability might affect the second patency rates of VA.

**SA-PO816**

**Triferic Has a Safety Profile Similar to Placebo: An Integrated Safety Analysis of Phase 2 and 3 Studies**

**Authors:** Vivian H. Ling, Raymond D. Pratt, Carrie D. Guss, Ajay Gupta.

**Methods:** The Triferic clinical program included 3 large placebo-controlled efficacy studies lasting 36 to 48 weeks (Controlled Studies), one large placebo-controlled short-term safety study, 3 open-label (OL) safety studies of up to 48 weeks, and 3 small controlled early Phase 2 studies. Patients randomized to Triferic in the 2 pivotal controlled studies who completed the randomized treatment and transitioned to the OL study received Triferic for up to 72 weeks.

**Results:** Exposure-adjusted most frequent adverse event rates (AE) are presented in the table below.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Controlled Studies</th>
<th>Placebo</th>
<th>All Triferic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events/100 Patient-Years of Exposure</strong></td>
<td>Triferic</td>
<td>Placebo</td>
<td>All Triferic</td>
</tr>
<tr>
<td>Procedural hypotension</td>
<td>291.5</td>
<td>290.6</td>
<td>226.6</td>
</tr>
<tr>
<td>AVF Site Complication</td>
<td>35.3</td>
<td>39.1</td>
<td>39.7</td>
</tr>
<tr>
<td>Headache</td>
<td>34.6</td>
<td>21.1</td>
<td>33.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>29.6</td>
<td>34.8</td>
<td>36.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28.3</td>
<td>20.5</td>
<td>28.0</td>
</tr>
<tr>
<td>HD-induced Symptom</td>
<td>27.7</td>
<td>25.5</td>
<td>68.1</td>
</tr>
<tr>
<td>Cough</td>
<td>26.4</td>
<td>18.0</td>
<td>17.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25.8</td>
<td>31.1</td>
<td>33.0</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>22.7</td>
<td>26.7</td>
<td>19.6</td>
</tr>
</tbody>
</table>

**Conclusions:** Triferic was well tolerated in long-term controlled and OL studies. Triferic, administered at each treatment, maintained Hgb and iron balance compared to placebo. The safety profile in short and long-term studies supports a favorable benefit-risk profile for use as a maintenance iron therapy for CKD-HD patients.

**Funding:** Pharmaceutical Company Support - Rockwell Medical Inc.

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**SA-PO817**

**Structural, Physical and Functional Characterization of Ferric Pyrophosphate Citrate (FPC, Triferic), A Novel Iron Compound for Pharmaceutical Applications**

**Authors:** Ajay Gupta,1 Garry J. Handelman,2 Raymond D. Pratt,1 1R&D, Rockwell Medical Inc., Wixom, MI; 2Univ Massachusetts, Lowell, MA.

**Background:** Ferric pyrophosphate citrate (FPC) is the first iron compound approved for parenteral administration that is not an iron-carbohydrate complex. FPC has a molecular mass of about 1313 Da, and high solubility of FPC in aqueous solutions allows its administration via the dialysate.

**Methods:** FPC is a complex iron salt in which Fe³⁺ is bound to pyrophosphate (PPi) and citrate by coordinate covalent bonds. Extended X-ray absorption fine structure (EXAFS) spectroscopy showed that the Fe in FPC is in the ferric (Fe³⁺) state and does not complex with sulfate. EXAFS analysis demonstrated that Fe forms a stable complex with 6 O atoms at 2.02 Å in the first coordination sphere and with 2 P and 4 C atoms at 3.22 Å and 2.98 Å, respectively, in the second coordination sphere. FPC demonstrates stability in both the solid and solution forms.

**Results:** The uptake rate of FPC iron by human apo-transferrin was measured in vitro by monitoring absorbance at 411 nm. At an identical set of conditions we observed 75% TF saturation in n=10, 15, and >9 x 10^8 sec for Fe(TNA), FPC and Fe(citrate), respectively. We conclude that TF loading from FPC is rapid and of similar magnitude to that from ferric nitrooacetic acid, but over four orders of magnitude faster than from ferric citrate. The observed rapid binding kinetics allows for facile Fe³⁺ uptake by transferrin for transport to the bone marrow for hemoglobin synthesis. Pharmacokinetic studies of FPC administered IV to healthy volunteers demonstrate dose-proportional kinetics with a t½ of approximately 1.4 hours. No non-transferrin bound iron has been detected at TSAT levels of up to 100%.

**Conclusions:** FPC is a novel iron compound that is ideally suited as a maintenance treatment for CKD 5HD patients. FPC replaces ongoing iron losses and maintains hemoglobin levels. The small doses of iron and the lack of a carbohydrate shell contribute to the favorable safety profile. FPC represents a new paradigm for rational iron replacement in patients on chronic hemodialysis.

**Funding:** Pharmaceutical Company Support - Rockwell Medical Inc.

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**SA-PO818**

**Proton Pump Inhibitors and CYP2C19 Are Associated with Iron-Deficiency Anemia in Hemodialysis Patients: A Cross-Sectional Study**

**Authors:** Akiko Nakashima,1 Ichiro Ohkido,1 Keitaro Yokoyama,1 Mitsuyoshi Urashima,1 Takashi Yokoy,1 1Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan; 2Div of Molecular Epidemiology, Jikei Univ School of Medicine, Tokyo, Japan.

**Background:** Hyporesponsiveness to erythropoietin stimulating agents (ESA) is an important phenomenon in dialysis patients. As chronic proton pump inhibitor (PPI) use reduces gastric acid secretion, it seems possible that chronic PPI use might lead to iron malabsorption and anemia. In addition, PPI is mainly metabolized by cytochrome P₄₅₀ (CYP) enzymes, particularly CYP2C19, in the liver. The genotypes of CYP2C19 affect the pharmacokinetics and pharmacodynamics of PPI. However, there is no study investigating the relationship between PPI use and anemia status that includes the effect of CYP2C19 genotype in hemodialysis patients.

**Methods:** This cross-sectional cohort study analyzed 1530 hemodialysis patients. DNA was isolated from leukocytes in peripheral blood. We used polymerase chain reactions and direct sequencing to analyze CYP2C19 genotypes. We analyzed anemia status with and without PPI usage, including the association with CYP2C19 genotypes.

**Results:** PPI use was associated with a significantly lower mean serum hemoglobin concentration. Iron and TSAT were also lower in PPI users. ESA dosage was significantly higher in patients receiving PPIs(mean [SD] PPI: 5685 [3288] IU/week; non-PPI: 2899 [2734] IU/week; P<0.001), and multiple regression analysis indicated a significant relationship between PPI use and ESA dosage(β: 494.1 [2734] IU/week; P=0.036). CYP2C19 genotypes were significantly associated with iron status and anemia. Multiple regression analysis demonstrated that CYP2C19 poor metabolizer (PM) type was significantly associated with ESA dosage in PPI users (β: 901.1 P<0.001).

**Conclusions:** In this study, we found that PPI use is associated with iron status and anemia in hemodialysis patients. Among the dialysis patients receiving PPIs, CYP2C19 genotype was associated with hemoglobin levels, ESA dosage, and iron status.

**Funding:** Pharmaceutical Company Support - Rockwell Medical Inc.

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**SA-PO819**

A 4-Week Dose Response Study of the Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 in Japanese Anemic Hemodialysis Subjects

**Authors:** Yukihiro Endo,1 Tomoko Kohno,1 Yukiko Imai,1 Natsumi Kawase,1 Katsutoshi Hara,2 John J. Lepore,3 Alexander Ralph Cobitz,4 1Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan; 2GlaxoSmithKline, Tokyo, Japan; 3GlaxoSmithKline, King of Prussia, PA.

**Background:** Hypoxia inducible factor (HIF)‐prolyl hydroxylase inhibitors, such as GSK1278863, are an emerging class of oral agents for treatment of anemia associated with chronic kidney disease (CKD). Dose response of GSK1278863 for anemia correction in Japanese hemodialysis-dependent (HDD) subjects is reported.

**Method:** We evaluated the relationship between GSK1278863 dose and hemoglobin (Hgb) response in Japanese HDD subjects with anemia of CKD in a 4-week, randomized, double-blind, placebo-controlled study (funded by GlaxoSmithKline). Subjects on thrice weekly hemodialysis for at least 8 weeks and with Hgb of 8.5–10.5 g/dl after stopping their

**Funding:** Pharmaceutical Company Support - Rockwell Medical Inc.

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

Underline represents presenting author.

818A
Controlled Trials of Chronic Kidney Disease (CKD): A Meta-Analysis of Randomized Continuous Erythropoiesis Receptor Activator (CERA) for the Anemia of Kidney Disease

SA-PO820

Background: Treatment of renal anemia in hemodialysis (HD) patients requires an adequate ESA dosage to maintain stable Hb levels. Guidelines in Japan recommend determining the ESA dosage based on Hb levels measured twice a month. An algorithm for the administration of continuous erythropoietin receptor activator (CERA) has been prepared and implemented to treat patients on HD. The 2-year study results were previously reported during the ASN Kidney Week 2014 (TH-PO 820).

Methods: Based on the algorithm, CERA was administered for 1 year to 102 HD patients being treated with rHuEPO. After the 1st year, the algorithm was reviewed, and some cases of fluctuating Hb levels because of terminating and restarting CERA administration were found. Therefore, the algorithm was revised. Consequently, CERA administration was continued for another 2 years. The target Hb level was 10.5-11.0 g/dL, and Hb levels, CERA dosages, and iron dosages were investigated. CERA was administered once every 2 weeks, and the dosages were changed within a range of 25 mg/dose based on Hb levels. The standard iron dosage was not changed during the evaluation period.

Results: Hb levels at the baseline and 1, 2, and 3 years after the baseline measurement were 10.9 and 11.1, 11.2, and 11.2 g/dL, respectively. The corresponding CERA dosages administered every 2 weeks, were 62 ± 16, 38 ± 25, 36 ± 23, and 33 ± 21 mg, respectively, and ERI values were 0.11 ± 0.04, 0.06 ± 0.05, 0.06 ± 0.04, and 0.06 ± 0.04, respectively. To reduce fluctuations in Hb levels to a possible extent, terminating CERA administration was avoided. Serum ferritin levels gradually decreased from 147 ± 92 to 122 at the baseline to 112 ± 95, 88 ± 67, and 67 ± 47 ng/ml in the 1st, 2nd and 3rd years, respectively, and weekly iron dosage decreased from 13±1.5 at the baseline to 11 ± 2.6 and 11 ± 2.4 mg in the 2nd and 3rd years, respectively.

Conclusions: Three years of twice-monthly CERA administration, based on the algorithm, could maintain stable Hb levels, improve ERI, and reduce iron dosage. Twice-monthly CERA administration based on the algorithm effectively controlled anemia in HD patients.

SA-PO821
Continuous Erythropoiesis Receptor Activator (CERA) for the Anemia of Chronic Kidney Disease (CKD): A Meta-Analysis of Randomized Controlled Trials Valeria M. Saglimbene, Suetoniu Palmer, Giovanni F.M. Strippoli, D’Aiutamento Medical Scientific Office, Univ of Otahgicho, Choranche Kidney and Transplant.

Background: Targeting high hemoglobin levels with erythropoiesis-stimulating agents (ESA) leads to adverse effects in people with chronic kidney disease (CKD). Whether there are treatment differences between different ESA agents is uncertain.

Methods: We did a systematic review of randomized controlled trials evaluating treatment effects of CERA compared with other epoetins (darbepoeitin alpha and epoetin alpha or beta) or placebo/no treatment, in people with any stage of CKD. We systematically searched Cochrane databases. Results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference and 95% CI for continuous outcomes using random-effects meta-analysis.

Results: 17 studies involving 5397 participants were eligible. Studies compared CERA with epoetin (n=8 studies), darbepoeitin (n=5), differing frequency (n=2) and dose (n=4). Compared to epoetin and darbepoeitin CERA had similar effects on mortality, hypertension, need for blood transfusion and iron therapy.

Conclusions: This study demonstrated that CERA 1.00 (0.73-1.65) at the baseline to 112 ± 95, 88 ± 67, and 67 ± 47 ng/ml in the 1st, 2nd and 3rd years, respectively, and weekly iron dosage decreased from 13±1.5 at the baseline to 11 ± 2.6 and 11 ± 2.4 mg in the 2nd and 3rd years, respectively.

Conclusions: The factors that influence the risk of CVD death included smoking, history of ischemic heart disease and hypercalcemia. The risk factors occurring heart failure included history of IHD, and it was shown that the effects of smoking and history of IHD on prognosis were stronger than the effects of anemia. The evaluation of changes in Hb over time revealed that the low Hb sustained for a long time would increase the risk. In addition, the risk of death was high in the high-dose rHuEPO group suggesting the risk in the low HbEPO response patients.

SA-PO823
Anemia Management in ESRD Patients Admitted to the Hospital Priyanka Govindan, Arjun V. Sharma, Dept of Nephrology, Univ of Washington Medical Center, Seattle, WA.

Background: Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. Anemia can be managed successfully with appropriate investigations and therapy in the ESRD population. The aim of the study was to see how appropriate the management of anemia was in our hospital in patients on dialysis and to identify areas for improvement.

Methods: Selected patients were those with ESRD on hemodialysis and peritoneal dialysis who underwent in-hospital dialysis at the University of Washington Medical Center from July 1st 2014 to Sep 30th 2014. The patients who had been undergoing dialysis for less than 12 weeks were considered to have AKI and were excluded from the analysis. In addition, the patients who underwent dialysis only in the Intensive Care units were excluded. The data was collected from the electronic medical records of the individual patient charts. Gender, Age, Anemia status, Lowest Hemoglobin, Iron panel, Reticulocyte count were noted in addition to treatment with iron, blood transfusions and ESA.

Results: A total 145 dialysis patients were identified and 65 of them had both ESRD and anemia. 73.86% of these patients were found to be anemic by KDIGO. Patients in the 66-69 age range had the largest number of anemia with a total of 20 falling in this category. 18 patients had a Hb of <6 mg/dl and anemia was not treated with TH-PO 820.

Conclusions: Routine investigations for the management of anemia are being missed regularly. Worse anemia was associated with fewer investigations. We suspect that the management of anemia in patients with ESRD can be improved with more comprehensive labs and therapy. We intend to follow up with an intervention involving the EMR making it easier to work up anemia in the hospital.
SA-PO824

Variability in Hemoglobin (Hb) Levels in Hemodialysis (HD) Patients in the Current Era

**David T. Gilbertson**, 1 **Yan Hu**, 1 **Yi Peng**, 1 **Sarb Shergill**, 2 **Bradley J. Maroni.** 1

1CDRC/MMRF, 2Akebia Therapeutics, Inc.

**Background:** Hb variability in dialysis patients has been characterized using a number of methods. The majority of this work occurred prior to the 2011 change in CMS reimbursement policy and ESA labels. We therefore examined Hb variability and patient demographics from current data and compared the results to those obtained prior to implementation of these policy changes.

**Methods:** We used CMS ERD data to define a cohort of chronic HD patients who were alive from Apr 1 through Dec 31, 2012. Using a method from Ebben et al. (ClinJASN 1:1205-1210, 2006), monthly Hb values were categorized as low (L), intermediate (I), and high (H), where L and H were based on monthly Hb values below or above the 25th and 75th percentiles, respectively. Variability was then classified based on the Hb categories during a 6-month period, resulting in 6 categories of variability (see figure legend).

**Results:** The figure compares the percentage (%) of patients in each Hb variability group in 2004 compared to 2012. The 25th and 75th percentiles in the 2012 data were 10.2 and 11.5. Corresponding 2004 values were 11 and 12.5. Similar % of patients were observed in 2004 and 2012 for the LL and IH categories. A higher % of patients was consistently intermediate (I) in 2012 than 2004 (9.5% vs. 6.0%), whereas a larger % was observed for LI and a smaller % for LH. Compared to the overall 2012 cohort, II patients were older (mean=65.2), and LL or LH patients were younger (mean=58.2 and 57.8). LH had the highest % who were black (48.8%).

**Conclusions:** While Hb levels have decreased during the last few years, Hb variability is still present. The lower % of patients in the LH group is consistent with a narrowing of the overall Hb distribution. Further studies are needed to assess the association of variability with outcomes in the current era.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

SA-PO825

Prevalence and Predictors of Naturally Occurring Normal Hemoglobin Concentration in Hemodialysis Patients

**Zakaria Abdulnabi, Veeda O. Landers, Shalini Bumb, Abdulah Alrifai, Jay B. Wish, Peter B. DeOreo, Thomas H. Hostetter, Mirela A. Dobre.**

**Case Western Reserve Univ, Cleveland, OH.**

**Background:** Epidemiological data and clinical observations suggest that erythropoietin producing cells exist even in ESRD kidneys. A small subset of ESRD patients have naturally occurring normal hemoglobin levels, without the use of blood transfusions or erythropoetin stimulating agents (ESA), but limited data exists in this field. The aim of this study was to evaluate the prevalence and predictors of naturally occurring hemoglobin concentration ≥ 12 mg/dL in hemodialysis patients.

**Methods:** This analysis is a retrospective chart review of ESRD patients receiving hemodialysis at Centers for Dialysis Care in East Cleveland, OH, from April-September 2013. Data collected included demographics, cause of renal disease, comorbidities, duration of ESRD, dialysis access, indices of dialysis adequacy, systolic blood pressure, hemoglobin level, PTH, albumin, calcium, phosphorus. Multivariable regression models were used to identify independent associations with the outcome of interest.

**Results:** In this cohort of 449 community dialysis patients, the prevalence of naturally occurring hemoglobin level ≥12 mg/dL, without the use of ESA, was 5.3%, slightly higher than previous reports of around 2%. In unadjusted analyses, compared to ESRD patients with a hemoglobin level >10 mg/dL, maintained with the use of ESA, the patients with naturally occurring hemoglobin level ≥12 mg/dL were more likely to be younger, male, with an arteriovenous fistula, longer dialysis vintage, lower systolic blood pressure and higher serum albumin level. In adjusted analyses, male sex, serum albumin and systolic blood pressure were the strongest predictors of naturally occurring higher hemoglobin concentration. Further studies to evaluate the mechanisms underlying these associations, including factors stimulating sites of extrarenal erythropoiesis are warranted.

**Funding:** NIDDK Support

SA-PO826

Estimation of Pre-Dialysis Hemoglobin Concentration Using the Crit-Line®

**Monitor Stephanie Thijssen, Hanjie Zhang, Doris H. Fuertinger, Peter Kotanko.**

**Renal Research Inst, New York, NY.**

**Background:** Pre-dialysis laboratory measurements of hemoglobin (Hb) are generally used for anemia management. In some clinics, bi-weekly or even weekly Hb measurements are performed for this purpose. The Crit-Line® Monitor (CLM) provides Hb non-invasively and continuously during hemodialysis (HD), but initial readings early during HD are systematically lower than pre-HD laboratory values due to hemodilution caused by the priming fluid. We present a method of correcting CLM Hb for hemodilution.

**Methods:** Pre-HD reference Hb (Hb_Comp) was measured by Spectra East Laboratories. Hb obtained by CLM (Hb_CLM) was averaged between minutes 4 and 6 after start of the HD treatment. The difference between the two (Hb_Comp - Hb_CLM) was estimated as ΔHb = (V_sal * 0.5 * (t_CLM/1.2 _sal) - V_CLM) * Hb_CLM/BV, with V_sal = amount of priming fluid (saline) infused at start of HD, t_clm = time point of Hb_CLM measurement (5 min into HD), t_1/2_sal = plasma half life of infused saline (20 min, adapted from ATC Consensus Statement, 2004). V_CLM = cumulative ultrafiltration volume up until t_clm, and BV = pre-HD blood volume (obtained by estimating post-HD BV via Nadler equation (using post-HD weight, sex, height), then dividing by end-HD relative blood volume and subtracting V_sal). Corrected Hb_CLM was calculated as Hb_corr = Hb_CLM + ΔHb.

**Results:** 5,731 HD treatments from 952 chronic HD patients in the USA were analyzed. Without correction, Hb_CLM was found to be systematically lower than Hb_Comp by on average 0.425 g/dL (SD 0.59 g/dL). After correction for hemodilution, the difference (Hb_corr - Hb_Comp) was reduced to -0.008 g/dL (SD 0.59 g/dL).

**Conclusions:** When applying a correction for the hemodilution caused by infusion of the priming fluid at the start of the HD, Crit-Line® Hb is nearly identical on average to the pre-HD Hb measured by a reference laboratory. More and more clinics are employing Crit-Line® Monitors for fluid and anemia management. Crit-Line® Hb corrected in this way may be used for anemia management, which could reduce blood draws and costs.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO827

Hemodialysis (HD) Patients Who Can Maintain Fair Hb Level (>10g/dl) without Iron or Erythropoietin (Epo) Administration Showed Higher Serum Soluble Transferrin Receptors(sTfR) and Normal Epo, Vitamin C (VC) Levels

**Norioko Saito, 1 Kazuhide Saito, 1 Tetsuo Morioka, 1 Hisaki Shimada, 1 Kozo Ikarashi, 1 Yutaka Tsutaba, 2 Shunsuke Sakai, 2 Shigeru Miyazaki.**

**1Nephrology, Shironaku-en Hospital, Niigata, Japan; 2Urology, Niigata Univ, Niigata, Japan.**

**Background:** HD patients have severe anemia and their Hb levels were recommended to be maintained at greater than 10g/dl using iron and Epo supplementation. Certain HD patients showed Hb levels ≥10g/dl without iron or Epo. We evaluated the predictors of good erythropoiesis and iron metabolism markers in these patients in order to analyze the background mechanism.

**Methods:** 21 HD patients who could maintain Hb level at 10g/dl and greater without iron or Epo for more than 3 months (G1) were enrolled in this study. 23 HD patients with Hb level less than 10g/dl without iron or Epo for more than 2 months (G2) and 30 healthy volunteers (G3) were also enrolled as control. Blood samples were collected before HD and Epo, hepcidin (HPC), sTfR, VC and standard hematological parameters were examined. The data are indicated as median (interquartile range).

**Results:** In G1, ferritin(20(14-36) ng/ml), transferrin saturation(14(8-19)%), HPC(0(0.7-0.2-4.5)mg/ml) were significantly lower than those in both G2 and G3, respectively. The percentage of hypochromic RBCs(%HypoHe)(2.7(1.5-4.8)%) was higher than those of GN and G2. 2. MCV values were not significantly different in all three groups. 3. sTfR level, a marker of erythropoietic activity, of G1(30.0(22.1-36.5)nmol/L) was significantly higher than those of GN and G2. 4. Epo level(7.3(5.1-15.2)mIU/mL), reticulocytes(12(9-15)‰) were significantly different from those of GN, whereas significantly higher than those of G2, respectively. 5. In G1, negative correlation was revealed between VC and %HypoHe(ρ=-0.473, p<0.048), whereas positive correlation between %HypoHe and sTfR(ρ=0.816, p<0.001). By multivariate analysis, %HypoHe was the predictor of sTfR(β=0.834, p<0.001).

**Conclusions:** HD patients with fair Hb level revealed higher sTfR, %HypoHe and normal Epo, MCV, VC and low HPC levels. These results indicated that iron utilization of these patients was upregulated and this may participate in the maintenance of erythropoiesis.

**Funding:** Private Foundation Support

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

Underline represents presenting author.
SA-PO828
Acute Effects of Erythropoietin Administration on Blood Pressure in Dialysis Patients  
Nawf Hamad Al-Gublan, Kristin M. Corapi, Ishir Bhan.  
Nephrology, Massachusetts General Hospital, Boston, MA.

Background: Erythropoiesis-stimulating agent (ESA) doses are often held in patients with end stage renal disease (ESRD) because of hypertension. However, missed doses may exacerbate anemia of chronic disease. The acute effects of ESA on blood pressure are unknown. We hypothesized that ESA administration during dialysis would not be associated with a significant change in blood pressure.

Methods: With institutional review board approval, we retrospectively reviewed the medical records of 100 hemodialysis patients who were admitted to our hospital between 1/2013-4/2015. All patients in this study were prescribed, and received, ESA’s during dialysis. Patients were excluded if dialyzed in the ICU, received vasopressors, were treated for hypertensive urgency (>180/110 mmHg), initiated on hemodialysis, or only underwent ultrafiltration without dialysis. Blood pressure just prior to and 2 hours after ESA were compared using a paired t-test.

Results: The mean age was 61.6 years (±12.8), 42% were male, 66% were Caucasian, 16% African-American, and 10% Asian. Mean change in blood pressures immediately prior to ESA administration and 2 hours after are summarized.

<table>
<thead>
<tr>
<th>Pre-Dialysis</th>
<th>Just Prior to ESA</th>
<th>2 Hours Post ESA</th>
<th>Mean Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>136±25</td>
<td>132±27</td>
<td>-4.5 (1.74)</td>
</tr>
<tr>
<td>DBP</td>
<td>68±11</td>
<td>67±10</td>
<td>-1.2 (0.25)</td>
</tr>
</tbody>
</table>

No statistically significant increase in SBP or DBP was noted. In fact, we observed a significantly lower SBP 2 hours after ESA dosing. In a subgroup analysis of patients with an SBP > 160 immediately prior to ESA administration, an even greater decrease in SBP was noted 2 hours after ESA compared to a subgroup with an SBP < 160 (p=0.004).

Conclusions: We demonstrated a decrease in systolic blood pressure 2 hours after ESA administration with no significant change in diastolic blood pressure. Withholding ESA during dialysis due to hypertension may be unnecessary.

SA-PO829
Serum Ferritin Predicts Mortality Regardless of Inflammatory and Nutritional Status in Incident Peritoneal Dialysis Patients  
Erika Schröder, Tae-Hyun Yoo, Shin-Wook Kang.  
1 Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea; 2 Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Serum ferritin levels have been proposed as a prognostic factor in hemodialysis (HD) patients, due to its close relationship with inflammation and malnutrition. Since iron supplementation methods and factors affecting nutritional status are somewhat different from those of HD patients, the impact of serum ferritin on clinical outcomes was investigated in incident peritoneal dialysis (PD) patients.

Methods: A prospective cohort of 408 PD patients from the Clinical Research Center for End-Stage Renal Disease was selected. Patients were divided into three groups according to tertiles of Ln ferritin concentrations (group 1: ≤4.69 ng/mL, group 2: 4.69-5.58 ng/mL, group 3: ≥5.58 ng/mL). Cox proportional hazard analysis was performed to determine the independent prognostic value of serum ferritin levels for all-cause mortality.

Results: The mean age was 52.1±13.2 years and 236 (57.8%) were male. During a median follow-up of 25 months, 46 (11.3%) patients died. Univariate Cox analysis revealed that the mortality risk was significantly higher in group 2 [hazard ratio (HR)=2.65, 95% confidence interval (CI)=1.11-6.34, P=0.029] and group 3 (HR=3.16, 95% CI=1.33-7.48, P=0.009) compared to group 1. Moreover, multivariate Cox proportional hazard models revealed that Ln ferritin was independently associated with an increased risk of all-cause mortality (per 1 ng/mL increase, HR=1.94, 95% CI=1.31-2.88, P<0.001), even after adjustment for variables representing inflammatory and nutritional status.

Conclusions: Higher serum ferritin level was a significant independent risk factor for all-cause mortality regardless of systemic inflammation and nutritional status. Therefore, determining serum ferritin levels could be a useful marker to predict clinical outcomes in incident PD patients.

SA-PO830
Improving Anemia Therapy in Hemodialysis Patients: Interim Results of a Clinical Audit  
Juan M. Ardavin Ituarte, Antonio Sousa, Erika Schröder, Fundação Renal Portuguesa, Portalegre, Portugal; 1Via Medis, Riesa, Germany; 2Oxylse Ltd, London, United Kingdom.

Background: An earlier pilot audit (ASN 2013, PUB200) suggested that the use of a novel bloodline (Oxylse), which reduces the contact between blood and air, could improve the acute effects of Erythropoiesis Stimulating Agent (ESA) therapy by prolonging red cell survival. The aim of this investigation was to explore this effect in a larger population.

Methods: Patients (n=110; >18 years, HD ≥ 3 months via AV fistulae) were entered into a 6-month open label, single crossover audit following a 3 month Run-In. Patients reverted to control bloodlines (Nikkiso/Gambror) in the Crossover phase after treatment with Oxylse. Hemoglobin (Hb) levels, IV iron sucrose and ESA doses were reported.

Results: Data analysis was conducted on 66 patients from two clinics. Twenty six patients dropped out due to transplantation and intercurrent events, death (n=14) and clinic transfers (n=4). Hb was maintained over the Treatment phase (11.22-11.34 g/dL). Mean ESA doses reduced by 34% (p<0.01) at month 8, equal to 1,909 IU/week/patient. IV iron dose did not change significantly during the audit.

Patients of a shorter dialysis vintage (<4 years, n=35) showed a greater reduction in ESA usage (-42%, p<0.01) compared with those of a longer vintage (>4 years, n=31, -23%). By month 11 (Crossover) ESA doses increased by 9.7 IU/week/kg; 32% of the reduction seen during Treatment.

Conclusions: The reduction in ESA doses observed during Treatment, and the initial reversal in the Crossover, suggest that this novel bloodline can improve anemia therapy in HD patients. The audit design increases the confidence in the data validity. These results could have clinical and financial benefits for HD service delivery.

Funding: Pharmaceutical Company Support - Oxylse Ltd.

SA-PO831
First in Human Feasibility Study Assessing the Tablo Hemodialysis System  
Luis E. Morales-Buenrostro, 1 Jose Antonio Nino-Cruz, 1 Javier Zúñiga-Varga, 1 Juan M. Arduvin Juarte, 2 May L. Yau, 2 Luis Alvarez, 2 1 Dialysis Dept, Neftos Investigacion SC, Mexico City, DF, Mexico; 2 Outset Medical Inc, San Jose, CA; 3 Palo Alto Medical Foundation, Menlo Park, CA.

Background: Self-care, at home or in-center, is a must for patients who want more independence and control, or have geographical or mobility constraints. Widespread adoption of this modality requires an easy to use dialysis machine with real-time water treatment capabilities. We conducted a first in human feasibility study to assess the safety and performance of the Tablo™ Hemodialysis System, that may meet these requirements.

Methods: We enrolled 5 patients receiving hemodialysis 3 times/week, with a well-functioning fistula or high-flow catheter. Primary outcomes of measure were Kt/V and adverse events.

Results: A total of 27 treatments in 5 patients were analyzed. Patients had the following characteristics: 40% female (n=2), mean age of 50 years, weighed 66 kg, height of 160 cm, 40% (n=2) fistula, 60% (n=3) high-flow catheter, average treatment time of 183 minutes, average fluid removal of 0.57 L, 80% (n=4) had an unknown etiology of ESRD, and 20% (n=1) had hypertension. Heparin was administered in 52% of treatments. The average single pool Kt/V was 1.4. One patient had only one treatment and was withdrawn from the study due to commute issues. Subjects were monitored during dialysis treatment by in-center staff, per institutional protocol. Only one interdialytic event, mild headache, was reported. In total, 3 subjects reported cramping (n=6/27 treatments) and 1 had hypotension (n=1/27 treatment). There were no unanticipated adverse events, serious adverse events or deaths in the study.

Conclusions: The Tablo™ Hemodialysis system was safe and showed good performance during treatments with shorter times, minimal fluid removal and heparin utilization. The standards of conventional dialysis were maintained without serious adverse events related to the device. The incorporation of an integrated water treatment module and touchscreen with animated step by step instructions was extremely easy to use. This system will allow self-care access, both in-center and at home, in a larger number of patients.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.
SA-PO832

The Big Red Kidney Bus: Mobile Dialysis Holiday Peter G. Kerr,1 Lesley Ross,1 Jo M. Fairbairn,2 Anne C. Wilson.3 ‘Nephrology, Monash Health, Clayton, Vic, Australia; 2Kidney Health Australia, South Melbourne, Vic, Australia.

Background: The availability of hospital based hemodialysis for those wishing to travel is scarce and often results in restricted opportunities for patients on dialysis to have a holiday. The Kidney Health Australia (KHA) and Monash Health (MH) Big Red Kidney Bus Project (BRKB) offers patients the ability to dialyse on the BRKB whilst on holiday at one of a range of Victorian tourist destinations.

Methods: The aim of the BRKB Project is to provide safe, fully staffed mobile haemodialysis care, to enable people, their families and carers to take a break. KHA owns the bus, manages the bookings and marks the BRKB nationally. MH, a regional health care provider oversees the clinical assessment and treatment and provides medical supervision, dialysis nurses and renal technicians.

The BRKB is a modified bus accommodating 3 hemodialysis machines, dialysis chairs and complete water treatment. Typically, holiday dialysis on the BRKB operates across 2 sessions per day, 6 days per week duplicating the dialysis parameters of the patients’ home unit.

The bus is driven to and parked at caravan parks around Victoria for 6-week periods, during which time patients may book in for dialysis sessions. Their accommodation is up to them to decide on – with the option of using cabins in the parks or local motels (or their own caravans).

Results: Since its inaugural visit in October 2014, 148 different patients have taken advantage of the BRKB. The bus has visited 6 sites around the State and has site bookings for the next 10 months. Participating holiday-makers were overwhelmingly positive about the service. They found the booking system easy to use. The dialysis service on the bus was delivered to the standard of care experienced at their home units. The professionalism of the nursing staff and friendliness was commended and all participants would recommend the service to others. Most had actively recommended the service to others.

Conclusions: The BRKB is a unique project that provides patients with the opportunity to dialyse on the bus while taking a much-needed holiday.

Funding: Private Foundation Support

SA-PO833

Patient and Caregiver Values, Beliefs and Experiences when Considering Home Dialysis as a Treatment Option: A Semi-Structured Interview Study Rachael C. Walker,1 Kirsten Howard,1 Rachael L. Morton,1 Suettania Palmer,2 Mark R. Marshall,1 Allison Tong.3 1Univ of Sydney; 2Univ of Otago; 3Middlemore Hospital, New Zealand; 4Univ of South Australia.

Background: Home dialysis is associated with higher quality of life and economic benefits to health care systems compared with facility dialysis. However, little is known about the decision-making process of patients when considering home dialysis as a treatment option.

Methods: This semi-structured interview study aimed to describe patient and caregiver values, beliefs and experiences when considering home dialysis, to inform policy and practice strategies that align with patient preferences. We conducted semi-structured interviews with adults with CKD Stage 4-5D (on dialysis <1 year) and their caregivers, treated in 3 nephrology centers in New Zealand. Transcripts were analyzed thematically.

Results: 43 patients (18 pre-dialysis, 13 peritoneal dialysis, 4 home hemodialysis and 9 facility hemodialysis) and 9 caregivers participated. We identified 5 themes related to decision-making when considering home dialysis; lacking decisional power (complexity of information, limited exposure to home dialysis, feeling disempowered, deprived of choice, pressure to choose); sustaining relationships (maintaining cultural involvement, family influence, trusting clinicians, minimizing social isolation); reducing lifestyle disruption (sustaining employment, avoiding relocate, considering additional expenses, seeking flexible schedules, creating free time); gaining confidence in choice (guarantee of safety, depending upon professional certainty, reassurance of peers, overcoming fears); and maximizing survival.

Conclusions: Patients feel disempowered when choosing home dialysis and make decisions that sustain their relationships, maintain lifestyle values and maximize survival. Confidence in their modality decision is gained by medical professional and peer support combined with overcoming safety concerns. Pre-dialysis programs that address these patient experiences may support home dialysis as a treatment option.

Funding: Pharmaceutical Company Support - Baxter Clinical Evidence Council research program

SA-PO834

Patient Experiences of Training and Transition to Home Hemodialysis: A Longitudinal Mixed Methods Study Camilla Sara Hansen,1,2 Jeremy R. Chapman,3 Jonathan C. Craig,4 David C. Harris,4 Lukas K. Kairaitis,5 Mary Ann Nicdao,6 Mary Mikhaeel,7 Allison Tong.1,2 ‘School of Public Health, The Univ of Sydney, Sydney, NSW, Australia; 3Centre for Kidney Research, The Children’s Hospital at Westmead, Sydney, NSW, Australia; 4Centre for Transplant and Renal Research, Westmead Hospital, Sydney, NSW, Australia; 5Dept of Renal Medicine, Westmead Hospital, Sydney, NSW, Australia.

Background: Home hemodialysis (HD) can offer better survival and quality of life outcomes compared with in-centre HD. However, psychosocial barriers such as fears of needles and medical isolation may limit home HD uptake. This study aims to describe patients’ perspectives on training and transition to home HD; to inform strategies to optimize home HD programs.

Methods: Three semi-structured interviews were conducted prospectively with 20 patients before, during and after home HD training at an Australian renal unit. The CHOICE satisfaction survey was administered during the first and final interview. Transcripts were analyzed thematically.

Results: We identified six themes: persevering despite trepidations (intimidation of machinery, acquiring to fatal risks, reconciling cunatrations, dispelling concerns of neglect, tolerating concessions); optimizing learning pathway (practicing problem solving, learning from mistakes, grasping technical complexity, minimizing cognitive overload); developing confidence (believing in own abilities, depending on caregiver partnership, faith in crisis support); interrupted transition momentum (lacking individual attention, language barriers, installation delays, illness and complications, acclimatizing to new conditions); noticing immediate gains (reclaiming normality, satisfying self-sufficiency, personalizing treatment regime); depleting resources and energy (exhaustion, draining financial reserves, imposing caregiver burden). There was no significant change in satisfaction with care after commencing home HD.

Conclusions: Individualized home HD training fosters confidence and competency in patients; however patients may face anxiety and exhaustion with medical responsibilities. Ensuring access to respite, medical assistance, and psychosocial support may alleviate treatment burdens for patients commencing home HD.

Funding: Private Foundation Support

SA-PO835

Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Hemodialysis Patients Yoshitsugu Obi,1 Elani Streja,2 Connie Rhee,3 Vanessa A. Ravel,4 Alpesh Amin,5 Csaba P. Kovesda,6 Rajnish Mehrotra,3 Kamnyar Kalantar-Zadeh7.1 UC Irvine; 2UTHSC; 3UW.

Background: We have previously reported that an incremental hemodialysis regimen (e.g., dialysis initiation at twice weekly) was associated with more preserved residual kidney function over a year of dialysis therapy (WCN 2015, Cape Town). Here, we compared survival between the incremental vs. conventional regimen.

Methods: In a longitudinal cohort of 33,277 patients who initiated maintenance hemodialysis over four years (1/2007-12/2010) and survived the first year, 364 patients treated with the incremental regimen were matched to 4,797 patients treated with the conventional regimen on age, gender, race, the use of central venous catheter as blood access, and a history of congestive heart failure at the initiation of dialysis. The incremental hemodialysis regimen was associated with ~20% higher residual renal urea clearance (KRU) and 24-hr urine volume (UV) after 1 year of dialysis initiation. We then examined survival after the first year.

Results: Patients were 69±12 years old, 39% female, 13% non-Hispanic Black, and 66% diabetic. Median KRU and UV were 4.74 (IQR, 3.23-6.65) mL/min/1.73m2 and 1,150 (IQR, 800-1,650) mL/day, respectively. Baseline KRU and UV modified the association between the incremental regimen and mortality: the incremental regimen was associated with higher mortality in patients with KRU <3.0 mL/min/1.73m2 or UV <600 mL/day, but not in those with higher levels of KRU and UV.

Funding: NIDDK Support

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

Underline represents presenting author.

822A
SA-PO836
Seasonal Trends in Dialysis Initiation and Rising Home Dialysis: Results from the USRDS
Hui Liu,1 Yang Jiao,2 Douglas Lehmann,2 Richard Hirth,3 Yi Li,4 Rajiv Saran.1 1Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI; 2Dept of Biostatistics, Univ of Michigan, Ann Arbor, MI; 3Dept of Health Management and Policy, Univ of Michigan, Ann Arbor, MI.

Background: Motivated by increasing interest in home dialysis and incentive for it in the bundled payment system, we examined incident trends in home dialysis use in the United States Renal Data System (USRDS).

Methods: Using USRDS data (2007-2013), monthly counts of all new ESRD cases in the US, as well as incident home hemodialysis (HHD) and incident peritoneal dialysis (PD) patients were tracked. Incident HHD patients were those who started HHD within 90 days of entry into an ESRD program and incident PD patients who started PD as their initial modality.

Results: In 2013, over 55% of US facilities offered only in-center HD, 24.7% both HD and PD and 13.5% offered HD, PD and HHD. Figure 1 shows trends in monthly ESRD and PD utilization in the US during 2007-2013. The incidence rate of ESRD has been stable since 2010, but the number of new PD starts has risen steadily since 2009 and has somewhat further accelerated since 2011. Figure 1 also shows a seasonal trend for new ESRD and PD starts: incident ESRD cases tend to peak in the first 3 months of the year, while new PD starts tend to peak by mid-year. Rising HHD use is evident since 2007, without seasonal variation. A substantial variation in the annual growth rate of PD is notable across the states.

Conclusions: We report steady rising home dialysis use in the US, both HHD and PD, since 2007 and 2009, respectively. This rise predates the implementation of the bundled payment system in 2011, although PD use seems to be rising faster since 2011. Research into this seasonality in ESRD incidence and the impact of rising home dialysis use are warranted.

Funding: NIDDK Support

SA-PO838
Understanding Barriers to Home-Based and Self-Care In-Center Hemodialysis
May L. Yau,1 Luis Alvarez,2 Michelle Carver,3 Geoffrey A. Block,2 Glenn Matthew Chertow.1 1Outset Medical, Inc, San Jose, CA; 2Sutter Health, Menlo Park, CA; 3Denver Nephrology, Denver, CO; 4Stanford School of Medicine, Palo Alto, CA.

Background: Despite superior outcomes and lower associated costs, few patients with end stage renal disease undergo selfcare (SC) or home hemodialysis (HHD). Few studies have examined patient and physician barriers to SC and HHD and the degree which innovative technology might facilitate adoption.

Methods: We surveyed 250 in-center patients (pts) receiving hemodialysis and 51 board-certified nephrologists to identify key barriers to adoption of SC and HHD.

Results: Overall, 172 (69%) pts reported that they were “likely” or “very likely” (figure 1) to consider SC hemodialysis if they were properly trained on a new hemodialysis system designed for SC.

Conclusions: We report steady rising home dialysis use in the US, both HHD and PD, since 2007 and 2009, respectively. This rise predates the implementation of the bundled payment system in 2011, although PD use seems to be rising faster since 2011. Research into this seasonality in ESRD incidence and the impact of rising home dialysis use are warranted.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

SA-PO838
Dialyzer Clearance, Residual Renal Function and Middle Molecule Levels in Daily Dialysis
Christos Argyropoulos, Maria-Eleni Roumelioti, Mark L. Unruh. Internal Medicine, Div of Nephrology, UNM-HSC, Albuquerque, NM.

Background: Beta 2 Microglobulin (B2M) has emerged as a predictor of cardiovascular morbidity, mortality and LVH in patients with CKD and ESRD. Daily dialysis leads to higher B2M removal and has been associated with improvements in LVH and mortality in randomized trials. It is not known how B2M levels vary with dialysis membrane clearance (Kd) in daily dialysis regimes.

Methods: We adopted a population kinetic model (PKM) for the intraindividual variability in the generation, distribution and extrarenal removal of B2M (ASN 2014-SA-PO969). We used the PKM to simulate B2M concentrations in patients dialyzed with HF membranes in thrice weekly or daily sessions. For the latter we applied the intervention protocols for Short (SD) and Long Daily (LD) dialysis utilized in the FHN trials. The impact of Kd relative to residual renal function (RRF) on B2M was examined across the three dialysis modalities.

Results: B2M was lower in SD or LD relative to thrice weekly HF dialysis irrespective of RRF, the highest differences from HF (∆, 95%CI were obtained in anuric pts: 7.5, 7.4-7.6 mg/dl) at higher RRF irrespective of modality.

Conclusions: In simulations, higher dialyzer clearance is associated with lower plasma B2M in patients on daily dialysis, especially at lower levels of RRF. Whether these differences translate to improved cardiovascular outcomes should be confirmed in clinical studies.

There were significant interactions (p<0.001) between modality and RRF, as well as modality and Kd. A Kd of 60 ml/min resulted in lower B2M in LD and SD v.s. HF patients.

<table>
<thead>
<tr>
<th>Modality</th>
<th>RRF (ml/min)</th>
<th>∆B2M (mg/l) KD (60 v.s 20 ml/min)</th>
<th>LCI</th>
<th>UCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>0</td>
<td>6.8</td>
<td>6.7</td>
<td>7.6</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>8.2</td>
<td>7.5</td>
<td>8.9</td>
</tr>
<tr>
<td>LD</td>
<td>0</td>
<td>8.6</td>
<td>7.8</td>
<td>9.2</td>
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</tbody>
</table>

The differences between lower and higher dialyzer clearances were minimal (<1.1 mg/dl) at higher RRF irrespective of modality.

Nephrologists believed that pts were capable of performing dialysis-relevant tasks, including: weighing themselves (98%), wiping down the chair and machine (84%), clearing alarms during treatment (53%), taking vital signs (46%), and cannulating vascular access (41%), but thought that patients would not be willing to do the same.
SA-PO839
Wessex Kidney Centre Experience of Nocturnal Home Haemodialysis Using the NxStage System One Venkat Gangaram, Amanda Jane Laird, Laura Hignell, Natalie L. Borman. Renal Medicine, Wessex Kidney Centre, Queen Alexandra Hospital, Portsmouth, United Kingdom.

Background: Wessex Kidney Centre (WKC) Portsmouth established Home Haemodialysis (HHD) programme in 2009. In the absence of an in-house technician and limited capital the programme was set up using NxStage system one (NSO). WKC has now established a rapidly growing HHD programme has been excellent with self reported 97 patients to date includes nocturnal therapy.

Results: A total of 18 patients have received NHHD with mean time of 12.3 months (range 1 to 31). All patients dialyse alternate nights processing 40-60 litres using dual needleling access and a single bolus of Enoxaparin Sodium. Patients have regular transonic monitoring of their access and home visits. Two NHHD patients successfully dialyse alone. The mean age is 47.7 years (range 26 to 80), 78% male, 94% Caucasian with mean BMI 26.9. The Access used was AV fuma 56%, AV graft 22% and CVC 22% of patients. 14 patients changed from short daily HHD (SDHHD), 3 patients from in-centre Haemodialysis and 1 from Peritoneal dialysis. Laboratory parameters have been favourable as shown below.

<table>
<thead>
<tr>
<th></th>
<th>Ca-PO4</th>
<th>PO4</th>
<th>K</th>
<th>Hb</th>
<th>Alb</th>
<th>Ca-PO4</th>
<th>sKt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-NHHD</td>
<td>2.4</td>
<td>1.6</td>
<td>4.9</td>
<td>11.3</td>
<td>35</td>
<td>3.8</td>
<td>2.44</td>
</tr>
<tr>
<td>6 months</td>
<td>2.4</td>
<td>1.4</td>
<td>4.7</td>
<td>12.3</td>
<td>36</td>
<td>3.3</td>
<td>2.57</td>
</tr>
<tr>
<td>12 months</td>
<td>2.4</td>
<td>1.36</td>
<td>4.6</td>
<td>12.3</td>
<td>36</td>
<td>3.0</td>
<td>2.50</td>
</tr>
</tbody>
</table>

Retention has been excellent with one patient returning to in-centre HD after 25 months of HHD. Two patients switched to SD HHD as it more suited to their lifestyle and five patients have been transplanted. Pill burden has reduced, with less or no phosphate binders (mean number of binders reduced from 6 to 2) and a 40 % reduction in antihypertensive medication. Patients experience improved improvements in quality of life including facilitating return to employment. A number of patients have successfully travelled taking their NSO both within UK and abroad.

Conclusions: In Conclusion, NHHD using NSO is a viable alternative for HHD patients with our data suggesting good clinical outcomes. Patients have improved quality of life and with less pill burden, flexibility and more opportunity to engage in social activities.

SA-PO840
Current and Future Training of Home Haemodialysis Nurses Ruth Silverton, 1 Philippa Catherine Brown, 1 Paul Laboi, 1 Nicola Thomas. 1 Dept of Renal Medicine, York Hospital, United Kingdom; 2School of Health and Social Care, London South Bank Univ, United Kingdom.

Background: The UK National Institute for Health and Care Excellence recommend that >10% of dialysis patients be treated by home haemodialysis (HHD), however only 4.1% of patients in the UK are undergoing this modality. Success with HHD can be attributed to a supportive health policy, formal infrastructure, committed individuals and home dialysis experience; providing a patient-centred approach. Lack of nursing expertise is reported as a barrier to home dialysis for 30% of patients. A 2010 survey by the Australian HOME network revealed insufficient resources in dialysis units to provide support and education to patients. A potential barrier to HHD in the UK is specific training for renal nurses on the facilitation of shared or self-care.

Methods: The extent of current training provision for dialysis nurses in order to educate patients in home therapies/shared care was evaluated via an online survey. A link to the survey was sent to the British Renal Society database and the survey was available online for 1 month. There were 63 respondents.

Results: Over 76% of respondents (n=48) had worked in renal care for >10 years, with a third (n=21) receiving more than 5 days of structured training in how to teach self care. The majority of this training (51%) was as part of an ‘in-service programme’, with just over half (53%) of all nurses surveyed feeling adequately prepared for educating patients. The preferred mode of further training was face to face at a national event (38%), with a quarter (n=14) citing e-learning as the preferred option.

Conclusions: Data from the survey highlights a lack of adequate, standardised training for HHD nurses, demonstrating the need for a structured programme that ensures up-to-date best practice. As a result, we plan to pilot a specific HHD training scheme that involves patients and carers in curriculum planning and delivery, with content including; assessment of patients’ learning styles, how to facilitate shared decision-making with patients, and how to evaluate effectiveness of the HHD programme.
clearance. Increase of the dialysate flow did not further increase urea removal. Urea removal was dependent on urea plasma concentration (C-U). Limited release of ammonia-um was observed (0.1±0.03 mole per removed mole of urea).

Conclusions: EO by graphite electrodes combined with AC shows promising urea removal in vivo. Research aimed at increasing the efficacy and biocompatibility testing is warranted.

SA-PO843
Unplanned “Crash” Home Dialysis Starts: Single Center Experience from a University Hospital in the United States
Kristen P. Tamura, Jose A. Morfin, Nephrology, UC Davis Medical Center, Sacramento, CA; Nephrology, UC Davis Medical Center, Sacramento, CA.

Background: There is a high incidence of starting dialysis from the hospital to the in-center unit, and frequently these starts are unplanned and unexpected (“crash”). To this end, we sought to implement an educational program to identify patients suitable for a home dialysis modality, unplanned home hemodialysis (UHHD) and unplanned peritoneal dialysis (UPD).

Methods: We performed an retrospective observational analyses on patients who were started on dialysis from January 2013 to April 2015 in a diverse patient population admitted to UC Davis Medical Center in Sacramento, CA. We devised a systematic and comprehensive screening educational program to provide all modality options. We identified patients suitable UHHD, and UPD, both which were transitioned to a home dialysis training program upon discharge. Clinical characteristics and outcomes were compared to groups who had a standard start home dialysis (SHHD, SPD) during the study period. Our measured outcomes include the following: average training days, interval of technique failure (patient dropout), access status and complications, infections, hospitalizations and mortality in the first 90 days.

Results: Preliminary results reveal the groups tended to have similar demographic profiles with the average age for patients starting an unplanned home dialysis 51.5 years of age, 60% non-white race, but with a trend toward more males at 59% compared to standard starts.

Conclusions: This is the first study to compare QOL between Tx-pts and wait-listed NHHD patients compared to standard HD modalities. In this preliminary analysis, QOL was worse in NHHD compared to standard HD modalities. Further study is needed to validate this finding.

SA-PO845
Association of Vascular Access Type with Mortality, Hospitalization, and Transfer to In-Center Hemodialysis in Patients Undergoing Home Hemodialysis
Matthew B. Rivara, Melissa Sooboo, Elani Streja, Miklos Zsolt Molnar, Alfred K. Cheung, Ronit Katz, Onyebuchi A. Arah, Allen R. Nissenson, Jonathan Himmelfarb, Kamyr Kalantar-Zadeh, Rachna Mehrotra, Kidney Research Institute, Seattle, WA; Harold Simon Center for Kidney Dis Research & Epidemiology, Univ of California Irvine Med Ctr, Irvine, CA; Div of Nephrology, Univ of Ten Health Science Ctr, Memphis, TN; Div of Nephrology, Univ of Utah, Salt Lake City, UT; Epidemiology, Fielding School of Pub Health, Los Angeles, CA; DaVita, Inc., El Segundo, CA; David Geffen Sch of Med at UCLA, Los Angeles, CA.

Background: In individuals undergoing in-center hemodialysis (HD), use of central venous catheters (CVCs) is associated with worse clinical outcomes compared to use of arteriovenous access. However, it is unclear whether a similar difference in vascular access type risk is present in patients undergoing home HD, as these patients have higher dialysis treatment frequency and lower rates of exposure to sources of nosocomial infection.

Methods: We examined the associations of vascular access type with all-cause mortality, hospitalization, and transfer to in-center HD in patients who started HD from 2007-2011 in 464 facilities in 43 states in the United States. We analyzed the data using competing-risks hazards regression with vascular access type at the start of home HD as the primary exposure in a propensity score-matched cohort (1052 patients; 526 with CVC, 526 with arteriovenous access).

Results: Compared to arteriovenous access use, CVC use was associated with increased risk for mortality (hazard ratio [HR] 1.78; 95% confidence interval [95% CI] 1.21 to 2.61) and hospitalization (HR 1.38; 95% CI 1.19 to 1.59). CVC use was not associated with increased risk for transfer to in-center HD (HR 1.07, 95% CI 0.83 to 1.35, p=0.012). The results of analyses in the entire unmatched cohort (2481 patients), with vascular access type modeled as baseline exposure at start of home HD or as a time-varying exposure, were similar.

Conclusions: In a large nationally representative cohort of home HD patients, CVC use was associated with increased risk for mortality and hospitalization.

Funding: NIDDK Support

SA-PO846
Time to Transplant Associates with Home Dialysis Morbidity
Ritu Suri, Gibson E. Nesrallah, Liha Li, Lakshman Gunaratnam, Centre de Recherche, Centre Hospitalier de l’Univ de Montreal, Univ de Montreal, Montreal, QC, Canada; Humber River Hospital, Toronto, ON, Canada; Nephrology Div, Western Univ, London, ON, Canada.

Background: We recently showed that prevalent end-stage renal disease patients starting home daily hemodialysis (DHD) have reduced cardiovascular and infection-related hospitalization risk compared to those starting peritoneal dialysis (PD). As current hospitalization precludes being active on the transplant wait-list, we investigated whether DHD patients receiving home DHD would be more likely to be transplanted than those receiving PD.

Methods: We matched 2997 adult starting home daily hemodialysis (DHD) in a single US dialysis provider’s facilities from 2004-2011, to 2997 contemporaneous USRDS patients starting PD by US state and propensity-scores. Demographics, comorbidities (form 2728 and hospitalization codes), and outcomes were ascertained from USRDS. We used Cox regression stratified on matched sets censoring for death, and competing risk analysis using Fine’s approach for stratified data, to compare times to transplantation between groups.

Results: Baseline variables were balanced between groups after matching, with standardized differences <10%. During 12,558 years of follow-up (mean 2.1±1.4 years), 514 DHD and 428 PD patients were transplanted. DHD patients were 19% more likely to be transplanted than PD patients (DHD 8.2 vs PD 6.8 per 100 patient-yrs; HR 1.19, 95%CI 1.05-1.35, p=0.012). Competing risk analysis accounting for death and follow-up losses yielded a HR of 1.18 (95%CI 1.04-1.33, p=0.010). Time to waiting-list did not differ between groups (HR 0.97, 95% CI 0.90-1.06, p=0.54), but once waitlisted, PD patients were significantly more likely to be permanently removed from the wait-list (PD 14.2% vs DHD 10.2%, RR 1.39 (95%CI 1.09-1.78), p=0.008).

Conclusions: In this prevalent cohort, home DHD patients were more likely to be transplanted than matched PD patients, and less likely to be permanently removed from the wait-list during follow-up. Mean times to wait-listing were similar, suggesting that the groups were well-matched. Further study is needed to validate the factors responsible for the differential transplantation rates observed in home DHD and PD patients.

Funding: Private Foundation Support
SA-PO847
Spectrum of Mutations in PKD1 and PKD2 Genes in 100 Unrelated Italian Pedigrees with ADPKD – Sanger Sequencing versus Next Generation Sequencing (NGS) Madalena Gigante,1 S. Diella,1 Matteo Accetturo,2 Paola Pontrelli,1 Giovanni Stailone,1 Giuseppe Grandalíamo,1 Loretto Gesualdi,1 Univ of Foggia, Foggia, Italy; DETO, Univ of Bari, Bari, Italy.

Background: ADPKD is caused by mutations in PKD1 or PKD2 genes. Although, clinical studies and case reports describing one or few ADPKD families have been reported in Italian population, to date a comprehensive molecular study is still lacking.

Methods: PKD1 and PKD2 genes were analyzed in 150 Italian ADPKD patients from 100 unrelated pedigrees - the largest Italian cohort analyzed to date in a single study - using Sanger sequencing and NGS. The potential pathogenicity of the newly identified variants was evaluated by combining different in silico methods.

Results: We identified the largest number of definitively and probable pathogenic mutations (n=78) reported in a single study in Italian population, achieving an overall detection rate of 90%. 55 mutations (52 PKD1 and 3 PKD2) have not been previously described, expanding the spectrum of known ADPKD mutations. We identified 12 de novo PKD1 mutations in sporadic patients without family history, providing a definitive diagnosis of ADPKD. We found the largest number of de novo mutations reported in a single study (15%) demonstrating, for the first time, that the prevalence of PKD1 de novo mutations may be underestimated. 4/32 (15%) mutations identified in a single study and (iii) provide a new NGS method with a detection rate comparable to Sanger sequencing but with significantly lower cost and reduced turnaround time.

Funding: NIDDK Support

SA-PO848
The Use of Screening MR Angiography in Patient with ADPKD Claudine Christiansen, Ruben Poesen, Dirk R. Kuypers, Bert Bammens, Bjorn Meijers. Nephrology, Univ Hospitals Leuven, Belgium.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with the development of intracranial aneurysms and an elevated risk of hemorrhagic stroke (HS). It is suggested that screening MR angiography reduces the incidence of hemorrhagic stroke. Current screening criteria include positive family history in relatives, neurological symptoms and planned major surgery. The efficacy of these screening criteria has, however, not been fully evaluated.

Methods: We performed a single-center retrospective analysis of all ADPKD patients followed at the University Hospitals Leuven, between January 1990 (date of the first MR angiography) and August 2014. Baseline demographics and occurrence of screening criteria, screening MR angiography, intracranial aneurysm and hemorrhagic stroke were evaluated.

Results: We identified 865 patients with ADPKD. Those who were seen at least three times (median age 51y; 49% males) were included for analysis. Mean duration of follow up was 11.6 years. In this cohort, current screening criteria were met in 183 ADPKD patients (29.2%). Of these, 136 (74.3%) had screening MR angiography. In patients with no MR angiography, presence of screening criteria was associated with an elevated risk of hemorrhagic stroke (12.8% vs. 4.0%, P 0.02). Use of MR angiography in patients with screening criteria was related with a lower risk of hemorrhagic stroke during follow-up (2.2% vs. 12.8%; P 0.01).

Conclusions: In patients with ADPKD, current screening criteria for intracranial aneurysm are associated with an 3-fold elevated risk for future hemorrhagic stroke and performing MR angiography seems effective in reducing this risk.

SA-PO849
Influence of Genotype on ADPKD Progression in the HALT PKD Cohort Christina M. Heyer,1 Kaelue Z. Abebe,1 Vicente E. Torres,1 Ronald D. Perrone,1 Marie C. Hogan,1 William E. Braun,1 Godela M. Brosnaham,1 Peter G. Czarnecki,1 Charity G. Moore,1 Peter C. Harris,1 Dana Miskulin,1 The HALT PKD Investigators.1 Mayo Clinic Rochester, MN; 2U of Pittsburgh, Pittsburgh, PA; 3U of Colorado, Denver, CO; 4Tufts, Boston, MA; 5Cleveland Clinic, Cleveland, OH; 6Brighton and Women’s Hospital, Boston, MA; 7Carolina’s Health Care System, Winston-Salem, NC.

Background: We assessed here the influence of the ADPKD disease gene (PKD1 or PKD2) or PKD1 mutation type (truncating or non-truncating) on the rates of renal disease progression over 5 years in the HALT PKD cohort.

Methods: PKD1 mutation type was divided into strength groups: truncating (MSG1), and more or less penetrant non-truncating (MSG2 and MSG3). Correlations were made between gene type/MSG and changes in eGFR or height adjusted total kidney volume (htTKV).

Results: PKD1 patients had a faster eGFR decline than PKD2 (3.3 vs. 1.87 ml/min/1.73m2/yr; P<0.0001) but the rate of htTKV increase did not differ (6.44 vs. 6.81%/yr; P=0.42). Baseline PKD1 htTKV was larger than PKD2 (733, 557ml/m2; P<0.0001) and so PKD1 kidneys expanded to a greater extent (268, 217ml/m2/yr; P=0.0001). Rates of change in eGFR or htTKV did not differ between PKD1 MSG1 and MSG2 (P=0.15 and 0.70), but MSG3 baseline kidneys were smaller relative to MSG1 and MSG2 (611, 733, 777ml/m2; P=0.004) and so the volume increase was less (221, 262, 277ml/m2; P=0.004). PKD2 patients were less likely to reach a study endpoint (death, ESRD or 50% eGFR decline; P=0.0003), but there was no difference between PKD1 MSG1, 2, 3 (P=0.61). Patients with no mutation detected, had a slower increase in htTKV (4.8%/yr; P=0.008 vs. PKD1). The study showed a difference in TKV increase between the low and standard blood pressure groups (5.6 vs. 6.6%/yr; P=0.006). The magnitude of difference was similar when restricted to PKD1 MSG1 (5.7 vs. 6.7%/yr; P=0.0516) or PKD1 MSG1 and 2 (5.8 vs. 6.6%/yr; P=0.0543), but not significant in the smaller populations.

Conclusions: PKD1 MSG3 kidneys are smaller but not because they grow more slowly; possibly because they have less early cysts, similar to PKD2 vs. PKD1. Since genic and allelic effects do not alter progression rates, restricting analysis by genetic factors did not improve significance.

Funding: Clinical Revenue Support

SA-PO850
Climate Temperature Affects the Age of End-Stage Kidney Disease in Autosomal Dominant Polycystic Kidney Disease (PKD) Marwan M. Abbas,1 Michael E. Bleyer,3 Elizabeth Swain,1 Kendrah O. Kidi,2 Gregory B. Russell,2 Anthony J. Bleyer,1 Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC; 2Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC.

Background: Vasopressin receptor 2 antagonists decrease cyst size in PKD. We postulated that patients in hotter climates would have more concentrated urine, and this would affect the age of ESRD in PKD.

Methods: We obtained demographic data and cause of ESRD on 1,332,402 individuals who had their first occurrence of ESRD between ages 30 and 90 between 1971 and 2012 from the US Renal Data System (USRDS). We obtained annual mean temperatures from 1990 to 2010 for US weather stations and linked a participant’s zip code to the nearest weather center. We correlated the mean age of onset of ESRD for PKD and other causes of ESRD with 5 degree temperature intervals. We created a multivariate model for PKD patients, with the dependent variable age of ESRD and independent variables race, gender, year starting dialysis, residual GFR at start of ESRD, annual median income by patient zip code, and temperature as discrete variables in 5 degree intervals.

Results: Figure 1 shows the mean age of onset of ESRD by disease. Cold and warm temperature extremes were associated with increasing age of ESRD for PKD, but other diseases.

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The multivariate model showed that temperature had a minimal effect on age of ESRD compared to other variables in the model.

Conclusions: There was a U-shaped relationship for age of ESRD according to temperature that was present in PKD and other diseases. However, in a multivariate model, climate temperature had a minimal effect on age of ESRD in PKD.

Funding: Clinical Revenue Support
Urinary Biomarkers and Prediction of Disease Progression in Autosomal Dominant Polycystic Kidney Disease

The Burden of Tolvaptan Treatment for Autosomal Dominant Polycystic Kidney Disease

Results: We included 40 patients (male: 28, female: 12). The median age was 46.5 years (interquartile range: IQR 24 - 69 y). The median baseline eGFR was 65 mL/min/1.73 m² (IQR: 26.9 - 58.8) and the median baseline TKV was 1.917 mL (IQR: 1.378 - 2.905). The median starting dosage of tolvaptan was 60 mg (IQR: 30 – 60) and the median treatment period was 8 months (IQR: 6 - 11). We observed no statistical variations in eGFR (p = 0.787) and TKV (p = 0.561) during treatment. There were no significant changes in PASM scores for general fatigue (p = 0.817), anorexia (p = 0.393), back pain (p = 0.682), and abdominal distension (p = 0.607) during treatment. Although analysis of variance demonstrated that aquaretic burden including thirst and dry skin were significantly increased after Tolvaptan treatment (p < 0.003), 35 % of the combination of patients did not completely sense thirst at all during treatment, and 42 % (n = 17) of patients spontaneously improved without any additional treatment or tolvaptan withdrawal.

Conclusions: Although analysis of variance demonstrated that aquaretic burden including thirst and dry skin were significantly increased after Tolvaptan treatment, almost third of the patients did not completely sense thirst at al from beginning of Tolvaptan treatment, and the remaining third part of patients spontaneously improved.

Adapted PKD Disease Predicts Actual Progression of Autosomal Dominant Polycystic Kidney Disease in TEMPO3Δ

Results: We included 104 ADPKD patients, 40±11yrs, 39% female, eGFR 77±10 mL/min/1.73 m² and htTKV 852 (510-1243) mL/m². During a follow-up of 3.8±1.2 yrs, annual change in eGFR was -3.3±2.6, in mGFR -3.3±0.3 mL/min/1.73 m² and in htTKV ±2.5±9.5%. BMI and MCP-1 were associated with annual change in eGFR (β = -0.23, p=0.02; β = 0.38, p<0.001 resp) and mGFR (β = -0.24, p=0.03; β = 0.24, p=0.03 resp), even when adjusted for conventional risk markers, but not with annual change in htTKV. Similar results were obtained when patients with an eGFR ≤60 mL/min/1.73 m² were selected. Combined BMI and MCP-1 had an added predictive ability for annual change in eGFR (R² = 0.178 vs. 0.324, p=0.008) and in mGFR (R² = 0.134 vs 0.217, p=0.07). The best predictive model for annual change in eGFR included age, htTKV, MIF, b2MG and MCP-1 (R² = 0.343, p=0.025), and for annual change in mGFR, gender, b2MG, MIF and MCP-1 (R² = 0.3, p=0.052).

Conclusions: BMI and MCP-1 both predict disease progression, and have an added predictive value on top of conventional risk markers. These markers have therefore potential to serve as a predictive tool for clinical practice.

The Novel Surrogate Marker of Autosomal Dominant Polycystic Kidney Disease

Background: Experimental studies suggest a detrimental role for Arginine vasopressin (AVP) in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). Copeptin consists of the C-terminal portion of Pro-AVP and has been shown to be a reliable and stable substitute for circulating AVP concentration. In contrast to serum or plasma, urinary proteins do not undergo detectable degradation by endogenous proteases after voiding. It is unknown, however, whether urinary copeptin concentration are associated with disease severity in patients with ADPKD.

Methods: Serum and Urinary copeptin concentration were measured by immunoassay in ADPKD patients with CKD stage ≤ 4. We compared our measurements with clinical parameters including estimated Glomerular Filtration Rate (eGFR), Total Kidney Volume (TKV) and height-adjusted (ht)TKV. Multivariate linear regression was used to assess the predictive ability of the markers above conventional risk markers.

Results: Included were 104 ADPKD patients, 40±11yrs, 39% female, eGFR 77±10 mL/min/1.73 m² and htTKV 852 (510-1243) mL/m². During a follow-up of 3.8±1.2 yrs, annual change in eGFR was -3.3±2.6, in mGFR -3.3±0.3 mL/min/1.73 m² and in htTKV ±2.5±9.5%. BMI and MCP-1 were associated with annual change in eGFR (β = -0.23, p=0.02; β = 0.38, p<0.001 resp) and mGFR (β = -0.24, p=0.03; β = 0.24, p=0.03 resp), even when adjusted for conventional risk markers, but not with annual change in htTKV. Similar results were obtained when patients with an eGFR ≤60 mL/min/1.73 m² were selected. Combined BMI and MCP-1 had an added predictive ability for annual change in eGFR (R² = 0.178 vs. 0.324, p=0.008) and in mGFR (R² = 0.134 vs 0.217, p=0.07). The best predictive model for annual change in eGFR included age, htTKV, MIF, b2MG and MCP-1 (R² = 0.343, p=0.025), and for annual change in mGFR, gender, b2MG, MIF and MCP-1 (R² = 0.3, p=0.052).

Conclusions: BMI and MCP-1 both predict disease progression, and have an added predictive value on top of conventional risk markers. These markers have therefore potential to serve as a predictive tool for clinical practice.

The burden of tolvaptan treatment for autosomal dominant polycystic kidney disease

Background: Last year, Japan became the first country in the world to approve tolvaptan treatment, and the remaining third part of patients spontaneously improved.

Methods: This report uses baseline data for placebo subjects from the TEMPO 3:4 ADPKD clinical trial to support this approach to disease progression modelling by constructing a model predicted and observed TKV and eGFR. Simulations were performed by utilizing the PKDOC model with subject-specific baseline TKV and eGFR measurements from subjects enrolled in TEMPO 3:4.

Results: Bias (mean of the relative error) and precision (square mean of relative error) of TKV and eGFR were derived to assess the predictive performance of the PKDOC model. The model resulted in very robust predictions of TKV and eGFR with mean (95% CI) bias values of 2.98% (1.1-5.1) and 3.03% (1.4-4.7), respectively. Mean (95% CI) precision on TKV and eGFR were 42.9% (19.1-68.7) and 57.9% (34.0-43.4), respectively. The coefficient of determination (r²) for observed and model predicted TKV and eGFR data were 0.957 and 0.877, respectively.

Conclusions: The disease progression model developed with PKDOC data and applied to the TEMPO placebo dataset demonstrated excellent predictive power for TKV and eGFR.

Funding: Other NIH Support - Access to NIDDK Databases through PKDOC collaboration, Pharmaceutical Company Support - Otsuka Pharmaceuticals, Private Foundation Support

Polycystic Kidney Disease Imaging Biomarkers – The Texture of Things to Come

Background: Medical imaging is essential for polycystic kidney disease (PKD) diagnosis, monitoring, and outcome prediction. Research studies use total kidney volume (TKV) as an imaging biomarker to follow the progression of PKD. However, TKV overlooks underlying structural and functional complexities of the kidneys. We hypothesize that texture analysis may provide quantitative measurements of renal tissue structure to improve patient outcome prediction.

Methods: A retrospective cohort of 20 patients (38 exams) was identified who had imaging prior to reaching end-stage renal disease (ESRD). Image texture features were generated from the baseline MR images and analysis of the correlation to known time-to-ESRD was performed. A total of 18 texture features were computed for each MRI scan. The analysis workflow is shown in Fig. 1. Results: Texture features were well correlated to time-to-ESRD and many individual texture features outperformed height-adjusted TKV (htTKV) as shown in Figs. 2 and 3. Examination of MRIs and the corresponding energy image feature (measure of heterogeneity) for two different patients with markedly different times-to-ESRD are also shown for comparison. In addition, entropy (measure of image randomness) and gray-level non-uniformity (measure of neighboring pixel similarities) were also found to be well correlated (r-values of 0.66 and 0.73, respectively).
Conclusions: We present the first use of texture analysis for PKD assessment. Results are promising in terms of identifying new imaging biomarkers that correlate with disease progression. This approach could function as a surrogate to more difficult imaging methods (e.g., quantitative MRI) and costly analysis (e.g., cyst segmentation). It is likely that combining texture analysis with other patient data will allow for substantial improvements to PKD prognosis.

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SA-PO856

Accuracy of Traditional and Novel Renal Filtration Markers for Estimating GFR in ADPKD Patients

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Background: The best method for estimating GFR in ADPKD is unclear. Changes in tubular handling of filtration markers may affect estimating equation accuracy.

Methods: Among 51 adults with ADPKD and eGFR >20 cc/min/1.73m², we measured GFR using iothalamate plasma clearance (iGFR), serum creatinine (SCr, IDMS-traceable assay), Cystatin C (CysC, Dimension VISTA assay) and beta-trace protein (BTP, immunonephelometric assay, Siemens). We estimated GFR (eGFR) using validated equations based on SCr (CKD-Epi, MDRD), Cystatin C (CKD-Epi, CysC), both CysC and SCr (CKD-Epi-CysC) or SCr and BTP (White equation). We compared the bias, precision, overall accuracy, and classification (for iGFR<60 cc/min/1.73m²) of each estimating equation.

Results: Mean age was 51±12 years, 71% were female, 84% Caucasian, and mean iGFR was 68.4±34.2 cc/min/1.73m². Of the 5 equations, the CKD-Epi-CysC had the highest bias (overestimating GFR), lowest precision and accuracy, and was least sensitive for between the SCr- and BTP-based estimating equations. (Table)

Conclusions: Patients randomized to placebo using statins were older, had larger TKV and lower eGFR at baseline, and their TKV and eGFR slopes were steeper compared to statin nonusers (Table). Similarly, patients randomized to tolvaptan using statins had lower eGFR, with a non-significant trend to larger TKV compared to statin non-users; however, there was no difference between TKV and eGFR slopes of statin users and nonusers randomized to tolvaptan. Statin use did not affect a composite end point of clinically relevant ADPKD events in the placebo (HR=1.035, P=0.01) or tolvaptan (HR=0.954, P=0.65) group.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical

SA-PO858

Systems Biology of Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is a group of hereditary disease states characterized by cystic kidneys and often accompanied by other manifestations such as cystic liver and hypertension. PKD occurs in 1 in 500 people, usually resulting from a dominant mutation in one of two genes, PKD1 or PKD2. There are no treatments for PKD and it is the leading genetic cause of renal failure. Numerous studies have identified pathways that are misregulated in PKD but targeting these individual pathways has not led to a successful therapeutic intervention or molecular biomarker.

Methods: To identify potential biomarkers and develop a systems-level understanding of PKD, we are using transcriptomics, and quantitative proteomics and phospho-proteomics to evaluate the state of cystic and normal kidneys in a mouse model of PKD. Kidney cysts also induce injury to the surrounding tissues, confounding any analysis of the “cystic state”. In an effort to separate the injury signature from the cystic signature, we are also evaluating the state of the injured kidney using a folate model of acute kidney injury and fibrosis. The multi-kinase inhibitor Roscovitine has been shown to prevent cystogenesis in mouse models of PKD but its mechanism of action remains unknown. To gain insight into the mechanism(s) of Roscovitine and to identify biomarkers that change with treatment, we are also using the above “omic” strategies using kidneys from mice following treatment.

Results: From the transcriptomic experiments, we have a list of potential biomarker candidates that are currently being tested by qPCR in mouse tissue at various stages of disease progression. Phosphorylation at motifs for CDKs, CK1, CaMK, and others are reduced in kidneys treated with Roscovitine. The primary transcription factor family found to be suppressed with Roscovitine treatment is the E2Fs, likely a result in the loss of CDK signaling.

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828A
Conclusions: These experiments will not only provide candidate biomarkers for PKD progression, but will also yield a deeper understanding of the state of the cystic kidney. Funding: Pharmaceutical Company Support - Santen Genezyme, Private Foundation Support

SA-PO859
Prognostic Enrichment Strategies in the TEMPO 3:4 ADPKD Clinical Trial

Background: An image classification of ADPKD based on diffuse (class 1) vs. asymmetric (class 2) cyst distribution along with estimated cyst growth determined by age and height-adjusted total kidney volume (htTKV, subclas A-E) has been proposed for prognostic enrichment by excluding patients with a lesser risk for progression (classes 1A-B and 2).

Methods: This enrichment strategy was compared, post-hoc, to exclusion criteria used for TEMPO3-4 to examine tolvaptan effects on ADPKD progression in patients with early but progressive renal disease (18-50 year-old, TKV = 750 mL, eGFR >60 mL/min).

Results: 1436 TEMPO 3-4 subjects with baseline MRIs were classified, finding only 10% class 2 or 1B and no 1A subjects. TEMPO3-4 enriched classes 1C-E (90%) compared to the published cohorts (62%, Irazabal 2014 JASN). TKV and eGFR slopes steepened from class 1B to 1E (both P<0.001, Table).

Purpose: Tovaptan effects on TKV and eGFR slopes 5.78% to 2.91% and -3.93 to -2.82 mL/min/1.73m² compared to the published cohorts (62%, Irazabal 2014 JASN). TKV and eGFR slopes steepened from class 1B to 1E (both P<0.001, Table).

Conclusions: Strategies for prognostic enrichment such as the image classification should be used in the design of RCTs for ADPKD to increase their power and reduce their cost.

Funding: NIDDK Support

SA-PO861
Long-Term Safety Profile of Tolvaptan in Japanese ADPKD Patients

Background: Tolvaptan was first approved in Japan for autosomal dominant polycystic kidney disease (ADPKD) based on results of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3-4 trial (TEMPO) to determine 3-year efficacy and safety. The purpose of this study was to investigate adverse drug reactions (ADRs) of tolvaptan for up to extended 3 years after TEMPO in Japanese ADPKD patients.

Methods: This open-label study was conducted in 135 patients participating in the preceding TEMPO. Doses of tolvaptan were adjusted from 60 to 120 mg/day.

Results: Main ADRs: thirst (77%), polyuria (57%), polydipsia (38%), and hyperuricemia (15%) were noted during up to 3 years in TEMPO. Hepatic function-related ADRs were observed more frequently for tolvaptan than for placebo early during treatment. In this study, 8 patients (6%) experienced >3-fold increases above upper limits of normal serum ALT, AST, and GGT at 3 to 9 months after tolvaptan initiation, but all recovered after tolvaptan cessation. Of these 8 patients, 7 had been allocated to placebo in TEMPO. However, the residual one patient allocated to tolvaptan similarly had shown increased serum ALT in TEMPO. None of the 8 patients met Hy’s Law criteria. No ADRs besides those seen in TEMPO were newly observed in this study.

Conclusions: Hepatic function-related ADRs occurred early during treatment and were reversible. Tolvaptan was thus indicated to be a promising drug for treatment of ADPKD for up to 6 years while carefully monitoring ADRs including hepatic function abnormalities.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Co., Ltd.

SA-PO860
Prognostic Enrichment Design in Clinical Trials for ADPKD: The HALT PKD A Trial

Background: Patients with mild ADPKD phenotype are less likely to be informative in clinical trials. An image classification into typical (diffuse cyst distribution) class 1A and atypical (asymmetric cyst distribution) class 2 has been proposed for prognostic enrichment design in clinical trials.

Methods: In a secondary analysis, data regarding maternal and fetal outcomes and complications of the HALT PKD trials, 38 pregnancies occurred despite counseling and review with participants. We now present maternal and fetal outcomes from these pregnancies.

Results: In the TEMPO 3:4 ADPKD clinical trials, 38 pregnancies occurred despite counseling and review with participants. We now present maternal and fetal outcomes from these pregnancies.

Conclusions: ADPKD is the most common hereditary disease. Fertility rates are not impaired in ADPKD women, however, preexisting hypertension and proteinuria associate with increased maternal and fetal complications. In the HALT PKD trials, 38 pregnancies occurred despite counseling and review with participants. We now present maternal and fetal outcomes from these pregnancies.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Co., Ltd.
SA-PO863

Renal Concentrating Capacity and Copeptin Concentration in Patients with ADPKD and IgA Nephropathy with Impaired Renal Function


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Background: ADPKD patients have an impaired maximal urinal concentrating capacity (Umax). Whether this is an aspectic effect of renal function impairment, or specific for ADPKD is yet unknown. We hypothesized that ADPKD patients have a more severely impaired Umax in comparison with non-ADPKD renal disease patients, which leads to an exaggerated vasopressin (AVP) response that may be damaging to the kidney.

Methods: 15 ADPKD (eGFR>60) and 15 IgA patients, matched for age, sex, and eGFR underwent a water deprivation test to determine Umax. Urine and plasma osmolality (Uosm and Posm), albuminuria (ACR) and plasma copeptin (surrogate marker for AVP in pmol/L), were measured at baseline and after water deprivation (average 17 hours). Height adjusted total kidney volume (htTKV) was measured by MRI.

Results: Umax was lower in ADPKD compared with IgA patients. Upon water deprivation Posm increased in ADPKD (p=0.003), but not in IgA (p=0.1), whereas copeptin increased in both groups similarly. (ADPKD: p=0.001; IgA: p=0.02). Copeptin after water deprivation was negatively associated with Umax in both groups (ADPKD: R=-0.72, p=0.002; IgA: R=-0.70, p=0.004). In ADPKD, copeptin, cotatin and albuminuria were correlated after water deprivation (R=-0.71, p<0.003), independently of eGFR or htTKV. Furthermore, htTKV in ADPKD was associated after water deprivation with Posm (R=0.52, p=0.048), copeptin (R=0.58, p=0.03) and Umax (R=0.45, p=0.04).

Conclusions: ADPKD patients have a lower Umax compared with IgA patients with similar renal function. Remarkably, this is not accompanied with an exaggerated increase in AVP. Notwithstanding, ADPKD severity was associated with stronger increases in Posm, copeptin and albuminuria during water deprivation. This suggests that in ADPKD water deprivation may be deleterious and should be avoided.

Funding: Government Support - Non-U.S.

SA-PO864

Total Abdominal Organ Volume Is a Major Risk Factor for Malnutrition in Ambulatory Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: In Autosomal dominant polycystic kidney disease (ADPKD), malnutrition may develop as renal function decreases and abdominal organ volume enlarged. In this study, we evaluated the nutritional status of outpatient ADPKD patients by using subjective global assessment (SGA) and investigated the risk factors for malnutrition.

Methods: In this single center, cross sectional study, anthropometric and laboratory data including serum creatinine (sCr), albumin, and cholesterol were collected, and total kidney and liver volume were measured. Total abdominal organ volume was defined as the sum of total kidney and liver volume and adjusted by height (htTAV).

Results: A total of 208 patients (47.9%) were included and mean age was 48.3±12.2 years. Mean estimated glomerular filtration rate (eGFR) was 65.3±5.2 5.ml/min/173m². Mean sCr ratio was 6.6±0.6. 168 patients (58.3%) were in chronic kidney disease stage 1 or 2, 99 (34.4%) stage 3 and 217(7.3%) stage 4. Total 21 patients (7.3%) were mild to moderately malnourished (SGA 4-5) and 63 patients(21.7%) were at risk of malnutrition (SGA 6). There was no difference in SGA score distribution with sex. Physical scores related to nutritional status in total and male were age, height, weight and body mass index. However none of these parameters were related in female. Lower hemoglobin level and poor renal function were in worse male but not female. AND ACR and eGFR.

Conclusions: Nutritional risk was detected in 30% of ambulatory patients with ADPKD and relatively preserved renal function. Intraabdominal organ growth in ADPKD may affect the nutritional status independently from the renal deterioration.

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

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Results: Among 186 patients who underwent PHCF, 91% were Caucasian women with ADPKD with a mean age of 49 years. Major peri-operative complications (Clavien III/IV) occurred in 24% of the patients. Operative mortality (<90 days) was 2.7% with one death from liver failure. Overall survival was 95%, 90%, 76.5% and 59% at 1, 5, 10 and 15 years respectively. Imaging records for volumetry were unavailable in 37 patients. Of the remaining 149 patients, 30 patients had imaging for one LV, 65 for two LV and 54 for all three LV. Median LV was 6812 ml preoperatively and 2502 ml after PHCF leading to a median postoperative liver volume reduction of 61%.

At follow-up (mean 7.8 years), median LV was 2500 ml. Interestingly, 29 out of 61 patients with available LV2 and LV3 showed further regression in LV upon follow up (median -14.8%); while the rest showed mild growth of 9.5%. Overall volumetric comparison of preoperative to follow-up liver imaging showed sustained liver volume reduction (median 60%).

Conclusions: Sustained long-term reductions in LV after PHCF can be achieved in selected patients with severe, highly symptomatic PLD. In our experience, liver-related death and subsequent liver transplantation are infrequent after PHCF.

SA-PO869

Effect of Genotype on the Severity and Volume Progression of Polycystic Liver Disease (PLD) in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: PLD is the most common extrarenal manifestation in pts with ADPKD. Here we analyzed the influence of genotype and gender on the severity of PLD.

Methods: Clinical data was retrieved from electronic records in a large cohort of pts who were mutation screened, determined to be PKD1 or PKD2 and had available CT or MR liver imaging during 2000-2014 at the Mayo Clinic (n=445). Liver volumes (LV) were measured by stereology on axial images and adjusted to height (HtLV).

Results: Among the 445 pts, 220 (49.5%) had truncating PKD1, 153 (34.4%) nontruncating PKD1 and 72 (16.1%) PKD2 mutations. Compared to nontruncating PKD1 and PKD2, pts with truncating PKD1 were younger at time of first imaging (43.6 vs 47.6 and 50.4; p<0.001), had lower median survival time to ESRD (62.4 vs 66.9 and 81.4; p<0.001Log-Rank), and larger kidney volumes (785 vs 614 and 548 ml/m2; p<0.001). LV in pts with PKD1 truncating, PKD1 nontruncating and PKD2 were not different (HtLV 1039, 1076 and 1058 ml/m2, respectively;p=0.53). Female pts had larger HtLV compared to males (1104 vs 1019 ml/m2; p<0.001). Annualized median liver growth rates were 1.65, 1.74 and 1.2% for truncating PKD1, nontruncating PKD1 and PKD2, respectively (p<.75). Females younger than 48 had higher annualized median growth rates compared to those older than 48 (2.65 vs 0.09%;p<0.001). When adjusting for age, gender and baseline LV, growth rate remained unaffected by the ADPKD genotype.

Conclusions: Among the 220 with available imaging data, those with truncating PKD1 were younger, had less survival to ESRD, and smaller liver volumes than the other genotypes.

SA-PO868

Outcomes of Combined Partial Hepatectomy and Cyst Fenestration for Massive Polycystic Liver Disease

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Background: Partial hepatectomy and cyst fenestration (PHCF) selectively provides clinical benefit in highly symptomatic patients Polycystic Liver Disease (PLD). This study aims to ascertain whether the reduction in liver volume achieved by PHCF is sustained long-term.

Methods: Clinical data was retrieved from the electronic records in all PLD patients who underwent PHCF between 1985 and 2014. Preoperative Liver volumes (LV1), postoperative (LV2) and late follow up (LV3) were measured from MR or CT images.

Conclusions: Renal function did not change significantly during the period that patients were on metformin. We will continue to observe these patients and accumulate more patients with PKD and diabetes but not on metformin to see if metformin is beneficial in PKD patients.

SA-PO867

11Beta-Dichloro Inhibits Cyst Progression in an Adult ADPKD Model

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Background: ADPKD is the most common monogenic disorder for which no effective therapy exists. We have previously shown that the novel antitumor agent 11β-dichloro specifically induced apoptosis in Pkd1 null cells (ASN 2013 FR-OR100). Administration of 11β-dichloro resulted in amelioration of cystic disease in the Pkd1fl/fl;Pkd1-Cre neonatal ADPKD model. In the current work we explored the pathways involved in the pro-apoptotic effect of 11β-dichloro and investigated whether the beneficial effect seen in the early model is also present in an adult inducible Pkd1-Cre;Pkd1fl/fl model which is more akin to the human disease.

Methods: Pnx8rtTA;TetO-cre;Pkd1fl/fl mice were induced with doxycycline for 2 weeks beginning at P28. 11β-dichloro was administered by IP injection at a dose of 10 mg/kg, 3 times a week for 12 weeks beginning from P42; At the end of treatment the kidneys were harvested for analysis.

Results: 11β-dichloro treated adult mice resulted in a decrease in KW/BW ratio as compared to vehicle injected controls (2.6±0.1 vs. 6.1±0.4); There was no difference in body weight between treated and control. These changes were accompanied by a decrease in the cyst index (29±6.5 vs. 49±11.4), BUN (41±2.4 vs. 83±2.7), and creatinine (0.18±0.007 vs. 0.37±0.02). 11β-dichloro specifically increased apoptosis in cyst-lining cells but not in wild-type. UPR and ROS have been implicated as potential drivers of the 11β-dichloro-dependent pro-apoptotic phenotype. We found that upregulation of the UPR marker XBP1s and its transcriptional targets Bip and Erj4 was specific to the Pkd1 null cells compared with wild-type, in vitro and in vivo. Treatment with 11β-dichloro increased mRNA levels of the antioxidant genes catalase and SOD1 specifically in the Pkdl cystic kidneys and not in vehicle-treated kidneys.

Conclusions: 11β-dichloro specifically induces UPR, ROS, and apoptosis in cystic vs. wild-type kidneys. In an adult inducible cystic model, the compound ameliorates cystic disease progression and improves kidney function.

Funding: Other U.S. Government Support, Private Foundation Support

SA-PO868

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Underline represents presenting author.

831A
Diagnostic and Therapeutic Advances in PKD
Poster/Saturday

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

832A

HRQoL was assessed by comparing subjects in CKD2-5 to subjects in CKD1 at baseline. 

(PRO) questionnaires, including the ADPKD-IS, ADPKD-UIS, BPI, EQ-5D, and SF-12v2.

Duration, or had hypertension, parameters that might be associated with cyst wall stiffness.

Renal TAE was more effective in patients who were younger, had shorter dialysis duration, or had hypertension, parameters that might be associated with cyst wall stiffness.

Renal TAE was more effective in patients who were younger, had shorter dialysis duration, or had hypertension, parameters that might be associated with cyst wall stiffness.

Conclusions: In contrast to the renal phenotype, ADPKD gene type or PKD1 mutation type were not significantly associated with the severity or growth rate of PLD in ADPKD.

SA-PO870 Eligibility for Renal Transcatheter Arterial Embolization in Patients with Autosomal Dominant Polycystic Kidney Disease 

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Background: In patients with ADPKD, massive renal enlargement is a serious problem. Renal transcatheater arterial embolization (TAE) is effective for reducing renal volume, but there is large variation of its effectiveness and the reasons remain unclear. We investigated factors influencing the renal volume reduction rate (RVRR) for one year after TAE.

Methods: All patients with ADPKD who received renal TAE at Toranomon Hospital from 2006 to 2013 were enrolled. We calculated RVRR by the calculation formula (1 - renal volume at each time after TAE / renal volume before TAE)*100, and analyzed factors affecting RVRR. We also compared sequential change of large cysts (>5cm), by classified them into four groups as cysts with wall thickening (>4mm), cyst with acute hemorhage, normal cysts, and the others.

Results: 449 patients (228 men, 221 women, mean age: 57.0 ± 9.1 years) were enrolled. The RVRR at 1 year after TAE ranged from 3.9 to 84.8%, and the least squares mean RVRR calculated using mixed model was 45.73% (95% confidence interval [95% CI]; 44.36 to 47.10%). Multivariate analysis using mixed model revealed that large cysts with wall thickening (regression coefficient: -5.830, 95% CI: -9.140 to -2.520, p=0.0006), age (5years) (-0.087, -1.073 to -0.621, p=0.0001), dialysis duration (12months) (-0.115, -0.193 to -0.037, p=0.0039), systolic blood pressure (10mmHg) (0.283, 0.065 to 0.501, p=0.0109), and number of microcoils used for renal TAE (1.333, 0.784 to 1.882, p<0.0001) had a significant influence on the RVRR. Among large cysts, only cysts with wall thickening did not decrease in volume. Significantly more microcoils were needed to achieve complete renal artery occlusion in patients with younger age and less dialysis duration.

Conclusions: Cyst wall thickening had an important influence on cyst volume reduction. Renal TAE was more effective in patients who were younger, had shorter dialysis duration, or had hypertension, parameters that might be associated with cyst wall stiffness. Renal artery narrowing may occur in older patients or those on longer dialysis, which might contribute to renal TAE being less effective in these patients.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO871 Patient Reported Health Related Quality of Life in ADPKD: Analysis from OVERTURE 

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Background: ADPKD imposes a burden on health-related quality of life (HRQoL). Few studies have systematically examined the impact of renal and extra-renal symptomatology on patient’s HRQoL. The purpose of this analysis was to capture disease specific burden across all disease stages while determining specificity and sensitivity of existing and new HRQoL instruments.

Methods: The impact of disease progression on HRQoL in 3,409 ADPKD subjects involved in the OVERTURE observational study were evaluated by patient report outcomes (PRO) questionnaires, including the ADPKD-IS, ADPKD-UIS, BPI, EQ-5D, and SF-12v2. HRQoL was assessed by comparing subjects in CKD2-5 to subjects in CKD1 at baseline.

Magnitude of change of 0.2, 0.5 and 0.8 standard deviations (SD) represent small, moderate and large effects on HRQoL. Other measures of disease severity, including TKV, were assessed independently.

Results: HRQoL in ADPKD was impacted at different disease stages depending on the sensitivity and specificity of the PRO used. The disease-specific ADPKD-IS scale distinguished physical, emotional and fatigue related burden as early as CKD1. Similarly, the SF-12 PCS scale was able to distinguish burden by CKD3. The SF-12 MCS and EQ5D were not sensitive to disease progression until CKD5. The impact of disease burden prior to ESRD was driven by specific questions focused on physical activity, anxiety, and exhaustion. Subjects were more bothered by the shape of their abdomen in an independent question as early as CKD3 which associated with larger kidney volumes (htTKV > 635mL/m).

Conclusions: Studies to date have had limited success in their attempt to characterize HRQoL in ADPKD patients by using general health surveys. Disease specific instruments better capture the burden experienced by patients in earlier stages of ADPKD prior to gross kidney enlargement and effects associated with ESRD and dialysis.


SA-PO872 Fibroblast Growth Factor 23, Renal Progression and Death in Patients with Autosomal Dominant Polycystic Kidney Disease 


Background: No prospective studies examined fibroblast growth factor 23 (FGF23) and clinical outcomes among individuals with autosomal dominant polycystic kidney disease (ADPKD). We tested the hypotheses that higher serum FGF23 is a risk factor for kidney disease progression and mortality in adults with ADPKD.

Methods: We measured intact FGF23 levels (Kainos) in stored baseline serum samples in 1,002 patients who participated in the HALT-PKD randomized controlled trial of two different blood pressure control strategies. We used Cox proportional-hazards models to examine the associations between continuous levels and quartiles of iFGF23 and the primary composite endpoint of time to a 50% reduction in estimated glomerular filtration rate (eGFR) from baseline, end stage renal disease (ESRD) or death.

Results: At baseline, participants had a mean age of 42 ± 10 years, mean eGFR of 71.4 ± 26.4 mL/min/1.73m², mean serum phosphate of 3.4 ± 0.5 mg/dL, and median (IQR) iFGF23 of 52.6 (38.6 - 73.7) pg/mL. During a median follow-up of 5.6 years, 226 patients (22.6%) reached the composite endpoint. After adjusting for demographic factors, traditional cardiovascular risk factors, baseline eGFR, and randomized treatment group in Cox proportional hazards models, ascending quartiles of FGF23 were associated with a stepwise increased risk for the composite endpoint (HR 1.0 [reference], 1.54 [95% CI, 0.69 - 3.47], 2.92 [CI, 1.58 - 6.19], and 3.41 [CI, 1.61 - 7.22]). Similar results were obtained when FGF23 was examined on a continuous scale (HR 1.94 [95% CI, 1.39 - 2.69] per 1 SD in FGF23 increase).

Conclusions: Higher serum FGF23 is an independent predictor of kidney disease progression and death in adults with ADPKD. Further studies are required to determine the mechanisms underlying these relationships and to test whether interventions that reduce FGF23 levels might be renoprotective.

Funding: NIDDK Support

SA-PO873 Natural History of Polycystic Liver Disease in the HALT ADPKD Cohort 

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Background: Although hepatomegaly in polycystic liver disease (PLD) is common, few studies have evaluated natural history & factors associated with progression. Goal: Examine change in height adjusted liver volume (hltLV) & factors influencing progression in patients in HALT-PKD-A randomized clinical trial.

Methods: Baseiline PLD group (mild (hltLV=1000mL,n=240) moderate (1000-1800mL, n=271) & severe (>1800mL, n=28; 81% female) & follow up hltLVs, quality of life (QOL,SF-36), influence of telmastratn (T) vs placebo (P) on progression were assessed (n=558, age 15-49y, eGFR > 60 mL/min). We assessed factors influencing hltLVs such as treatment group, age, gender, genotype (in separate models) & factors influencing progression over time were examined using linear mixed models.

Results: Annual hltLV growth rates were 0.76, 0.91 & 1.08% (P<NS) in the mild, moderate & severe groups, respectively (figure 1). Neither baseline age or genotype associated with annual hltLV increase. There were strong negative relationships of eGFR (p=0.02) & serum albumin (p=0.003) with hltLV. Prior pregnancy & higher parity (both age adjusted) associated with hltLV but not with progression over time. Increases in BltLV were associated with increased rates of fatigue (weakness (p=0.003) and declines in SF-36 physical functioning over time (p=0.02). Progression was independent of drug assignment (T: 0.90% vs P:1.07% p<NS) & BP target (low 0.81 vs std. 1.15% p=NS).

Funding: PPD, San Diego, CA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Towards Personalised Medicine – Treating a Renal Ciliopathy
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Background: Renal ciliopathies are genetic disorders presenting with nephronophthisis, cystic kidneys or cystic dysplasia. Pathogenesis of ciliopathies may include altered signalling or defective DNA damage response. Due to the huge genetic/phenotypic variability in ciliopathies it is pertinent to explore the most important contributor to individual phenotypes. We investigated disease mechanisms of a patient with Joubert Syndrome aiming to provide a personalised medicine approach to treatment.

Methods: We identified a family with 2 affected siblings with a ciliopathy phenotype. Ciliopathy gene panel sequencing followed by Sanger sequencing and segregation analysis was undertaken to provide a molecular genetic diagnosis. We established Human Urine derived Renal Epithelial Cell (HUREC) cultures from one sibling and a control. Cultured cells where characterised and their response to therapeutic agents quantified.

Results: The siblings exhibited a cerebro-retinal-ciliopathy phenotype with renal corticomedullary cyst formation and progressive renal failure. Panel sequencing followed by Sanger sequencing confirmed biallelic mutations in CEP290 (c.2817G>T, p.K939N; c.2984G>C, p.Q958P*) in both affected patients. The c.2817G>T is located in the last base of exon 25 and is predicted to lead to a splicing defect. There was no difference in mitosis or centriole numbers in control and proband’s cells. Control cells formed spheroids in 3D culture (100%) whilst the proband’s cells showed a defect in spheroid forming index (17%) and absent primary cilia. In the proband cells there was a rescue of spheroid forming index in response to treatment with hedgehog agonists SAG (smoothened agonist) (67%) and purmorphamine (75%) and a rescue of primary cilia.

Conclusions: In a family with a ciliopathy we have confirmed a molecular genetic defect in CEP290. Using HURECS we have characterised, at a personalised medicine scale, the cellular defect. This data suggests that renal ciliopathies may have potential therapeutic targets and investigation through individual HUREC based model is an exciting new development.

Effect of Metformin on the Progression of Autosomal Dominant Polycystic Kidney Disease
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder resulting in end-stage renal disease (ESRD), without an approved treatment. In an animal model of ADPKD metformin therapy resulted in amelioration of cystic renal growth. We sought to determine whether patients with ADPKD and type 2 diabetes treated with metformin had slower progression to ESRD than similar patients treated with other antidiabetic drugs.

Methods: We conducted a population-based cohort study of adult patients with ADPKD and type 2 diabetes between January 1/2000 and December 31/2014. We identified 322 adults with ADPKD and type 2 diabetes, of whom 119 were treated with metformin only and 203 with other antidiabetic agents. Among these we identified 31 subjects treated with metformin only who could be matched for age, sex, race, history of hypertension and coronary artery disease, and baseline renal function to 31 subjects not treated with metformin. The primary outcomes were incident ESRD and all-cause mortality.

Results: The median age of the enrolled participants was 61 years, 45% were women. Approximately 74% and 26% had a history of hypertension and myocardial infarction, respectively. The baseline MDRD-eGFR in participants receiving and not receiving metformin was 49±12 and 47±14 mL/min/1.73m² (p=0.70). After a median follow-up of 4.5 years, incident ESRD occurred in 29% and 16% of those not exposed and exposed to metformin, respectively, with an OR of 2.13 (95% CI 1.10-3.46; p=0.02). Deaths occurred in 32% and 26% of those not exposed and exposed to metformin, with a OR of 1.37 (95% CI 0.5-2.47; p=0.60).

Conclusions: Metformin therapy may slow progression to ESRD in ADPKD adults with type 2 diabetes compared to other antidiabetic drugs. Because metformin has an excellent safety record, a trial to slow the progression of ADPKD in the absence of diabetes is warranted.

Funding: NIDDK Support
Methods: Information about hospitalizations was prospectively collected in the HALT-PKD Studies, 2 multi-center trials involving people with ADPKD and GFR 60 ml/min (Study A) and GFR 25-60 ml/min (Study B). The primary diagnosis was designated after review of discharge summaries and independently adjudicated by a committee.

Results: Total patient years (pyrs) of follow-up in the 558 Study A patients and 486 Study B patients was 3,141 and 2,056. The incidence rates (IRs) of all-cause hospitalization, in Study A and B, respectively, was 67.7 and 123.3 per 1000 pyrs, which compares to 80.3 and 118.0, in respective age-matched general populations (CDC/NHIS National Hospital Discharge Survey, 2010). The IRs in Study A and B, respectively, for cardiovascular-related hospitalizations was 9.9 and 13.6 per 1000 pyrs. The primary diagnosis related complications were lower in ADPKD patients with GFR 60-90 ml/min and higher in patients with GFR 25-60 ml/min. PKD-related complications were more common than cardiovascular related diagnoses as the primary reason for hospitalization in both Study A and B.

Funding: NIDDK Support, Private Foundation Support

SA-PO877

Effect of Statins on the Progression of Autosomal Dominant Polycystic Kidney Disease (the HALT PKD Investigators) Godela M. Brosnahan,1 Kaleab Z. Abebe,2 Frederic F. Rahbari-Oskou,3 Charity G. Moore,4 Kyongtae Ty Bac,5 Robert W. Schrier,6 Jared J. Grantham.7 "Univ of Colorado; "Univ of Pittsburgh; "Emory Univ; "Univ of Kansas.

Background: ADPKD is the most common hereditary disease resulting in end-stage renal failure (ESRD), without an approved treatment. In a small randomized trial comparing pravastatin for 3 years to placebo in 43 patients age 15-82 years, the statin group experienced a slower rate of renal enlargement. No large trial has tested the effect of statins in ADPKD adults.

Methods: We performed a secondary analysis of the HALT-PKD trials, categorizing participants into 3 groups based on statin use: 1) never users, 2) less than 3 y, and 3) at least 3 y of use. For subjects in Study A (n=558, age 15-49 y, eGFR > 60 ml/min/1.73m²) we compared the percent change in height-adjusted total kidney volume (htTKV), in height-adjusted total liver volume (htTLV) and the rate of decline in eGFR between the 3 statin use groups. For participants in Study B (n=486, age 18-64 y, eGFR 25-60 ml/min/1.73m²) we compared time to composite endpoint of death, ESRD or 50% decline in eGFR. Follow-up was 5-8 y.

Results: In Study A only 59 subjects used statins for >3 y and 37 for <3 y. There was no difference in the rate of annual htTKV increase (6.4%, 7.1%, 5.9%; p=NS) or htTLV growth (1.02%, 1.15%, 0.65%; p=NS) between the 3 groups, after controlling for sex, age, and treatment arm. The rate of eGFR decline was faster in group 2 (4.07 ml/min/yr) than in groups 1 and 3 (2.93 and 2.82 ml/min/yr; p=0.015), after adjusting for the more favorable baseline characteristics of group 1 (more females, younger age, higher baseline eGFR). In Study B 118 subjects used statins for >3 y and 76 for <3 y. There was no difference in time to endpoint between the 3 groups.

Conclusions: In this secondary analysis of the HALT PKD trials, statin therapy for 3 years did not slow the rate of renal or liver enlargement or of eGFR decline in ADPKD adults, but these results are limited by the small numbers of statin users in Study A, different statin drugs and doses, and non-randomized allocation to groups.

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SA-PO878

Assessment of a Dosage-Sensitive Mutational Network for PKD in a Large Cohort of Patients with Early and Severe Forms of Polycystic Kidney Disease Carsten Bergmann,1,2 John Devane,2 Steffen Neuber,1 Eva Decker,1 Uyen Tran,1 Oliver Wessely,3 Elisabeth B. Ott,1 'Center for Human Genetics, Bioscientia, Ingelheim, Germany; "Renal Div, Univ Hospital, Freiburg, Germany; "Cellular & Molecular Medicine, Cleveland Clinic.

Background: ADPKD patients with early and severe disease manifestations only make up a minor proportion, but are crucial for a better understanding of PKD. Affected families have a high recurrence risk for babies with a severe clinical course often resulting in perinatal death. Especially in prenatal cases the diagnostic distinction between different forms of PKD and other ciliopathies can be difficult and illustrates the need for more comprehensive genetic testing.

Methods: An accurate genetic diagnosis is crucial for genetic counselling, prenatal diagnostics and the clinical management of patients. To this end, we established a sequence capture based NGS approach targeting 95 genes for cystic and polycystic kidney disease. This includes PKD1, which - due to the presence of pseudogenes - is difficult to test. As an additional advantage over conventional Sanger sequencing we were able to detect copy number variations. The biological significance of some of the detected alleles were subsequently tested in vitro and in vivo studies using a range of animal models including zebrafish, Xenopus and mice to validate some of our findings in terms of a functionally proven dosage-sensitive network.

Conclusions: This study is the most comprehensive analysis performed so far and points towards a general and underestimated concept for the modification of disease gene expression.

SA-PO879

Determinants of Progression in Early Autosomal Dominant Polycystic Kidney Disease - Is It Blood Pressure or Renin-Angiotensin-System Blockade? The HALT PKD Trial Godela M. Brosnahan,1 Kaleab Z. Abebe,2 Charity G. Moore,3 Theodore I. Steinmann,4 Frederic F. Rahbari-Oskou,3 Susan Spillane,1 Kyongtae Ty Bac,5 Robert W. Schrier.6 "Univ of Colorado; "Univ of Pittsburgh; "Beth Israel Deaconess; "Emory Univ.

Background: The HALT PKD Study A (558 subjects age 15-49 years, eGFR > 60 ml/min/1.73m²) showed that intensive control of systolic blood pressure (SBP) to 95-110 mmHg was associated with a slower rate of kidney volume growth compared to standard control (SBP 120-130 mmHg). It is unclear whether this result was due to lower BP per se or to greater blockade of the renin-angiotensin-aldosterone system (RAAS) by allowing higher drug doses in the low BP group.

Methods: In this secondary analysis of HALT PKD Study A categorizing participants into 3 groups based on lisinopril (L) and telmisartan (T) dosage at 4 months, after initial dose titration: 1) high, defined as L ≥ 40 mg + T ≥ 80 mg daily, 2) middle (everyone but high or low) and 3) low, defined as L < 20 mg + T < 40 mg daily. We compared the percent change in height-adjusted total kidney volume (htTKV) and the rate of eGFR decline between the 3 groups during follow-up for 5-8 years.

Results: Participants in the high dose group (n=51) were more likely male and assigned to the low BP arm; they had higher baseline BP and lower eGFR at 4 months than subjects in the mid- (n=272) and low-dose (n=165) groups. After adjustment for age, sex, genotype, target BP (low or standard), and eGFR at 4 months, there was no significant difference in the rate of kidney growth (5.63, 6.40 and 5.83%yr) or eGFR decline (3.00, 2.94 and 3.29 ml/min/yr) between the low, middle and high dosage groups.

Conclusions: In this secondary analysis of HALT Study A young ADPKD adults, a higher dosage of RAAS blocking drugs was not associated with a slower rate of htTKV growth or of eGFR decline, after adjustment for allocation to intensive BP control. Low BP appears to be the main determinant for reducing kidney volume growth.

Funding: NIDDK Support, Other NIH Support - cooperative agreements (grants DK62408, DK62401, DK62410, DK62402, and DK62220) with the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, the National Center for Research Resources General Clinical Research Centers (RR000039 Emory University, RR00558 Mayo Clinic, RR000054 Tufis University, RR000051 University of Colorado, RR23940 Kansas University, and RR02496 Beth Israel Deaconess Medical Center), and the Centers for Translational Science Activities at the participating institutions (RR025008 Emory University, RR024150 Mayo Clinic, RR025752 Tufis University, RR025780 University of Colorado, and RR024989 Cleveland Clinic), Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals Inc donated telmisartan and matched placebo, Merck & Co Inc donated lisinopril, Private Foundation Support
**SA-PO880**

The Short Term Effect of Tolvaptan for CKD Stage 4 Autosomal Dominant Polycystic Kidney Disease  

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Background: In Japan, the treatment of tolvaptan, a V2 receptor antagonist, started from March 2014. Indication criteria of tolvaptan for ADPKD treatment in Japan is adult patients with more than 750ml total kidney volume (TKV) and more than about 5%/year increasing rate of TKV. It is contraindication to use tolvaptan for patients with eGFR<15ml/min/1.73m². It is recommended to reduce dose of tolvaptan for patients with CCR<30ml/min. However, the treatment effect for patients with CKD stage 4 is still unknown. So, we evaluated the short time efficacy of tolvaptan treatment for patients with CKD stage 4.

Methods: Thirteen patients (5 females and 8 males, mean age; 52.5 years) with ADPKD who started tolvaptan at our hospitals from April 2014 to April 2015 were analyzed in this study. Although our standard starting dose of tolvaptan for patients with good renal function is 60mg/day, we administered 15mg/day for patients with eGFR<25ml/min/1.73m² patients. Patients were measured eGFR and TKV at the commencement of treatment and at 1.5 and 6 months later.

Results: The baseline median eGFR and TKV were 21.8 ml/min/1.73m² (range; 17.1-28.9) and 2.810ml (range; 1.031-5.847), respectively. The change of median eGFR from baseline at 1.5 months and at 6 months were -0.36 ml/min/1.73m² (p=0.39) and -1.80 ml/min/1.73m² (p=0.04), respectively. The change of median TKV from baseline at 1.5 months and at 6 months were -13ml (p=0.39) and -12ml (p=0.93), respectively. One female patient and four male patients temporarily stopped their treatment at 3 months and at 6 months because of their eGFR decreased to lower than 15 ml/min/1.73m². Hepatic toxicity, hypernatremia, and the other adverse severe events were not detected.

Conclusions: No severe adverse events were occurred and 85% of CKD stage 4 patients could keep treatment for 6 months without CKD progression. Tolvaptan was safe and tolerable for ADPKD patients with CKD stage 4 in lower dose.

**Funding:** Pharmaceutical Company Support - Otsuka pharmaceutical Co., Ltd., Government Support - Non-U.S.

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**SA-PO883**

Estimation of Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease  

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Background: Measuring total kidney volume (TKV) in autosomal dominant polycystic kidney disease (ADPKD) by magnetic resonance image (MRI) and manual tracing is time consuming. Two alternative MRI methods have recently been proposed to estimate TKV: eTKV (ELLIPSOID) and eTKV (ANNO) which require less time.

Methods: ADPKD patients with a wide range of kidney function were included, if they had an approved T2 weighted MRI. A test set of 10 MRIs was used for assessing the model. The outcome was the change of TKV from baseline (p=0.39) and -1.80 ml/min/1.73m² (p=0.04), respectively. The change of median TKV from baseline at 1.5 months and at 6 months were -13ml (p=0.39) and -12ml (p=0.93), respectively. One female patient and four male patients temporarily stopped their treatment at 3 months and at 6 months because of their eGFR decreased to lower than 15 ml/min/1.73m². Hepatic toxicity, hypernatremia, and the other adverse severe events were not detected.

Conclusions: No severe adverse events were occurred and 85% of CKD stage 4 patients could keep treatment for 6 months without CKD progression. Tolvaptan was safe and tolerable for ADPKD patients with CKD stage 4 in lower dose.

**Funding:** NIDDK Support

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**SA-PO882**

Genetic Background Radically Alters Disease Progression in the Pkd1<sup>RC/RC</sup> Model  

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Background: Studies in ADPKD patients and PKD mouse models have shown that genetic background influences the disease phenotype. Here, we evaluated the phenotype of the homozygous Pkd1<sup>RC/RC</sup> model in three new backgrounds: BalbC, 129S6, and F1 (C57BL6 X BalbC) and compared them to C57BL6.

Methods: To characterize the cystic disease burden, Pkd1<sup>RC/RC</sup> animals were imbeded into three different strains and aged to 3 months (n). At this point time %Kidney Weight/Body W, BUN levels, kidney cyst index were used to compare disease severity.
Corrected Total Kidney Volume (htTKV) for the Future Development of Polycystic Kidney Disease (CRISP III): The Predictive Value of Height

Therapeutic Effects of the Fibrokinase Inhibitor ANG3070 in Polycystic Kidney Disease

SA-PO884

Therapeutic Effects of the Fibrokinase Inhibitor ANG3070 in Polycystic Kidney Disease

SA-PO887

Hepatorenal Fibrocystic Diseases in Children

SA-PO888

Alterations in Renal Oxylipins in Models of Polycystic Kidney Disease: Potential for Cyclooxygenase Inhibition for Disease Treatment

Methods: Participants underwent protocol visits including MR imaging, iohalumate clearance and serum creatinine measurements. Baseline htTKV was evaluated in its capacity to predict later CKD stages both individually and in a multivariable model that includes age, race, gender, and baseline iohalumate clearance. Receiver operator characteristic area under the curves (AUCROCs) were developed for reaching CKD stage 3a, 3b, 4 or 5 after a range of 10 years of follow-up.

Conclusions: Kidney volume measured by MR at a single timepoint is a powerful predictor for the development of advanced stages of CKD over the ensuing 11 years. Consistent with prior analyses, greater kidney volume is strongly associated with higher rates of CKD progression, further supporting the notion that cyst enlargement is the primary cause of GFR loss and kidney failure.

Funding: NIDDK Support

SA-PO884

Therapeutic Effects of the Fibrokinase Inhibitor ANG3070 in Polycystic Kidney Disease

Methods: Male PCK rats (PCK/CrljCrl-pkhd1pck/Crl) were randomized to vehicle or ANG3070 (25 mg/kg, i.P., PO) at 6.5 weeks of age following confirmation of frank disease and sacrificed at 13.5 weeks. Age-matched male Sprague-Dawley rats served as wild-type controls.

Results: ANG3070 has no effect on mean arterial pressure. In PCK rats with diseased kidneys (figure1), randomization to ANG3070 treatment was therapeutic, reducing cyst index, renal interstitial fibrosis (hydroxyproline (HYP)), albuminuria and other urinary biomarkers of renal injury and serum creatinine (* p<0.05).

Funding: Other NIH Support - AR058041-02, Other U.S. Government Support

SA-PO885

Extended Follow-Up of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP III): The Predictive Value of Height Corrected Total Kidney Volume (htTKV) for the Future Development of CKD Stages 3a, 3b, 4 and 5 After Ten Years Follow-Up in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Extended Follow-Up of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP III): The Predictive Value of Height Corrected Total Kidney Volume (htTKV) for the Future Development of CKD Stages 3a, 3b, 4 and 5 After Ten Years Follow-Up in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Funding: Other NIH Support - AR058041-02, Other U.S. Government Support

Conclusions: With ongoing investigational new drug enabling toxicology studies suggesting a large safety index, these data support the continuing development of ANG3070 for PKD, a disease currently without cure. Supported by PR130909 and AR058041-02.

Funding: Other NIH Support - AR058041-02, Other U.S. Government Support

SA-PO885

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Arlene B. Chapman, Chengli Shen, Alan S.L. Yu, Michal Mrug, Frederic F. Rahbari-Oskouei, Vicente E. Torres, Jared J. Grantham, Michael F. Flessner, Kyongtae Ty Bae, Doug Landsittel, Peter C. Harris, William M. Bennett.

Background: Aberrant receptor tyrosine kinase signaling has been implicated in cyst expansion, renal interstitial fibrosis, increased kidney volume and reduced renal function in polycystic kidney disease (PKD). We investigated the effects of a novel, orally bioavailable, small molecule fibrokinase inhibitor, ANG3070, in experimental PKD.

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SA-PO888

Alterations in Renal Oxylipins in Models of Polycystic Kidney Disease: Potential for Cyclooxygenase Inhibition for Disease Treatment

Hepatorenal Fibrocystic Diseases in Children

Methods: Participants underwent protocol visits including MR imaging, iohalumate clearance and serum creatinine measurements. Baseline htTKV was evaluated in its capacity to predict later CKD stages both individually and in a multivariable model that includes age, race, gender, and baseline iohalumate clearance. Receiver operator characteristic area under the curves (AUCROCs) were developed for reaching CKD stage 3a, 3b, 4 or 5 after a range of 10 years of follow-up.

Conclusions: Kidney volume measured by MR at a single timepoint is a powerful predictor for the development of advanced stages of CKD over the ensuing 11 years. Consistent with prior analyses, greater kidney volume is strongly associated with higher rates of CKD progression, further supporting the notion that cyst enlargement is the primary cause of GFR loss and kidney failure.

Funding: NIDDK Support

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Funding: Other NIH Support - AR058041-02, Other U.S. Government Support

SA-PO885

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Methods: Male PCK rats (PCK/CrljCrl-pkhd1pck/Crl) were randomized to vehicle or ANG3070 (25 mg/kg, i.P., PO) at 6.5 weeks of age following confirmation of frank disease and sacrificed at 13.5 weeks. Age-matched male Sprague-Dawley rats served as wild-type controls.

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Funding: Other NIH Support - AR058041-02, Other U.S. Government Support

SA-PO888

Alterations in Renal Oxylipins in Models of Polycystic Kidney Disease: Potential for Cyclooxygenase Inhibition for Disease Treatment

Hepatorenal Fibrocystic Diseases in Children

RuIN Park, Yo Han Ahn, Hee Gyung Kang, Hye Won Park, IL-Soo Ha, Hae Il Cheong.

Methods: Participants underwent protocol visits including MR imaging, iohalumate clearance and serum creatinine measurements. Baseline htTKV was evaluated in its capacity to predict later CKD stages both individually and in a multivariable model that includes age, race, gender, and baseline iohalumate clearance. Receiver operator characteristic area under the curves (AUCROCs) were developed for reaching CKD stage 3a, 3b, 4 or 5 after a range of 10 years of follow-up.

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Funding: Other NIH Support - AR058041-02, Other U.S. Government Support
SA-PO888

Identifying Genetic Modifiers in Severe Polycystic Liver Disease (PLD) by Whole Exome Sequencing (WES) Amriza H. Haighdhi,
Young-Hwan Hwang,
Ning He,
Kairong Wang,
Winnie Y. Chan,
Xuewen Song,
Joost P.H. Drenth,
York P. Pei.

Methods: WES using Illumina HiSeq2000/2500 with SSV4.5 capture kit in 88 patients (24 affected discordant sib-pairs and 7 affected concordant sib-pairs for sPLD and 27 sporadic cases). All sPLD patients had a liver span >25 cm by CT/MRI or >5x normal liver volume. In addition to genome-wide analysis, we performed focused analysis on 168 ER genes (Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare deleterious variants of high and moderate impact as predicted by PolyPhen-2, SIFT, Mutation Assessor, Mammalian and Vertebrate nucleotide-level conservation, and Combined Annotation Dependent Depletion.

Results: Overall, we achieved a mean target coverage of 108X with 90% of targeted exomes having >30X read depth. We identified 4,696 rare deleterious variants that segregated with PLD disease severity in at least one family. From them, we found 7 non ER genes (TTN, DNAH10, DNAH14, HMCN2, NEB, OBSCN and ADAMT29) with rare variants that segregate in 4 to 6 families each and 8 ER genes (TSC1, TSC2, PRKCSH, SEC23C, SEC24D, SEC23B, ENTPD6 and PRKAT2) with rare variants that segregate in at least one family and 3-4 sporadic sPLD cases.

Conclusion: Our data indicate that sirolimus acts fundamentally at the vascular-containing compartment, suggesting that it may decrease the bleeding risk. In addition to its potential benefit as neovascular therapy for large/multiple AMLs undergoing NSS, our findings revealed that the use of sirolimus was safe and reduced surgical complications.

Funding: Government Support - N.U.S.

SA-PO889

TOSCA – Tuberous Sclerosis Registry to Increase Disease Awareness: Renal Manifestations of Tuberous Sclerosis Complex John C. Kingswood,
Anna C. Jansen.

Methods: Patients diagnosed with TSC were enrolled in TOSCA from 170 sites across 31 countries worldwide. Patients will be followed up for up to 5 years with interim analysis performed every year.

Results: Baseline core data from 2093 patients were entered in the registry as of September 30, 2014 (cut-off date for the 2nd interim analysis). Median age at consent was 13 years (range: 0.4-99.9 years). A total of 38 renal abnormalities were reported in 987 (47.2%) patients. Median age at diagnosis of angiomyolipoma was 13 years (0-67). Of the 853 (40.3%) patients with ongoing renal angiomyolipomas, 396 (41.9%) had multiple and bilateral lesions, 329 (34.8%) had single lesions, 40 (4.3%) had lesions >3 cm, 204 (21.6%) had growing lesions. Signs/symptoms associated with renal angiomyolipomas included either individually or in combination with others, were elevated blood pressure (48 [5.1%]), microscopic hematuria (35 [3.7%]), hematuria (47 [5.0%]), impaired renal function (36 [3.8%]), and pain (51 [5.4%]). Renal angiomyolipomas were treated in 274 (27.8%) patients; major treatment modalities included embolization in 78 (38.8%) and mammalian target of rapamycin (mTOR) inhibitors in 78 (28.8%) patients. Other renal features reported were renal malignancy (24 [1.1%]), multiple renal cysts (477 [22.8%]), polycystic kidneys (73 [3.5%]), and impaired renal function (43 [2.1%]).

Conclusion: The prevalence of angiomyolipomas of 47.2% in our cohort corroborates the data of 10-90% in the literature probably reflects their young mean age. Despite this intervention rate was high, emphasizing the need for active surveillance. This is in agreement with the findings of the intervention rate of 11 to 25% in TSC and the fact that the intervention rate was high, emphasizing the need for active surveillance.

Funding: Private Foundation Support

SA-PO890

Siroliimus Reduces Fundamentally the Vascular and/or Muscular Components of Angiomyolipomas and Can Be Neoadjuvant to Partial Nephrectomy in Patients with Tuberous Sclerosis Complex Large Tumors Associated with Surgical Risk Eliesser W. Watanabe,
Fernando I. Yamauchi,
Hilton M. Leao-Filho,
William C. Nahas,
Luiz F. Obuchi.

Methods: In a single blinded, crossover, placebo-controlled dose-response study 12 healthy subjects were treated, in a randomized order, with placebo (isotonic NaCl) or one of three doses of sodium nitrite 40, 120 or 240 mg/kg/hour for two hours. Each examination was preceded by 4 days standardized diet. Subjects were supine and water loaded throughout the day. Before, during and after sodium nitrite administration we measured diastolic, systolic and mean arterial blood pressure, heart rate, plasma renin, angiotensin II and aldosterone, GFR by chromate-EDTA clearance, fractional sodium excretion and urinary excretion rate of nitrate and nitrite (NO3-).

Results: As expected, sodium nitrite increased urinary NO production over 3 to 4 fold as compared to DBP, SBP and MAP, heart rate, plasma renin, angiotensin II and aldosterone, GFR by chromate-EDTA clearance, fractional sodium excretion and urinary excretion rate of nitrate and nitrite (NO3-).

Funding: Pharmaceutical Company Support - Novartis Pharma AG

SA-PO891

The ARPKD Registry Study – Initial Clinical Characterization of a Large ARPKD Cohort Sarah K. Heath,
Kathrin Großmann,
Heiko Billings,
Rudiger Buettner,
Ali Duzova,
Heike Goebel,
Dieter Haffner,
Thomas Illig,
Augustina Jankauskiene,
Mirna Mekahl,
Bruno Ranchin,
Anja Christine Sander,
Sara Testa,
Lutz Thorsten Weber,
Dorota Wicher,
Elke Wuehl,
Franz S. Schafer,
Max Liebau.

Background: ARPKD is an international, mostly European, pro- and retrospective, observational study in both pediatric and adult ARPKD patients to generate a deeply-characterized ARPKD cohort. Using web-based questionnaires regarding patients’ clinical data in combination with associated biobanking and reference histology ARegPKD will characterize long-term ARPKD courses and set roots for future translational research.

Methods: In June 2015 63 centers have registered and more than 130 patients have been included (73% 67.6% male, median age at inclusion 7.6 years, number of follow-up visits up to 17). Here we present data on general patient characteristics, genetic testing, renal and hepatic phenotype putting a special focus on the peri- and postnatal period (perinatal findings, ventilation modalities, sonographical findings, laboratory values).

Conclusion: ARegPKD can act as a natural registry characterizing ARPKD patients in order to provide evidence base for clinical treatment decisions and contribute to the understanding of this severe renal disorder of early childhood.

Funding: Private Foundation Support

SA-PO892

The Effect of Sodium Nitrite on Central and Peripheral Hemodynamics, Vasoactive Hormones, GFR and Sodium Excretion in Healthy Subjects Jeppe B. Rosenbaek,
Safa Al Thawrani, Janni Maiggaard Jensen, Frank H. Mose,
Erling B. Pedersen, Jesper N. Bech.

Background: Recent research has shown that sodium nitrite is readily converted to nitrite oxide (NO) by enzymes in vivo and exerts vasoactive effects. Previous studies based on nitric oxide synthase inhibition indicates a mediator effect of nitric oxide. The purpose of the present study was to examine the effects of sodium nitrite on central and peripheral blood pressure, heart rate, fractional sodium excretion and GFR.

Methods: In a single blinded, crossover, placebo-controlled dose-response study 12 healthy subjects were treated, in a randomized order, with placebo (isotonic NaCl) or one of three doses of sodium nitrite 40, 120 or 240 mg/kg/hour for two hours. Each examination was preceded by 4 days standardized diet. Subjects were supine and water loaded throughout the day. Before, during and after sodium nitrite administration we measured diastolic, systolic and mean arterial blood pressure, heart rate, plasma renin, angiotensin II and aldosterone, GFR by chromate-EDTA clearance, fractional sodium excretion and urinary excretion rate of nitrate and nitrite (NO3-).

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Funding: Pharmaceutical Company Support - Novartis Pharma AG

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
SA-PO083
The Spatial Distribution of Metabolites Determined by Imaging Mass Spectrometry in the Kidneys of Rats Treated with Furosemide

Background: In the kidney, metabolic processes vary among the cortex (COR), outer medulla (OM), and inner medulla (IM), and the concentrations of metabolites are different according to the kidney zones. We aimed to examine the regional differences of the significantly changed metabolites in the kidneys of rats treated with loop diuretics by exploiting the matrix-assisted laser desorption/ionization (MALDI) and imaging mass spectrometry (IMS).

Methods: Osmotic minipumps were implanted in male Sprague-Dawley rats to deliver 12 mg/day of furosemide (s.c.). Vehicle-treated control rats (n = 14) and furosemide-treated rats (furosemide rats, n = 15) were maintained in metabolic cages for 6 d on a fixed daily diet of rat chow (15 g/220 g bw/rat) with free access to water intake. The rats were then killed by cervical dislocation and their kidneys were excised and divided into three parts: COR, OM, and IM. Tissue samples were cryopreserved in liquid nitrogen and lyophilized. The samples were powdered to a fine powder and analyzed by IMS. Next, significant changes of metabolites were identified by IMS and MALDI-TOF/TOF, including choline compounds (choline, phosphocholine, phosphocholine derivatives and GPC), carnitine compounds (carnitine, dehydrocarnitine, acetyl carnitine and acyl carnitine) and betaine. Importantly, the spatial distribution and relative quantitation of identified metabolites were analyzed by IMS. Choline compounds were increased in COR and OM, but decreased in IM from furosemide rats. Carnitine compounds were increased in COR and IM in furosemide rats. Betaine and GPC were decreased in OM and IM in furosemide rats.

Conclusions: Together, IMS applied to the kidney sections successfully provided the spatial distribution and relative quantitation of significantly changed metabolites in the kidneys of furosemide rats.

Funding: Government Support - Non-U.S.

SA-PO084
Bicarbonate Supplementation Improves Vascular Function in Patients with Chronic Kidney Disease: A Pilot Study
Jessica B. Kendrick, Emily Decker, Kristen L. Nowak, Michel Conlon, 1Univ of Colorado Denver, Aurora, CO; 2Denver Health Medical Center, Denver, CO.

Background: Metabolic acidosis, as reflected by a low serum bicarbonate level, is associated with increased risks of endothelial dysfunction, hypertension and death. Metabolic acidosis induces inflammation and endothelin-1, both of which contribute to vascular dysfunction. Whether alkali therapy improves vascular function in patients with chronic kidney disease (CKD) is unknown.

Methods: Seven subjects (5 men and 2 women) with stage III/IV CKD and serum bicarbonate level 16-22 mEq/L completed a pilot, prospective, open-label, crossover study of 14 weeks duration examining the effect of oral sodium bicarbonate supplementation on endothelial function. The primary endpoint was change in brachial artery flow mediated dilation between treatment and control conditions. Each period was 6 weeks in duration with a two-week washout period in between. Patients were treated with oral sodium bicarbonate tablets two to three times per day for goal serum bicarbonate of ≥ 23 mEq/L.

Results: The mean (SD) age and GFR at enrollment was 59 (3.3) years and 21.9 (2.6) ml/min/1.73m2, respectively. The mean (SE) serum bicarbonate level increased after sodium bicarbonate administration from 18.4 (0.7) mEq/L to 23.7 (0.9) mEq/L. The mean (SE) serum bicarbonate level did not change in the control arm. Blood pressure control was similar in both arms. Brachial artery flow mediated dilation was 42.0% 45.0% after 6 weeks of sodium bicarbonate replacement (3.78 ± 1.58 to 5.35 ± 1.31%) whereas it decreased by 14% during control conditions (3.51 ± 0.53 to 3.01 ± 0.91%).

Conclusions: Bicarbonate supplementation in patients with CKD and low serum bicarbonate levels resulted in improved vascular function. Large randomized trials need to be performed to determine if treatment with alkali therapy can reduce cardiovascular disease in patients with CKD.

Funding: NIDDK Support

SA-PO085
Tenofovir-Related Distal Tubular Acidosis in HIV Infected Patients
Tamar Cunha, Talita Mourao Loyola, Carlos Perez Gomes, Maurilo Leite. Dept of Nephrology, Federal Univ of Rio de Janeiro, Rio de Janeiro, Brazil.

Background: Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor extensively used worldwide and is now the most prescribed drug on Highly Active Antiretroviral Therapy (HAART). TDF toxicity is mainly targeted at the proximal tubule, and tubular abnormalities can cause Fanconi Syndrome or acute kidney injury. Despite this, there are no studies evaluating other types of tubular toxicity. This study evaluated the presence of distal renal tubular acidosis (dRTA) in HIV patients on HAART.

Methods: Sixty one HIV patients older than 18 years on treatment with HAART for more than 3 months and GFR estimated by CKD-EPI equation greater than 45 ml/min/1.73m2 were evaluated. They were divided into two groups: 31 used HAART that included TDF and 30 used HAART with no current or previous use of TDF. They were submitted to fluid restriction for 12 hours and received 40mg of furosamide and 0.1mg of diosmin, following a urine collection test protocol similar to that of de Paulo et al (2007). We measured serum bicarbonate and the following parameters: hourly urine pH (0 to 4h) by potentiometry, urinary ammonium (unNH4+) by spectrophotometry and urinary titratable acidity (uTA) by NaOH (0h and 4h).

Results: dRTA was established when the urinary pH was lower than 5.3 in all measurements.

Conclusions: There was no significant difference between the groups in terms of age, gender, ethnicity, CD4 count or eGFR. The prevalence of dRTA was 6% in the group without TDF and 26% in TDF group (p = 0.04). In both groups, patients without dRTA showed increase in unNH4+ (p = 0.05 and p = 0.009, respectively) and in uTA (p = 0.94 and p = 0.05, respectively), unlike patients diagnosed with dRTA who showed an increase neither in unNH4+ (p = 0.44 and p = 0.34, respectively) nor in uTA (p = 0.52 and p = 0.11, respectively). In all cases with dRTA, the serum bicarbonate was normal, featuring an incomplete presentation.

Conclusions: The prevalence of incomplete dRTA in patients using TDF was significantly higher than the group not using the drug. This is the first study suggesting a possible association between TDF and dRTA. Subsequent studies will be necessary to corroborate this hypothesis.

SA-PO086
Comparison of Acid-Base Disorder Between Patients Undergoing Ileal Neobladder and Ileal Conduit
Jung-wooh Noh, Eunjung Kim, 2Jae-Ryong Koo. 1Internal Medicine, Nephrology, Hallym Univ Medical Center; Hallym Kidney Research Inst, Seoul, Korea; 2Internal Medicine, Nephrology, Hallym Univ Medical Center; Hallym Kidney Research Inst, Seoul, Korea; 3Internal Medicine, Nephrology, Hallym Univ Medical Center, Hallym Kidney Research Inst, Seoul, Korea.

Background: Since the 1980s, the orthotopic ileal neobladder(IBN) has been as a new option by eliminating the need for a cutaneous stoma and opeundra appliances of ileal conduit(IC). Although this method has improved patients’ quality of life, frequent incidence of metabolic acidosis(MA) have been reported. We compared occurrence of MA in INB group to IC group, and searched for risk factors affecting MA.

Methods: We conducted a retrospective study in 55 patients who underwent radical cystectomy and urinary diversion from January 2001 to December 2014 at Hallym University Medical Center. Patients who have any illness such as severe pulmonary disorder, take any medication that could lead to MA and sepsis were excluded. Acid-base balance and renal function were compared between INB and IC groups. MA was defined as a venous sample bicarbonate level of less than 21 mmol/L.

Results: MA was detected in 74.2% and 69.7% within 7 days(p=0.64), and in 31% and 14.8% at 1 month(p=0.1) after operation in INB and IC group. But cases on bicarbonate therapy were significantly more in INB group(p=0.02). Serum HCO3 levels(p=0.05) and base excess(p=0.02) were significantly lower in INB group in spite of more cases on bicarbonate therapy. Acute kidney injury(AKI) at 1 month was higher in INB group(p=0.008). Serum creatinine concentrations were significantly correlated with bicarbonate levels. Multiple logistic analysis showed that 1 mg/dl increase of serum creatinine level result in a 5.38-fold higher risk of MA (95% confidence interval, 1.14-25.3; P = 0.03). Patients without AKI, MA was detected in 13.5% in INB group, 12% in IC group at 1 month(p=1.0).

Conclusions: Despite there being no statistical difference, INB group may more easily develop MA compared with IC group especially in patients with elevated serum creatinine concentrations. In addition, a close association between the serum creatinine level and the degree of MA was observed in both groups.

Funding: Private Foundation Support

SA-PO087
Screening for Hyperlactatemia: Relationship Between the Anion Gap and Serum Lactate in Hypovolemic Shock
Richard M. Treger, 1Tristan Grogan, 2Eunjun Cho, 2Craig Anderson, 2Scott Budman. 1Nephrology, VHAAGL, LA, CA; 3 Medicine and Statistics Core, UCLA, LA, CA; 4 Emergency Medicine, UCI, Irvine, CA.

Background: In lactic acidosis (LA), a discrepancy between the increase in serum anion gap (AG) and serum lactate concentration has been noted. Previous studies evaluated patients in the Intensive Care Unit with established LA. No study has examined the relationship between AG and serum lactate within the first hour of the development of LA, specifically the sensitivity and specificity of an elevated AG for predicting hyperlactatemia.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
838A
Methods: Data were obtained prospectively from adult trauma patients at a single level 1 trauma center. Venous samples were drawn prior to initiation of intravenous fluid resuscitation.

Results: 117 patients with elevated serum lactate levels (>2.1 mmol/L) were included. The sensitivity of an elevated AG (>10) to reveal hyperlactatemia was only 41% whereas specificity was 84%. Sensitivity improved if the upper limit of normal AG was lowered and with increasing levels of serum lactate. (Table 1). The correlation between the AG and serum lactate level yielded an R² of 0.30 (p < 0.001) and the slope of this relationship was 0.29 ± 0.58 (95% confidence interval 0.23-0.35).

Table 1: Sensitivity and specificity from use of the AG as an indicator of hyperlactatemia for specific AG and lactate level thresholds

<table>
<thead>
<tr>
<th>Sensitivity/Specificity</th>
<th>Threshold for increased lactate concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>0.920.25</td>
</tr>
<tr>
<td>&gt;5</td>
<td>0.960.15</td>
</tr>
<tr>
<td>&gt;8</td>
<td>1.000.14</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1.000.14</td>
</tr>
<tr>
<td>Threshold for Anion Gap</td>
<td>&gt;8</td>
</tr>
<tr>
<td>&lt;8</td>
<td>0.740.47</td>
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<tr>
<td>&lt;10</td>
<td>0.690.39</td>
</tr>
<tr>
<td>&lt;12</td>
<td>0.880.37</td>
</tr>
</tbody>
</table>

Conclusions: Within the first hour of the development of LA due to hypovolemic shock, the AG was not a sensitive indicator of an elevated serum lactate level, but it was fairly specific. The sensitivity and specificity of the AG as an indicator of hyperlactatemia is consistent with prior studies examining later stages of LA. The AG increased to a greater extent than the serum lactate and approximately 70% of the change in serum lactate. Our results suggest that other anions contribute to the AG in LA.

SA-PO989

The ∆ Anion Gap/∆ Bicarbonate Ratio in Early Lactic Acidosis: Time for Another Delta?

Background: The ratio of Δ anion gap and Δ bicarbonate (ΔAG/ΔHCO₃) is used to detect co-existing acid-base disorders in patients with high AG metabolic acidosis. Classic teaching holds that in lactic acidosis (LA), the ΔAG/ΔHCO₃ is 1:1 within the first 60 minutes of onset (despite limited human data) and subsequently rises to 1.8-2.1. This study examined the ΔAG/ΔHCO₃ within the first hour of the development of LA.

Methods: Data were obtained prospectively from adult trauma patients at a level 1 trauma center. Venous samples were drawn prior to intravenous fluids.

Results: 108 patients were included. 63 patients had normal serum lactate levels (≤2.1 mM) with a mean AG of 7.1, the value used to calculate subsequent ΔAG values. ΔAG/ΔHCO₃ was calculated for 45 patients who had elevated serum lactate levels (>2.1 mM). The mean ΔAG/ΔHCO₃ for all patients with elevated serum lactate levels was 1.36 (SD 1.40). The correlation between ΔHCO₃ and AG showed a 95% prediction interval of ±6.15 (Figure 1).

Figure 1: Correlation between ΔHCO₃ and ΔAG

Conclusions: The mean ΔAG/ΔHCO₃ was 1.86 within the first hour of the development of LA due to hypovolemic shock, confirming a small prior human study. This contradicts the traditional belief that in LA the ΔAG/ΔHCO₃ is 1:1 within the first 60 minutes. The classic 1:1 stoichiometry is based on animal models (in which lactic acid is infused into the extracellular [EC] space, facilitating EC buffering of protons by bicarbonate), while our results demonstrate a higher initial ΔAG/ΔHCO₃ ratio in early endogenous LA in humans (which originates intracellularly, resulting in intracellular buffering of protons while lactate is predominantly distributed in the EC fluid). The wide 95% prediction interval suggests that ΔAG/ΔHCO₃ should be used cautiously in the diagnosis of mixed acid-base disorders.

SA-PO899

Blood Lactate as a Predictor for Mortality in Sepsis Patients with Lactic Acidosis Treated Sodium Bicarbonate: A Retrospective Analysis

Background: Recent studies have reported that blood lactate level in the critically ill patients is associated with in-hospital mortality, but the use of lactate level to monitor and guide therapy remains under investigation. In this study, we evaluated the efficacy of blood lactate level as a predictor for mortality in sepsis patients with lactic acidosis treated with sodium bicarbonate.

Methods: We conducted a single center analysis from May 2011 through April 2014. We retrospectively analyzed 109 sepsis patients with lactic acidosis treated with sodium bicarbonate.

Results: Among the 230 patients with lactic acidosis treated with sodium bicarbonate, we finally included 109 patients (47.4%) with lactic acidosis caused by sepsis. The non-survivors had lower albumin levels (P<0.009), higher SOFA and APACHE II scores (P=0.002, P=0.047, respectively), and higher blood lactate level at 6 hours, 24 hours, and 48 hours after checking the initial lactate level (P=0.002, P<0.001, P=0.001, respectively). In particular, decrement of at least 10% in lactate clearance for the first 6 hours, 24 hours, and 48 hours of treatment were more dominant in non-survivors than survivors. Lactate clearance at 6 hours, 24 hours, and 48 hours was significantly associated with mortality after adjustment for confounding variables, including age, gender, CRP, albumin, SOFA and APACHE II scores, ventilator care, CRRT, and use of inotropic (HR: 2.201, 95% CI: 1.197–4.046, P=0.011; HR: 3.948, 95% CI: 1.269–12.281, P=0.018; HR: 4.970, 95% CI: 1.679–14.710, P=0.004, respectively).

Conclusions: Serial blood lactate levels monitoring is useful in terms of predicting mortality since only 12% of the initial lactate and/or maximum lactate levels in sepsis patients with lactic acidosis treated with sodium bicarbonate.

SA-PO900

D-Lactate: It’s All In the Gut

Background: D-Lactic acidosis is a rare form of lactic acidosis that can occur in patients with short bowel syndrome.

Methods: 88 yo M with PMH significant for HTN and small bowel obstruction s/p subtotal small bowel resection presented to the ED with complaints of nausea, vomiting, constipation, loss of appetite, altered mental status and decreased urinary output.

On admission:

Vitals: Blood pressure: 115/68 mmHg, Pulse: 80/min, Temperature: 98.5 F and SpO2: 92%.

Examination: Distended abdomen with no peripheral edema.

Imaging: CT abdomen revealed dilated bowel loops but no bowel obstruction or free air in the abdomen/pelvis.

Labs: Na: 134mmol/L, K: 4.5mmol/L, Cl: 108mmol/L, CO₂: 16mmol/L, BUN: 45mg/dl, Creatine: 1.6mg/dl and Albumin 2.3g/dl. ABG: pH: 7.42, pCO₂: 31mmHg, HCO₃: 39mmol/L. He was found to have anion gap metabolic acidosis with a non-anion gap metabolic acidosis. Venous lactate: 1.11 mmol/L (Normal 0.5-2.2 mmol/L). Serum D-lactate was drawn revealing an elevation at 4.15mmol/L – thus confirming the diagnosis of D-lactic acidosis.

Treatment: Patient received IV fluids with bicarb. PO Flagyl was started and constipation was also treated. His neurological status along with his acidosis subsequently improved.

Conclusions: The diagnosis of D-lactic acidosis should be promptly considered in patients with malabsorptive disorder such as short bowel syndrome or following a jejunocolic bypass especially when no other cause of anion gap metabolic acidosis is found. Diagnosis is confirmed by a special enzymatic test measuring serum D-Lactate. Treatment involves a low carbohydrate diet, sodium bicarbonate infusion to correct acute acidemia and antibiotics to minimize D-lactate producing bacteria.

SA-PO901

Customized Base Solutions for Treatment of Acute Acidosis

Background: Acute acidosis is associated with cell dysfunction and increased mortality. Intravenous administration of hypertonic sodium bicarbonate (NaHCO₃) does not improve cellular function or clinical outcome. This is attributed to undesirable generation of CO₂, which decreases intracellular pH, and also to undesirable osmotic stress. Thus, designing a base that can raise pH without generating CO₂ or producing osmotic stress would address an unmet need.

Conclusions: The diagnosis of D-lactic acidosis should be promptly considered in patients with malabsorptive disorder such as short bowel syndrome or following a jejunocolic bypass especially when no other cause of anion gap metabolic acidosis is found. Diagnosis is confirmed by a special enzymatic test measuring serum D-Lactate. Treatment involves a low carbohydrate diet, sodium bicarbonate infusion to correct acute acidemia and antibiotics to minimize D-lactate producing bacteria.
Methods: Theoretical modeling has been performed using Mathematica software to determine equilibrium ion concentrations in mixed strong-weak base solutions. If these solutions have a significant proportion of strong base yet lower concentration, they are predicted to raise blood pH without increasing CO₂ or producing large osmotic stress. Strong bases examined include sodium carbonate (Na₂CO₃) and sodium hydroxide (NaOH); these were mixed with NaHCO₃. Acid-base parameters were measured in acidified canine blood mixed with the base solutions in a closed system using a blood gas analyzer. Treated blood was examined using an optical microscope.

Results: A near-isotonic base solution containing Na₂CO₃; NaHCO₃ at a ratio of 3:1 is predicted to raise blood pH without increasing CO₂ or causing osmotic stress. Addition of this base to acidified blood raised blood pH while reducing CO₂. By contrast, NaHCO₃ raised blood pH, but also generated CO₂. Examination of red blood cells exposed to the former 3:1 solution revealed no evidence of osmotic stress. Mixed base solutions of NaOH and NaHCO₃ are also promising as a lower sodium alternative.

Conclusions: Mixed strong-base solutions, rather than hypertonic NaHCO₃, can raise blood pH and serum bicarbonate levels, minimize osmotic stress, and limit CO₂ generation. A 3:1 mixture of Na₂CO₃; NaHCO₃ well below 1 M concentration appears to be effective in this regard.

SA-PO902

Chloride Alterations in Hospitalized Patients: Prevalence and Outcome Significance Qi Ouan, Charat Thongprayoon, Wisit Cheungpasitporn. Medicine / Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Background: Chloride (Cl) plays a fundamental role in the maintenance of serum osmotic pressure, acid-base balance, and cellular health. Cl channels are expressed in almost all cells in the body. Dysfunctions in the Cl channel result in a broad spectrum of diseases. Cl alterations in hospitalized patients have not been comprehensively studied in recent years.

Methods: We conducted a retrospective study of adult (>18 years old) hospital admissions at Mayo Clinic over a period of three years (2011 to 2013). Patients without admission Cl (either at admission or measured during hospitalization) were excluded. Outcome measures included all-cause mortality, length of hospital stay and discharge disposition.

Results: 76,719 unique patients from a total of 147,358 hospital admissions were enrolled. 55,523 (72.4%) had repeat Cl measurements within 48 hours. Admission serum Cl in the range of 105-108 mmol/L was found to be optimal based on hospital mortality. 60.6% (n=48,999) had admission Cl>105 mmol/L, and 13% (n=11,999) >108 mmol/L. Cl<100 or >108 mmol/L independently predicted poor outcomes including hospital death, longer length of hospital stay, and being discharged to a care facility. 17.1% (n=13,089) of the patients had anion gap >2+ mmol/L; their hospital mortality, when compared to those with anion gap ≤2 mmol/L, worsened progressively with rising Cl. Further examination of Cl evolution within 48 hours of admission showed Cl increase to be an independent predictor for hospital mortality. Further, the magnitude of Cl increase was inversely associated with the days of patient survival.

Conclusions: Non-optimal serum Cl values are common in hospitalized patients. Cl alterations are independent predictors for poor clinical outcomes. Post-admission Cl increase not only predicted hospital mortality but also inversely correlated with length of patient survival. These results indicate that more attention should be paid to Cl value. Further prospective and randomized studies are needed to determine whether avoidance of post-admission Cl increase would improve patient survival.

SA-PO903

A Retrospective Review of Paediatric Patients with Bartter and Gitelman Syndrome Patrick Walsh, Marc Bienias, Detlef Bockenhauer. ICH, UCL, London, United Kingdom.

Background: Bartter and Gitelman syndrome are rare autosomal recessive disorders of renal salt handling. They are characterized by disturbed electrolyte and acid-base homeostasis with potentially severe complications. Currently little is known about the long-term disease course and best treatment is controversial. We performed a retrospective case review to investigate the long-term disease course of patients with a diagnosis of Bartter/Gitelman syndrome.

Methods: Demographic and Laboratory data was recorded at presentation, and ages 1,2,3,4,5,10 and 15.

Results: 42 patients with a genetic diagnosis of Bartter/Gitelman were reviewed with a median follow up of 7.85 years (Range 0 - 18 years).

<table>
<thead>
<tr>
<th>Geno-type</th>
<th>Number of patients</th>
<th>Age at Presentation</th>
<th>Gestational Age</th>
<th>Nephrocalcinosis (% of patients)</th>
<th>GFR &lt;90% at 1 year</th>
<th>Albuminuria (&gt;2.5 Fe/moles 3.5 Mg/mmol)</th>
<th>Average Height at last follow-up (Z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartter</td>
<td>14</td>
<td>10.8 years</td>
<td>30.3</td>
<td>30.1</td>
<td>2.4</td>
<td>0.2</td>
<td>-1.2</td>
</tr>
<tr>
<td>Gitelman</td>
<td>11</td>
<td>5 years</td>
<td>39.4</td>
<td>37.4</td>
<td>4.7</td>
<td>0.9</td>
<td>-0.93</td>
</tr>
</tbody>
</table>

Bartter &2 presented earliest with prematurity and deranged electrolytes. All of the Bartter 1 patients and 70% of Bartter 2 had evidence of nephrocalcinosis on their first ultrasound. Hypomagnesaemia (<0.7mmol/L) was seen in 11/14 Bartter 3 and 8/11 Gitelman patients. Hypocalciuria developed over time and was seen earlier in Bartter 3 (3.8 years) than in Gitelman (7.9 years). Obvious complications of hypokalaemia were only seen in one patient with Bartter 3 (despite potassium levels <2.5mmol/L in 10 patients) in the form of hypokalaemic paralysis; he was admitted twice at ages 2 and 3 (Potassium 7 & 1.5 respectively). Decreased GFR was present in all Bartter 1 and 90% of Bartter 2 at last follow-up. 3 patients with Bartter 3 developed nephrologic renal proteinuria and one demonstrated biopsy evidence of FSGS.

Conclusions: The overall prognosis during childhood was good. Final heights were within the normal range and no child developed ESRD. Albuminuria was common in Bartter 3, indicating the need for long-term monitoring of renal function. Interestingly, hypomagnesaemia is often absent at presentation and develops over time in both Bartter 3 and Gitelman.

SA-PO904

Urine Calcium to Magnesium Ratio Aids to Diagnose Gitelman’s Syndrome without Hypocalciuria and Receiving Intravenous Magnesium Administration Chih-Jen Cheng,1,2 Shih-Hua P. Lin,1,2 Ming-Tso Yan,1,2 1-Tri-Service General Hospital; 2National Defense Medical Center; 3Cathay General Hospital.

Background: Although hypocalciuria is widely used to distinguish Gitelman’s syndrome (GS) from Bartter syndrome (BS), several patients with GS actually have not hypocalciuria and may be clinically misdiagnosed as BS. Intravenous magnesium administration to correct hypokalaeemia, another distinct finding in GS can significantly enhance urine calcium excretion and unmask the preexisting hypocalciuria. Because renal Mg²⁺ wasting is characteristic in GS, we hypothesize that urine Ca²⁺/Mg²⁺ ratio may be superior in diagnosing GS.

Methods: One hundred forty three Taiwanese GS patients (M:F = 87:56, age 25 ± 10) with definite SLC12A3 mutations was enrolled. Nine BS patients with CLCNKB mutations and 15 healthy subjects were enrolled as disease and normal control, respectively. Intravenous MgSO₄, was administered (elemental Mg 0.35 mmol/kg) in 8 GS patients with hypocalciuria. Relevant blood laboratory and at least two urine collection for all electrolytes excretion were determined. Hypocalciuria was defined as urine Ca²⁺/Cr ratio less than 0.1 mmol/mmol.

Results: Fourteen (9.8%) of 143 GS patients did not have hypocalciuria (Ca²⁺/Cr ratio ≥ 0.28 ± 0.09 mmol/mmol) and exhibited no significant difference in blood parameters compared with GS patients without hypocalciuria. Although their urine Ca²⁺/Cr ratio was significantly lower than that in CBS (0.51 ± 0.18 mmol/mmol), there was still overlapping between them. Notably, urine Ca²⁺/Mg²⁺ ratio was significantly lower in GS than CBS without overlap (0.46 ± 0.12 vs 1.57 ± 0.53 mmol/mmol, p<0.001). Acute MgSO₄ administration in GS patients markedly enhanced urine Ca²⁺ excretion (Ca²⁺/Cr ratio 0.05 ± 0.01 to 0.64 ± 0.01 mmol/mmol, p<0.001). However, urine Ca²⁺/Mg²⁺ ratio (0.21 ± 0.01 mmol/mmol) remained much lower than healthy subjects (1.35 ± 0.63 mmol/mmol, p<0.001) and CBS.

Conclusions: Urine Ca²⁺/Mg²⁺ ratio may be a good index to help diagnose GS without hypocalciuria and even receiving intravenous Mg²⁺ administration.

SA-PO905

A Blunted Response to Thiazide Diuretics Is Not Specific for Patients with Gitelman Syndrome Anneke Bech, Jack F. Wetzels, Tom Nijenhuis. Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: In Gitelman syndrome (GS), a defective sodium-chloride co-transporter (NCCT) in the distal tubule classically leads to hypokalaemia and hypomagnesaemia. A challenge with thiazide diuretics, testing the functional presence of NCCT, has been shown to differentiate GS from Bartter syndrome (BS) and normal controls. However, the performance of the thiazide test in renal magnesium wasting disorders other than GS and BS has not been studied.

Methods: Eleven patients who presented to our clinic between 2010-2014 with renal magnesium wasting and in whom a thiazide test was performed were included. An abnormal test result is defined as a maximal change of fractional chloride excretion (ΔFECl) < 2.3% [Colussi 2007]. The thiazide test in eight volunteers in our clinic showed a mean maximal ΔFECl 3.12 ± 0.48% with the lowest value being higher than 2.3%. Additional DNA mutation analyses were performed.

Results: Three patients had a mutation in SLC12A3 (GS), one patient had a compound mutation in CLCNKB and KCNJ1 (BS), 1 patient had a mutation in FXYD2 and five patients had a deletion of one HNF1β allele. The patients with GS showed a blunted response, the patient with BS showed a normal response, the patient with FXYD2 mutation showed a blunted response and the patients with HNF1β mutations showed different responses to thiazide diuretics.
SA-PO907

Impact of Hydration Status, Assessed by Bioelectrical Impedance Vector Analysis, on Mortality in Critically Ill Patients

Sara Samoni,1,2 Valentina Vigo,1 Luis Ignacio Bonilla,1 Gianluca Villa,1 Silvia De Rosa,1 Federico Nalesso,1 Fiorenza Ferrari,1 Alessandra Brendolan,1 Carlo Donadio,1 Claudio Ronco.1 1IRRI, Vicenza; 2‘Sant Anna School of Advanced Studies, Pisa; ‘Univ of Pisa, Pisa.

Background: Clinical trials have shown a positive correlation between fluid overload and adverse outcomes in pts admitted to intensive care unit(ICU).Currently,there is not a non-invasive method that can provide an accurate and timely assessment of whole body hydration status.Our aim was to evaluate the impact of hydration status,assessed by bioelectrical impedance vector analysis(BIVA),on ICU mortality in critically ill pts.

Methods: This is a prospective,dual-center study.We included 125 ICU pts with an ICU stay of 72 hrs or more.Anthropometric,medical history and laboratory data were collected.

Assessment of hydration status was performed by BIVA,using a single frequency analyzer,at the baseline and daily for a period of 72-120 hrs.Pts were considered normohydrated(NH) or hyperhydrated(HH) if BIVA hydration level was 72.7%-74.3% or >74.3% of fat-free body mass,respectively.

Results: The logistic regression analysis performed found a significant correlation between ICU mortality and maximum hydration level reached in observation period,either in patients with or without acute kidney injury(p<0.001).

SA-PO908

Sleep-Disordered Breathing Is Not Associated with Body Fluid Volume in Chronic Hemodialysis Patients

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Background: Sleep-disordered breathing (SDB), characterized by nocturnal intermittent hypoxia, is frequent in patients with chronic hemodialysis (CHD). Fluid retention may promote SDB in these patients, but the detailed information is lacking.

Methods: Eighty-eight CHD patients in Nasu-Minami Hospital and Japanese Red Cross Koga Hospital were included in this study (male: 62.1%, age: 68.1 ± 11.5 years, body mass index: 21.7 ± 3.1, duration of CHD: 5.3 ± 5.9 years, diabetes mellitus: 50.0%).

Overnight pulse oximetry and bioimpedance spectroscopy (InBody) for the assessment of body fluid volume were performed in the CHD patients.

Results: Sixty patients (68.2%) were classified into the SDB group (mild SDB 30.8%, severe SDB 37.2%). Body mass index (BMI) was significantly higher in the SDB group (24.3 ± 3.0 vs 22.9 ± 3.2, P < 0.05). After adjusting for age, gender, diabetes mellitus, hemoglobin and serum albumin in a logistic regression analysis, SDB was independently associated with increased BMI (odds ratio 1.23, 95% confidence interval 1.01–1.48). Total body water, intracellular water and extracellular water were similar among the three groups.

Conclusions: Our findings confirm and expand literature data about the correlation between hyperhydration and ICU mortality.Despite the importance of this problem,there are currently few methods to assess hydration status in critically ill pts.BIVA has been shown to be safe,non-invasive,easy to use and it may predict mortality,thus we suggest its routinely use in ICU pts.Randomized clinical trials are needed to define the precise role of BIVA in the goal-directed fluid management of critically ill pts in ICU.

SA-PO906

Assessment of Hydration Status by Bioimpedance Spectroscopy in Peritoneal and Hemodialysis Patients from a Single Center

Sara Samoni,1,2 Luis Ignacio Bonilla,1 Carla Estremaduroy,1 Alessandra Spinelli,1 Salvador Roberto Lopez,1 Faqz Husain-Syed,1 Carlo Crepaldi,1 Alessandra Brendolan,1 Claudio Ronco.1 1IRRI, Vicenza; 2‘Sant Anna School of Advanced Studies, Pisa.

Background: Fluid overload(FO) is frequent in peritoneal dialysis(PD) and hemodialysis(HD) pts.Due to the identified correlation between systolic blood pressure(SBP) and FO, some conditions,i.e.vascular stiffness and heart failure,can cause a significant proportion of pts to fall out from this model.Our aim was to assess the relationship between hydration status(HYD) and SBP in PD and HD pts.

Methods: We enrolled all DP and HD pts of our center.HYD was evaluated by bioimpedance spectroscopy using Body-Composition-Monitor(BCM Fresenius Medical Care) and expressed as means of 100-140,>140,<100 mmHg,respectively.Considering both parameters, we subdivided the cohort into 9 groups.Continuous variables were expressed as means ± SD for normally distributed data and compared with t-test.

Results: We enrolled 188 pts, 120 DP, 68 HD pts.Mean SBP was 141 ± 22 mmHg, respectively, Mean ADTH was 2.2 ± 3.1 in PD and 1.6 ± 3.9 L in HD pts.Among NSBP, the percentage of HH pts was significantly higher in PD than HD pts (p < 0.04) while among HSNB, the HD pts were more HH than PD pts (p < 0.02).

Conclusions: A blunted response to thiazide diuretics is not specific for GS and can also be found in other renal magnesium wasting disorders,such as caused by mutations in FXYD2 or HNF1β. Still, the thiazide test could prove to be a valuable tool for research and phenotyping patients, and increase our understanding of the pathophysiological processes and the interrelationship between transcription factors, transporters and ion channels.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO909

Association Between Brain Natriuretic Peptide and Fluid Volume Imbalance Between Intra- and Extracellular Water in Patients with Chronic Kidney Disease

Yasushi Ohashi, Reibin Tai, Toshiyuki Aoki, Shizuka Kobayashi, Atsushi Aikawa, Ken Sakai. Dept of Nephrology, School of Medicine, Faculty of Medicine, Toho Univ; Tokyo, Japan.

Background: Maldnourished and elderly patients with chronic kidney disease (CKD) may be susceptible to a extracellular fluid volume overload due to a decreased intracellular volume capacity. We assume that excessive fluid volume is redistributed on the basis of the basic fluid volume balance when they are exposed to fluid accumulation.

Methods: Using bioimpedance analysis, body fluid composition was measured in 129 patients with CKD from 2013 to 2015 and was separated into three components - (a) free water mass consisting of muscle, fat, and minerals, (b) intracellular water (ICW) content, and (c) extracellular water (ECW) content. Participants also measured brain natriuretic peptide levels at the time of the body fluid composition measurement. The relationship between the ratio of ECW to ICW and brain natriuretic peptide was examined.

Results: Patients with higher log-transformed plasma level of brain natriuretic peptide were more likely to be older and have lower body mass index (BMI), serum filtration rate (GFR), and serum albumin levels and higher proteinuria. In body fluid composition analysis, the brain natriuretic peptide levels increased along with a decrease in all contents of free water mass consisting of muscle, fat, and minerals (r=-0.49, P<0.001), ICW content (r=-0.34, P<0.001), and ECW content (r=-0.25, P<0.01). By the steeper decreased free water mass and ICW content than the decreased ECW content in those patients, the percentage of ECW in body weight increased, and the ratio of ECW to ICW had a positive correlation with the brain natriuretic peptide levels (r=-0.58, P<0.001). In multivariate analysis, age, BMI, GFR, the ECW/ICW ratio remained independently associated with the brain natriuretic peptide levels.

Conclusions: Brain natriuretic peptide is elevated in leaner and elderly patients with fluid volume imbalance between intra- and extracellular water. Fluid volume imbalance between intra- and extracellular water may express a reserve capacity for fluid volume overload and impact on cardiac preload.

SA-PO910

Blood Volume Estimation in Hemodialysis Patients


Background: Anthropometric formulas used to estimate absolute blood volume (ABV) are generally derived from healthy subjects. Most hemodialysis (HD) patients have an expanded ABV prior to HD, rendering these formulas inappropriate for estimation of pre-HD ABV (pre-ABV). Here, we compare the performance of several ABV formulas, used in conjunction with Crit-Line data, for assessment of pre-ABV.

Methods: We assume that post-HD ABV is closer to normal ABV, which we calculated based on height, sex and post-HD weight using several published formulas. Pre-BV was then calculated from post-HD blood volume using pre- and post-HD Hct measured by Crit-Line®. The calculated pre-ABV was then compared to pre-ABV measured immediately before HD using 131I-labeled albumin dilution.

Results: We compared 27 formulas for ABV estimation in 21 patients (2/3, mean ± SD: age 59 ± 14.7 years, height: 170.7 ± 10 cm, post-HD weight: 82.2 ± 16.7 kg). None of the equations showed good agreement with the measured data. The Nadler formula yielded the most accurate results (Fig. 1). As exemplified in Fig. 1, the equations yield a systematic trend in bias, with reasonable accuracy for ABV between 5-6 L but progressive underestimation and increasing heteroscedasticity towards higher ABV (caused by fluid overloading).

Conclusions: SDB is associated with increased fat mass, but not body fluid volume in CHD patients. Further studies are needed to evaluate some factors that can explain the high frequency of SDB in CHD.

Funding: Private Foundation Support

SA-PO911

Impact of Hospital-Associated Hypernatremia on Outcomes in an Unselected Patient Population: A Retrospective Cohort Study

Nicolaos E. Madias, Evangelos Tispotis, Bertrand L. Jaber. Internal Medicine, St. Elizabeth’s Medical Center, Boston, MA.

Background: Although hypernatremia has been associated with an increased risk of adverse outcomes, the majority of available studies have examined selected populations questioning the generalizability of their results to unselected patients.

Methods: The discharge data of 20,072 unselected adult patients admitted to a tertiary care facility over a 7-year period were analyzed. Based on the crude relationship between [Na+] and mortality, hypernatremia was defined as [Na+] > 142 mEq/L. Patients with community-acquired hypernatremia (CAH) and those with hospital-acquired hypernatremia (HAH) were compared to patients with normonatremia at presentation ([Na+] ≤ 138-142 mEq/L) in terms of in-hospital mortality, length of stay (LOS), and discharge disposition. Furthermore, patients with CAH in whom hypernatremia was present at hospital admission (HAggH) were compared to those without aggravation. Multivariable logistic and negative binomial regression analyses were conducted.

Results: CAH occurred in 20% of hospitalized patients and was associated with an adjusted odds ratio (OR) of 1.67 (95% confidence interval [CI] 1.38, 2.01) for in-hospital mortality, and 1.44 (95% CI 1.32, 1.56) for discharge to a short-/long-term care facility, and an adjusted 10% (95% CI, 7%-13%) increase in LOS. HAH developed in 25.9% of hospitalized patients and was associated with an adjusted OR of 3.17 (95% CI 2.45, 4.00) for in-hospital mortality, and 1.45 (95% CI 1.32, 1.59) for discharge to a facility, and an adjusted 49% (95% CI 44%, 53%) increase in LOS. HAggH developed in 8.9% of patients with CAH. Compared to patients with CAH and no further increase in [Na+], HAggH was associated with greater risk of in-hospital mortality (adjusted OR 1.84, 95% CI 1.32, 2.57) and discharge to a facility (adjusted OR 1.90, 95% CI 1.49, 2.41), and an adjusted 13% (95% CI 4%-23%) increase in LOS.

Conclusions: All forms of hypernatremia encountered in unselected hospitalized patients are independently associated with increased in-hospital mortality and heightened resource consumption.

SA-PO912

Utility of Urine/Plasma Osmolality Ratio for Assessing Volume Status in Hyponatremia

Sho Hasegawa, Maki Shibata, Takehiro Sugiyama, Fuimihiko Hinoshita. National Center for Global Health and Medicine, Tokyo, Japan.

Background: Assessing volume status is critical for managing hyponatremia. Physical examination (P/E) and laboratory data are often used for the assessment, but the utility of each parameter has not been validated in hyponatremic patients. A body composition monitor (BCM) uses bioimpedance spectroscopy and can quantify extracellular water (ECW) and volume excess or deficiency. Here, we examined which parameter is superior in assessing volume status of hyponatremic patients, using BCM data as the reference standard.

Methods: We enrolled hospitalized patients (n=41) with hyponatremia (<130 mEq/L) at our institution and conducted P/E, laboratory tests and BCM measurement. Patients with high plasma osmolality (>275 mOsm/kg) were excluded (n=5). We used %ECW (ratio of volume excess or deficiency to ECW) derived from BCM data as the reference standard of volume status. First, patients were divided into overhydration (%ECW>0%, n=29) and volume excess or deficiency (%ECW<0%, n=7) groups. Clinical signs obtained from P/E and parameters of volume status such as serum albumin (Alb), serum uric acid (UA), urine chloride, urine/plasma osmolality ratio (U/P Osm), UUN/BUN, BUN/creatinine, U/P creatinine, FENa, FEUN and FEUA were compared between the groups by Fisher’s exact test or Mann-Whitney U-test. Next, we performed univariate and multiple linear regression analyses to identify associations between each parameter and %ECW.

Results: Pre-BV was significantly higher in dehydration than in overhydration (median±IQR: 10.0±5.3 vs 13.0±1.3, p=0.01). Pre-BV, Alb and U/P Osm. Results showed that compared with Alb (β=-7.7±2.7, p=0.007), U/P Osm (β=-12.0±2.9, p=0.002) was more strongly associated with %ECW.

Conclusions: U/P Osm is superior to other commonly used parameters and clinical signs for assessing volume status in hyponatremic patients.
Sodium Concentrations of Body Fluid Losses: A Systematic Review
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Background: Unexplained wide ranges and discrepancies of sodium concentrations [Na+] have been noted for different body fluids. This has led to use of “cumulative fluid balance” regardless of composition, which cannot account for specific water and sodium requirements. Appropriate water and volume management may be facilitated by an accurate and detailed knowledge of water and sodium composition of body fluid losses and gains.

Methods: We performed a systematic review of [Na+] of body fluids lost in adult humans. Particular attention was paid to gastric fluid with high and low acid states, diarrhea due to different mechanisms, and peritoneal, pleural and wound fluids. Inclusion criteria were met for 106 full-text articles.

Results: [Na+] are fluid-specific and consistent. Mean [Na+] were statistically lower for acidic (mean ± SD 44 ± 21mEq/L) than for alkaline (55 ± 13mEq/L) gastric fluid; the difference is not clinically relevant. [Na+] are higher for bile (184 ± 24mEq/L) or pancreatic fluid (156 ± 3mEq/L) than all other body fluids, and similar for intact small bowel (119 ± 14mEq/L) and ileostomy outputs (116 ± 25mEq/L). Specific mechanisms for diarrhea are associated with [Na+]: stool [Na+] were significantly greater for cholera (128 ± 18mEq/L) and lower for osmotic-induced (28 ± 16mEq/L) than all other causes. Among osmotic diarrheas, sorbitol-induced [Na+] was higher (63 ± 11mEq/L) than for carbohydrate malabsorption (43 ± 20mEq/L), lactulose (26 ±19mEq/L), Idolax (16 ±13mEq/L) and polyethylene glycol (13 ±7mEq/L). Among secretory diarrheas [Na+] for idiopathic causes (55 ±22mEq/L) was lower than for neuroendocrine and villous tumors (75 ±13mEq/L) or non-osmotic laxatives (88 ±33mEq/L). Pleural, peritoneal, and edema fluid had [Na+] (137 ±13mEq/L) similar to plasma. [Na+] for sweat was 44 ±17mEq/L.

Conclusions: This is the first in-depth review of verifiable sodium concentrations of body fluids most commonly lost in hospitalized patients. We propose that these losses be replaced with appropriate water and sodium content of enteral and parenteral fluids to correct and avoid diuretics and perturbations of volume status.

SA-P0914
Hyponatremia in CKD: The Prevalence and Risk Factors
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Background: Kidney is a vital organ regulating water and sodium homeostasis, and it is plausible that patients with CKD are more prone to develop hyponatremia due to diminished urinary dilution ability, reduced solute intake, and/or medication which affects free water clearance. However, the prevalence and risk factors of hyponatremia among CKD patients have not been elucidated. The aim of the present study is to clarify the prevalence and risk factors contributing to hyponatremia in CKD patients.

Methods: Among 32,438 patients who visited our outpatient clinic between 2011 and 2014, 9,388 patients met the criteria of CKD, which is defined as either eGFR ≤60 ml/min/1.73m2 or the presence of proteinuria. Dialysis and transplant patients were excluded. Risk factors for hyponatremia were sought using multivariate logistic regression analysis.

Results: Prevalence of hyponatremia (serum Na<135mEq/L) was 8% in all CKD patients. Among moderate and severe CKD (stage 3, 4 and 5, N=6397), the prevalence of hyponatremia in moderate and severe CKD was older (P<0.01), female sex (P<0.01), diabetic (P<0.01) and more likely to have decreased eGFR (P<0.01). Multivariate logistic regression analysis identified CKD stage (OR:1.7-2.4, P<0.01), diabetes (OR:1.4, P<0.01) and renin-angiotensin-aldosterone system (RAS) inhibitors (OR:0.68, P<0.01) as independent risk factors for hyponatremia in moderate and severe CKD.

Conclusions: The present study shows that the prevalence of hyponatremia was 8% in CKD patients, and development of hyponatremia is correlated with progression of CKD in moderate and severe CKD. Worsening CKD and Diabetes are risk factors, while RAS inhibitors are protective for hyponatremia in CKD.

SA-P0915
Mild Hyponatremia on Admission Is Associated with Sepsis and Increased Mortality in Patients Presenting with a Hip Fracture
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Background: Hyponatremia is associated with an increased risk of falls and hip fractures in the elderly (JAMA 28: 2299-2304, 1999). Moreover, sepsis is a frequent co-morbidity in patients with hyponatremia (AJKD 65:145-142, 2015). We assessed if hyponatremia on admission was associated with sepsis and increased mortality in patients presenting with a hip fracture.

Methods: A cohort study in adult patients admitted with a traumatic hip fracture and at least one serum Na performed at admission. Hyponatremia (H), Na < 135 mEq/L, and normonatremic (N) patients were evaluated for complications occurring within 30 days of surgery, length of hospital stay, readmission rate, in-hospital mortality and mortality during 1 year follow-up. An unadjusted and adjusted odds ratio (OR) and hazard ratio (HR) were calculated for in-hospital mortality and 1 year mortality. Adjustments were made for age, gender, propensity score for hyponatremia, CVA, CHF, ischemic heart disease, arrhythmias, thromboembolic disease, sepsis and dementia.

Results: 1571 patients were included of whom 366 (23.2%) were hyponatremic ( Na 135 mEq/L vs 138 ± 3 mEq/L, p<0.001). Length of stay was 8 days in H vs. 7 days in N (p=0.055). There was in increased incidence of sepsis in hyponatremic patient, 9.8% in H vs. 6% in N (p=0.01) OR 1.7 (95% CI: 1.3-2.6). In-hospital mortality was significantly higher in H vs N patients (19.9 vs 14.7%; p=0.016), with an un-adjusted OR of 1.45 (95% CI: 1.07-1.96) and an adjusted OR of 1.15 (95% CI:0.84-1.6). Readmissions were 15.8% for H vs. 12.9% for N (p=0.14). One-year mortality was greater in H vs N patients (15.4 vs. 6.8%; p<0.001), with an un-adjusted HR of 1.8 (95% CI:1.4-2.35) and an adjusted HR of 1.45 (95% CI:1.1-1.9).

Conclusions: Mild hyponatremia on admission is associated with sepsis and increased in-hospital and late mortality in patients presenting with a hip fracture.
Persistent Hyponatremia at 72 Hours in Cancer Patients with Severe Hyponatremia Is Associated with Mortality Independent of Cancer Stage

**Background:** Hyponatremia is a common problem and a known independent risk factor for mortality in cancer patients. The impact of rate of correction of sodium on mortality is unknown. The study aim was to determine if the rate of correction in cancer patients with severe hyponatremia (Na < 120 mEq/L) is linked to 90-day mortality.

**Methods:** Patients with Na < 120 mEq/L were identified from the Memorial Sloan Kettering Cancer Center database from June 1, 2009 until June 30, 2014. 195 patients were identified. 55 patients were excluded from analysis because less than 72 hours after admission they either died (4), had no follow up data (16), were discharged (21), or made comfort care (14). The final cohort consisted of 140 patients who stayed in the hospital for at least 72 hours and had serial measurements of serum Na.

**Results:** The mean initial serum Na was 116.7 ± 3.0 mEq/L, the median rate of correction was 6 mEq/L with interquartile range 3.9 mEq/L in the first 24 hours, and the overall 90-day mortality was 10%. No patients with Na correction < 8 mEq/L in the first 24 hours (n=54) developed osmotic demyelination syndrome. In patients who died within 90 days, the mean serum Na at 72 hrs was 128.3 ± 4.4 mEq/L compared to 130.5 ± 4.9 mEq/L in survivors (p<0.01). When adjusting for cancer stage and rate of correction in a multivariate Cox model, serum Na < 130 mEq/L at 72 hrs was independently associated with 90 day mortality with adjusted HR 2.62 (1.47-4.64, p<0.001).

**Conclusions:** Cancer patients with severe hyponatremia are at heightened risk for 90-day mortality independent of cancer stage and rate of Na correction if their serum Na at 72 hrs is < 130 mEq/L. Based on this finding we recommend that cancer patients with severe hyponatremia should be corrected to >130 mEq/L at 72 hrs.

**SA-PO919**

Hyponatremia Correction Using CRRT: Does Kinetic Modeling Avoid Overcorrection? 1 Saurabh Dasgupta, 2 Lenar T. Yessayan, 3 Balazs Szamosfalvi, 4 Sevag Demirjian, 5 Nephrology, Cleveland Clinic, Cleveland, OH; 1 Div of Nephrology, NYU Langone Medical Center, New York, NY; 2 Dept of Biostatistics, Weill Cornell Medical College, New York, NY; 3 Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

**Background:** Hyponatremia is the most common electrolyte abnormality in inpatients. It must be corrected at a gradient of < 8 hrs to minimize the risk of central pontine myelolysis, which can be effectively achieved in patients with renal failure by CRRT. Sodium (Na) kinetic models can predict end dialysis water. A simplified single pool fixed volume kinetic model may be applicable when net Na generation (G) is <6 mEq/L. Our goal was to examine the correlation of predicted rate of correction of Na by the formula to that observed in ICU patients with hyponatremia treated with CRRT.

**Methods:** 66 critically ill subjects with serum Na <130 mEq/L at time of CRRT initiation were retrospectively identified. Median age was 60, and 52% were male. The predominant CRRT modality was CVVHD (97%), using dialysate Na of 140 mmol/L in most patients (92%) with average cumulative dose of 61L, delivered over median duration of 23.2 hrs. Predicted Na correction in the first 24 hours was calculated using a single pool fixed volume kinetic model. The values were then compared to actual measured serum Na using simple correlation, and Bland-Altman plot.

**Results:** The correlation factor was calculated to be 0.49 with a p value <0.001. The Bland Altman plot (figure) showed a mean difference of 2 mmol/L between the observed and predicted delta Na values, with a trend for overestimation of Na correction as delta sodium levels increased.

**Conclusions:** Increasing Hb spuriously decreases dNa and increases DNa. A linear correction for this artifact can reduce the discordance between iNa and dNa, promoting their interchangeable use.

**Funding:** Veterans Administration Support

**SA-PO921**

HHV-6 Encephalitis Resulting in Cerebral Salt Wasting and Hyponatremia

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**Background:** Hyponatremia is a common electrolyte abnormality that can be associated with hypo-, hyper-, or euolemic states. Low circulating volumes secondary to extra-renal losses, fluid overload states, and syndrome of inappropriate ADH are some of the more common causes of hyponatremia. One consideration that is uncommon and often overlooked is cerebral salt wasting (CSW). CSW is defined as “renal loss of sodium during intracranial disorders leading to hyponatremia and a decrease in the extracellular fluid volume.” It occurs in the setting of cerebral injury, most commonly associated with subarachnoid
hemorrhage, but also documented with other disorders of central nervous system. The mechanism of CSW is not completely understood, but is believed that a cerebral injury can lead to impairment of the sympathetic outflow causing primary natriuresis leading to hypovolemia and sodium depletion.

methods: Here we describe a case of CSW in a patient with human herpes virus-6 (HHV-6) encephalitis. The patient was a 29 year old male with a history of AML who presented with increasing confusion. He was found to have hyponatremia with a sodium of 126 mEq/L, a urine osmolality of 615 mOsm/kg, and a urine sodium of 144 mEq/L. On exam, he had evidence of hypovolemia with dry mucus membranes and orthostatic hypotension. He was initially treated with normal saline IV fluids. He had increasing diuresis with fluid resuscitation, with 6 liters of urine output on hospital day 1. The patient was continued on IV saline with the addition of oral salt supplements and started on fludrocortisone for suspected CSW. His hyponatremia improved and by hospital day #5 was 133 mEq/L. CT and MRI imaging of the head and brain were unremarkable for acute changes or pathology. A serum HHV-6 PCR showed 13,960 copies. He was treated with IV foscarnet with normalization of the serum and CSF PCR within 10 days.

conclusions: This case is important because the diagnosis of CSW is often confused with SIADH, as both share similar diagnostic criteria such as elevated urine sodium concentration and urine osmolality. The important clinical distinction is the patient, despite having a hypovolemic state would have polyuria and renal sodium wasting.

SA-PO922
Association of 6-Month Pre-ESRD Potassium with Immediate Post-ESRD Survival: A Transition to CKD Study

Background: Previous studies of the association between serum potassium level and mortality in dialysis patients have suggested that a range of 4.6-5.3 mEq/L portends greatest survival in this population. However, the optimal potassium range in the immediate pre-ESRD period among pre-dialysis CKD patients transitioning to ESRD is not known. We hypothesized that a similar pre-ESRD serum potassium range is also associated with higher survival in this population.

Methods: We investigated a cohort of 20,404 US veterans who initiated dialysis between 10/2007-9/2011 and had at least 1 potassium measurement during the last 6 month period before ESRD transition (6 month-predialysis). We examined the association of 6 month averaged potassium as a continuous predictor of all-cause mortality and early post dialysis mortality occurring in the first 3 months after transition using restricted cubic splines and Cox proportional hazard models adjusted for age, gender, race, ethnicity, geographic region and primary cause of ESRD.

Results: The analytic cohort had a mean ± SD age of 68.1±11.3 years old, among whom 30% were African-Americans, 7% Hispanic and 50% had diabetes as the leading cause of ESRD. The potassium level in the prelude period was associated with highest mortality in the first 3 months after transitioning to dialysis whereas potassium in 4.5-5.5 mEq/L range conferred the greatest early survival.

Conclusions: Lower serum potassium measurements during the final months prior to transition to ESRD are associated with higher early mortality. Whether pre-ESRD potassium levels should be kept between 4.5 and 5.5 mEq/L in the immediate pre-dialysis transition period warrants additional studies.

SA-PO923
Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Healthcare System

Background: The association of outpatient medication use with patterns and prevalence of hyperkalemia has not been rigorously examined.

Methods: We evaluated the association between baseline antihypertension medications [angiotensin converting enzyme-inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, loop/thiazide diuretics, and K-sparing diuretics] with the frequency and pattern of mild (K<5 mEq/L) and severe hyperkalemia (>5 mEq/L) over a 2 year window in 342,342 outpatients in the Geisinger Health System based on medication prescription orders. Patterns of hyperkalemia were classified as: never, transient (1-time), intermittent (>1-time but <50% of the time), and persistent (≥50% of the time). Analyses were adjusted for demographics, eGFR, systolic blood pressure, diabetes, and history of cardiovascular disease. Interactions between medication types with hyperkalemia risk were also tested.

Results: Potassium levels were checked <=1 time/yr in 53% of the cohort; 4% had levels checked >5 times/yr. Overall, 7.4% had ≥2 episodes of mild hyperkalemia; 0.4% had an episode of severe hyperkalemia. Among the different classes of antihypertensives, K-sparing diuretics had the strongest associations with both mild and severe hyperkalemia, followed by ACEis and then beta blockers, which were associated only with mild hyperkalemia (Figure). ARBs had similar effect size to beta blockers but were not statistically significant. Thiazide/loop diuretics were protective against mild hyperkalemia but not severe hyperkalemia. There were no consistent interactions between types of antihypertensive medication for risk of hyperkalemia.

Conclusions: Mild hyperkalemia is relatively common and associated with the use of ACEis and K-sparing diuretics but not ARBs in this single healthcare system.
Table. Variation in s-K+ (max-min) over 72 h during run-in on a 60 mEq K+ diet, n=27

<table>
<thead>
<tr>
<th>Time</th>
<th>baseline</th>
<th>+10 h</th>
<th>+24 h</th>
<th>+36 h</th>
<th>+48 h</th>
<th>+62 h</th>
<th>+71 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ in s-K+, mEq/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.44±0.24</td>
<td>0.42±0.24</td>
<td>0.39±0.24</td>
<td>0.34±0.24</td>
<td>0.29±0.24</td>
<td>0.15±0.12</td>
<td>0.12±0.09</td>
<td></td>
</tr>
<tr>
<td>P-value*</td>
<td>0.0030</td>
<td>0.0027</td>
<td>0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Comparing values from baseline to values at +10, +24, +36, +48, +62 and +71 h via paired t-test with Bonferroni correction (α=0.05; P<0.0083 is significant).

Funding: Pharmaceutical Company Support - Relypsa, Inc.

SA-PO925

Best EKG Criteria for Hyperkalemia in Chronic Hemodialysis Patients
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Background: To date the effects of hyperkalemia (HK) on the EKG of chronic hemodialysis (CHD) patients (pts) is inconsistent. We studied the EKGs of 128 consecutive CHD pts with clotted grafts or fistulas. EKGs from 46 HK pts >5.5 mEq/L were compared to 82 pts with normal potassium (NK) levels <5.5 mEq/L. Pts with RBBB or LBBB or cardiac events within 3 months were already excluded. There were no differences between HK and NK pts for dialysis duration, causes for ESRD, cardiac disease or serum levels of Na, Ca, HCO3, or phosphorus.

Methods: EKG analysis included: the height & width of the P waves, the T waves in V4 & the T waves in Lead 2, the time intervals of PR, QRS, QT, QTc, PR/QT, & slopes of ascending & descending T waves in Lead 2 & V4. For the first time ever in HK CHD pts, the EKG measurements in 32 HK pts with complete data were compared to their NK EKGs obtained 3 to 6 months from the HK event.

Results: Univariate stats between the 46 HK & 82 NK pts showed 4 differences in mean values: V4 T wave height 4.0 vs 2.9 mm, Lead 2 T wave height 2.7 vs 2.0 mm, & the V4 T wave ascending (.03 vs .02) and descending slopes (.04 vs .03). Multivariate analysis for all clinical & EKG findings between HK & NK pts found only the increased height of the T wave in V4 was significant, p=.05. In contrast, the EKG analysis of the HK pts to their NK EKGs revealed more differences: higher T wave height in V4, 5.0 vs 3.7 mm, higher lead T wave height in Lead 2, 4.0 vs 2.7 mm, shorter width of T wave in V4, 2.4 vs 4.1 ms or Lead 2, 2.1 vs 4.1 ms, longer PR 188 vs 167 ms, & steeper slopes in the T waves in Lead 2 and V4. Regression analysis of the change in potassium from NK HK pts to their NK EKGs revealed more differences: higher T wave height in V4, 5.0 vs 3.9 mm, steeper V4 T wave ascending (0.03 vs 0.02) and descending slopes (0.04 vs 0.03). Multivariate analysis for all clinical & EKG findings between HK & NK pts found only the increased size of ZS-9. Here we present Zr concentration data from urine and whole blood samples from HS-9 treated dogs to assess systemic absorption of long-term, high-dose ZS-9.

Conclusions: We conclude: 1) Comparison of a NK EKG to a HK EKG in CHD pts significantly helps to confirm HK EKG changes in CHD pts. 2) A shortened width and an increased height of the T wave in V4 are the most important HK EKG changes in CHD pts.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO926

Sodium Polyoxymethylene Sulfonate for the Treatment of Mild Hyperkalemia in Chronic Kidney Disease: A Randomized Clinical Trial
Katherine Desforges, Laurence Legape, Anne-Claude Dufour, Jessica Doiron, Katia Handfield, Robert Zel Bell, Michel Vallée, Michel Savoie, Sylvie Perreault, Louis-Philippe Laurin, William Beauchemin-St, Vincent Pichette, Jean-Philippe Lafrance. Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.

Background: Hyperkalemia affects up to 10% of patients with chronic kidney disease (CKD). Sodium polyoxymethylene sulfonate (SPS) has long been prescribed for this condition even though evidence is lacking on its efficacy for the treatment of mild hyperkalemia over several days.

Methods: The aim of this double-blind, randomized trial was to evaluate the efficacy of SPS in the treatment of mild hyperkalemia (5.0 to 5.9 mEq/L) in pre-dialysis outpatients. We randomly assigned 33 patients on stable medication to receive either SPS or placebo 30 g orally once a day for 7 days. Patients had to be on stable medication to be eligible for the study. The primary outcome was the comparison between study groups of the mean difference of serum potassium levels between the day following the last dose of treatment and baseline.

Results: The mean duration of treatment was 6.9 days. SPS was superior to placebo in the reduction of serum potassium levels (mean difference between groups of -1.04 mEq/L; 95%CI [-1.37 to -0.71]). A higher proportion of patients in the SPS group tended to attain normokalemia (defined as a serum potassium level of at least 3.5 mmol/L and less than 5.0 mmol/L) at the end of their treatment compared to the placebo group (73% vs 38%; P=0.07). Patients in the group treated with SPS had an increase in hypermagnesemia, hypocalcemia, constipation and nausea compared to the control group.

Conclusions: SPS is superior to placebo in the treatment of mild hyperkalemia over seven days in CKD patients. Its use was generally well tolerated in our study population, but does require monitoring of gastrointestinal side effects and electrolytic disorders.

SA-PO927

Assessment of Systemic Absorption of Sodium Zirconium Cyclosilicate (ZS-9): Blood and Urine Zr Concentration in Dogs During a 9-Month Oral Toxicity Study
Fiona Stavros, Henrik S. Rasmussen, Bhupinder Singh, Jose A. Menoyo. ZS Pharma, Inc., Coppell, TX.

Background: Hyperkalemia (HK; potassium [K+] >5.1 mEq/L) is a common and potentially life-threatening electrolyte disorder often occurring in patients with chronic kidney disease, heart failure and diabetes. Sodium zirconium (Zr) cyclosilicate (ZS-9), a potential HK therapy, is a selective K+ ion trap containing covariantly bound Zr atoms within an insoluble 25µm particle. Zr has a long history as an inert substance used in biomedical implants and dialysis, and is present in natural diets and household items. Systemic absorption of Zr is expected to be minimal given the low solubility and particle size of Zr. Here we present Zr concentration data from urine and whole blood samples from ZS-9 treated dogs to assess systemic absorption of long-term, high-dose ZS-9.

Methods: Beagle dogs received Control (n=10/sex) or high-dose ZS-9 (2000 mg/kg/day, n=10/sex). Blood samples were collected by venipuncture at baseline, and Weeks 6, 13, 26, and 39. Urine samples were collected directly from the bladder at necropsy (Week 39) and recovery (Week 43). Zr levels in Control and ZS-9 treated dogs were determined using inductively coupled plasma mass spectrometry with a lower limit of quantification (LLOQ) of 10 ng/mL (ppb) for both whole blood and urine. The analytical method was designed to measure the presence of both free Zr and ZS-9 bound Zr.

Results: Zr was below the LLOQ in all dog urine samples (N=28) and in all but one Control group whole blood sample (N=226). The one dog in the Control group had a blood Zr level of 10.9 ng/mL at Week 26.

Conclusions: There was no detectable Zr or increase in Zr in blood and urine samples following 39 weeks of 2000 mg/kg/day ZS-9 treatment; equivalent to a human dose of ~65 g/day. Zr was detected in one non ZS-9 treated animal. These results demonstrate an absence of systemic ZS-9 absorption after long-term, high-dose treatment in beagle dogs.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

SA-PO928

Admission Hypomagnesemia Linked to Septic Shock in Patients with Systemic Inflammatory Response Syndrome
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Background: The association between admission serum magnesium (Mg) levels and risk of developing septic shock in patients with systemic inflammatory response syndrome (SIRS) is limited. The aim of this study was to assess the risk of developing septic shock in hospitalized patients with SIRS with various admission Mg levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients with SIRS at admission who had admission Mg available from January 2009 to December 2013 were analyzed in this study. Admission Mg was categorized based on its distribution into six groups (4.0, 4.1 to 4.7, 4.8 to 5.1, 5.2 to 5.4, and >5.4 mEq/L). The primary outcome was septic shock occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of septic shock of various admission Mg levels using Mg with lowest incidence of shock, 2.1 to 2.3 mEq/L as the reference group.

Results: Of 2,589 patients with SIRS enrolled, septic shock occurred in 236 patients (9.1%). The lowest incidence of septic shock was when serum Mg was within 2.1-2.3 mEq/L. A reverse-checkmark curve emerged demonstrating higher incidences of septic shock

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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associated with both hypoMg (<2.1) and hyperMg (>2.3). After adjusting for potential confounders, hypoMg (<1.5 mg/dL) was associated with an increased risk of developing septic shock with odds ratios of 1.86 (95% CI 1.07,3.27).

Conclusions: Patients with SIRS and hypoMg (<1.5 mg/dL) at the time of admission had increased risk of developing septic shock during hospitalization.

SA-PO929
Risk Factors for Calcium-Alkali Syndrome in Post-Surgical Hypoparathyroidism
Savaya Kuriya, Masahiko Yazawa, Naoto Tominaga, Yujiro Sagagaki. Nephrology and Hypertension, St. Marianna Univ; Kawasaki, Kanagawa, Japan.

Background: Post-surgical hypoparathyroidism is a common complication of total thyroidectomy. Patients complicated by permanent hypoparathyroidism often require either both calcium or vitamin D supplement therapy to maintain serum calcium levels, and long-term therapy can lead to calcium-alkali syndrome (CAS). We examined the incidence rate, magnitude, and risk factors of CAS in patients being treated for post-surgical hypoparathyroidism.

Methods: We retrospectively observed 27 patients with neck tumors who had undergone total thyroidectomy with total parathyroidectomy without autotransplantation between January 2010 and October 2013 at St. Marianna University Hospital. All patients received calcium lactate and alfacalcidol. Medical records were reviewed for historical, clinical, laboratory and imaging data. Definitions were as follows: hypercalcemia, corrected serum calcium (cCa) ≥10.0 mg/dL; acute kidney disease (AKD), either or both >50% increase in serum creatinine (SCR) or >55% decrease in estimated glomerular filtration rate (eGFR); and metabolic alkalosis, difference in serum sodium (Na) and serum chloride (SCl) >38. Data were expressed as mean ± standard deviation (SD). For statistical analysis, the paired t test, Student’s t test, and chi-square test were used to compare two matched variables when appropriate. P<0.05 was considered statistically significant.

Results: Average duration between surgery and reaching peak cCa level was 392.7 ± 847.8 days, with levels peaking at 11.1 ± 1.2 mg/dL. Median cCa levels peaked at 11.1 mg/dL, at 847 days after surgery. Nineteen patients (70.3%) had hypercalcemia, 9 (33.3%) had AKD, and 7 (36.9%) had metabolic alkalosis. Baseline data of patients with AKD were as follows: male, 11 patients (73.3%); age, 76.9 ± 14.7 years; height, 162.9 ± 8.1 cm; weight, 64.4 ± 12.7 kg; systolic blood pressure (SBP), 128.9 ± 19.2 mmHg; diastolic blood pressure (DBP), 68.8 ± 10.3 mmHg; sodium, 137.6 ± 1.4 mEq/L; bicarbonate, 24.5 ± 3.0 mEq/L; baseline eGFR, 69.9 ± 16.6 mL/min/1.73 m2; serum insulin levels, 12.5 (2.7-24.6) mU/L; and baseline blood glucose levels, 85.1 (55.3-134.1) mg/dL. Hypercalcemia was strongly correlated with cCa levels and kidney function should be closely monitored in patients with post-surgical hypoparathyroidism.

SA-PO930
Body Temperature Rise in the Cell-Free and Concentrated Ascites
Reinforcement Therapy Is Correlated to Albumin Concentration Rather Than the Interleukin-6 Levels in the Ascites
Norikazu Maruyama, Masanori Abe, Kazuyoshi Okada. Div of Nephrology, Hypertension and Endocrinology, Dept of Internal Medicine, Nihon Univ School of Medicine, Tokyo, Japan.

Background: There is a fever as a side effect of Cell-free and Concentrated Ascites Reinforcement Therapy (CART). Cytokines in ascites after concentration is thought to be involved in the generation of heat after intravenous injection. To examine the fever related factors, we examined the relationship between inflammatory cytokines levels, total protein (TP), albumin (ALB) in peritoneal fluid and the heating after intravenous injection.

Methods: In this study, we have measured interleukin-1β (IL-1β), interleukin-6 (IL-6), TP, ALB concentration in the ascites fluid before and after concentrated, and observed vital changes in the patient before and after intravenous injection. A total of 8 patients with refractory ascites were studied.

Results: IL-1β was detected in ascites prior to concentration of the two cases, it could not be measured in the other specimen. IL-6 is present in high concentrations in all ascites before concentration (mean 4218.7 pg/mL), it was further increased after concentration (mean 23107.0 pg/mL). Although body temperature rise was observed after the intravenous injection of concentrated ascites in six out of eight, IL-6 concentration in the ascites fluid (r = 0.61063; P = 0.114), the total dose of IL-6 (r = 0.06755; P = 0.436), dose rate (r = -0.2876; P = 0.244) was no obvious correlation between the body temperature rise. On the other hand, respectively in the TP concentration and the ALB concentration of ascites, it was found correlated with body temperature rise after intravenous injection. In particular, a strong correlation between the ALB concentration and the increase in body temperature was observed (r = 0.8033; P < 0.01).

Conclusions: The correlation of body temperature rise after intravenous injection and IL-6 is weak, while the correlation between the concentrated ALB and body temperature rise was very strong. From these results, we considered that any substance bound to the ALB or ALB itself are associated with elevated body temperature.

SA-PO931
Contrast-Related Hyponatremia
What We Could Be Missing
Christine Joy C. Junia, Kalyani Perumal. Internal Medicine, John H. Stroger Jr. Hospital, Chicago, IL.

Background: Hyponatremia is a commonly encountered electrolyte abnormality. Long-established algorithms outline etiology and management guiding physicians to prevent neurologic sequelae. Close electrolyte monitoring is emphasized in acute hyponatremia due to higher morbidity and mortality. Contrast-related hyponatremia is an etiology of acute onset hyponatremia that is not routinely monitored and may easily be missed.

Methods: A 76-year-old woman with hypertension, diabetes and chronic kidney disease (CKD) III, eGFR of 44 was admitted for asthma exacerbation and received beta-agonist nebulizer treatment. Her home medications were Orimject and Insulin were restarted. She was tachypneic and wheezing, the rest of the physical exam was normal. Laboratory tests on admission: Na 135 meq/L, K 4.4 meeq/L, BUN 11 mg/dL, Creatinine 1.2 mg/dL, and normal urinalysis. An elevated D-Dimer prompted evaluation with CT Chest with contrast Omnipaque 350 (840 mOs/mg) to rule out pulmonary embolism. Her symptoms improved, however her sodium dropped from 135 to 122 meq/L. 48 hours after chest CT, creatinine 1.4 mg/dL. Work-up revealed plasma osmolality of 297 mosm/ kg, osmolar gap of 30. On the 4th and 5th hospital day, sodium levels were stable at 125 meq/L and 124 meq/L respectively. Her sodium on Day 8 improved to 133 meq/L without any intervention.

Conclusions: The 2014 USRDS data reports a rise in prevalence of CKD III from 4.5 to 6.0 percent. Primary care doctors manage 80 to 90 percent of these patients. There is a lack of data on contrast-related hyponatremia rise in diagnosticians. Over the past decade, CT Scan use in the emergency departments has increased over 200-300%. There are a few case reports of contrast-related hyponatremia, occurring mostly in patients with advanced CKD with eGFR<30. A consistent finding was the acute onset and an average drop in sodium of 12 meq/L. Contrast-related hyponatremia could be responsible for an acute drop in sodium. This is usually offset by osmotic diuresis that is impaired in chronic kidney disease. Our case highlights contrast-related acute hypotonic hyponatremia in the setting of mild kidney disease, a high-risk patient population that may benefit from post-diagnostic electrolyte monitoring.

SA-PO932
A Role for NHE3 in Renal Sodium and Acid-Base Handling in the Early Proximal Tubule and Further Downstream Segments
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Background: Systemic Na+/H+ exchanger 3 (NHE3) knockout in mice lowered blood pressure (BP) and induced metabolic acidosis, however, the role of intestine vs kidney and early vs further downstream segments is unclear.

Methods: Male mice with floxed NHE3 expressing Cre recombinase under the control of i) the SGLT2 promoter to knockdown NHE3 in the early PT (SGLT2-Cre/NHE3fl/fl, n=10) or ii) the Pax8 promoter for knockdown throughout the entire tubular system (Pax8-Cre/NHE3fl/fl, n=9) were compared with corresponding Cre-negative controls (n=10 and 7).

Results: Blood and spot urine samples were collected, BP measured by automated tail cuff and arterial cannulation, and GF levels monitored. NHE3+/cre ratios were higher in Pax8-Cre/NHE3fl/fl vs controls (40±5 vs 28±2, P<0.05) but not significantly different in SGLT2-Cre/NHE3fl/fl vs controls (31±2 vs 27±3). Urine pH and HCO3-/cre ratio were strongly increased in Pax8-Cre/NHE3fl/fl (7.8±0.11 vs 6.4±0.12, 15.5±3.1 vs 5.5±0.34, P<0.01), and only modestly higher in SGLT2-Cre/NHE3fl/fl vs controls (6.0±0.15 vs 6.1±0.12, P=0.07 and 0.45±0.20 vs 0.14±0.03, P=0.16). Urine pH and HCO3- were significantly higher in Pax8-Cre/NHE3fl/fl vs controls (31±2 vs 27±3). Blood spot urine samples were collected, BP measured by automated tail cuff and arterial cannulation, and GF levels monitored. NHE3+/cre ratios were doubled in both knockout mice vs their controls (Pax8-Cre: 32±3 vs 17±2; SGLT2-Cre: 22±2 vs 10±1, P<0.01).

Conclusions: Tubule-specific NHE3 knockout decreased urine pH and excretion of sodium, HCO3- and protein without metabolic acidosis. Comparison of the Cre models is consistent with a role of NHE3 in urinary acidification and reabsorption of sodium and bicarbonate in the early PT as well as in further downstream segments.

Funding: NIDDK Support, Veterans Administration Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effect of NBCe1 Deletion on Renal Ammonia Metabolism

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Background: Metabolic acidosis typically increases renal ammonia excretion, but people with proximal renal tubular acidosis (pRTA), despite the associated metabolic acidosis, do not have increased ammonia excretion. Genetic forms of human pRTA typically involve the proximal tubule bicarbonate transporter, NBCe1. Based on these observations, we postulated that NBCe1 has a role in renal ammonia metabolism that is in addition to its role in bicarbonate reabsorption.

Methods: We used previously reported mice with NBCe1 deletion. Because +/- mice have 100% mortality before d10-21, we studied mice at d8-11. Wild-type (WT), heterozygous (HET) and homozygous knock-out (KO) mice were generated by breeding WT male and female mice.

Results: Serum HCO3 was 26.4±1.0 in WT, 19.8±1.9 in HET, and 10.3±0.6 mmol in KO mice (P<0.05). Thus, NBCe1 deletion causes metabolic acidosis at d8. Although acidosis normally increases ammonia excretion, NBCe1 deletion decreased spontaneous ammonia excretion: 275±44, 212±11 and 94±69 mmol/g creatinine in WT, HET and KO mice, respectively (P<0.01). Serum Na and K were unchanged. Urine pH was 5.3±0.2, 4.8±0.1 and 4.2±0.1 in WT, HET and KO mice, respectively (P<0.01), indicating intact urine acidification and no ongoing HCO3 loss. NBCe1 deletion did not alter urine osmolality significantly (WT, 595±43 and no ongoing HCO3 loss. NBCe1 deletion did not alter urine osmolality significantly (WT, 259±50; KO, 276±34 mOsm/kg H2O; P=NS), which, in combination with intact urine acidification, suggests intact collecting duct function. The regulation of multiple proteins involved in ammonia metabolism was atypical of acidosis. NBCe1 deletion decreased expression of PDG and PEPC and increased expression of the ammonia recycling enzyme, glutamine synthetase. This pattern is the exact opposite of that expected with acidosis. Expression of the TAL ammonia transporter, NKCC2, and the collecting duct ammoniaturia, RHb and Rhcg, was unchanged.

Conclusions: We conclude: 1) NBCe1 deletion significantly alters proximal tubule ammonia metabolism, leading to decreased urinary ammonia excretion; and, 2) NBCe1, in addition to its role in HCO3 transport, may have an important role in ammonia metabolism.

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SA-PO934

Assessing Urine Ammonium Concentration by Urine Osmolal Gap in Chronic Kidney Disease

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Background: Acidemia is one of the risk factor for end stage kidney disease and mortality for patients with chronic kidney disease (CKD). Although ammonium is the crucial component of renal acid excretion, measurement of urine ammonium concentration (NH₄⁺) is not routinely available in most hospital laboratories. To estimate NH₄⁺, urine osmolal gap (UOG = urine osmolality – [2(Na + K) + urea + glucose]) is calculated and the formula (NH₄⁺ = UOG/2) has traditionally been used. However, studies evaluating it in CKD patients are scarce. The present study aims to assess the relationship between NH₄⁺ and UOG in CKD patients.

Methods: Spot urine samples were collected from 36 patients with CKD in our hospital (24 males, age 41-96 years, serum creatinine 0.9-12.4 mg/dl). We measured urine pH, Na, K, Cl, urea, glucose and NH₄⁺. NH₄⁺ was measured by colorimetric assay (modified Fujii-Okuda method). The Bland-Altman plot was used to evaluate the agreement between NH₄⁺ and UOG/2.

Results: NH₄⁺ ranged from 0.3-45.8 mmol/l (median, 6.2 mmol/l). UOG/2 correlated positively and significantly with NH₄⁺ (r=0.925, p<0.0001).

Conclusions: UOG is an accurate method to estimate NH₄⁺ in CKD patients and can be used to assess urinary acidification ability in CKD patients.

SA-PO935

Vacular H⁺-ATPase Regulation by 14-3-3 Proteins

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Background: The vascular proton-ATPase (V-ATPase) is highly expressed at the apical membrane of type A intercalated cells (ICs) in the collecting duct. This pump mediates proton transport across a membrane often against a gradient. Defects in V-ATPase function can lead to renal tubular acidosis. In kidney cells we showed that the metabolic sensor AMP-activated protein kinase (AMPK) phosphorylates the V-ATPase A subunit at Ser-384. AMPK regulates some transport proteins by inhibiting their function and promoting their ubiquitination and degradation. These mechanisms are likely important for inhibition of membrane transport during cellular metabolic stress. We noticed that Ser-384 exists within a 14-3-3 binding motif. Dimeric 14-3-3 bind to phosphorylated sites on target proteins and modulate protein function. We hypothesized that phosphorylation of AMPK and an additional kinase modulate A subunit binding to 14-3-3 proteins and A subunit ubiquitination.

Methods: We used transient transfections of V-ATPase A subunit mutants in Clone C ICs, followed by immunoprecipitation and immunoblotting.

Results: We have preliminary evidence that phosphorylation at Ser-384 and a new “Site III” in the V-ATPase A subunit are required for 14-3-3 binding. For example, 14-3-3 binding to the A subunit increased when we used a phosphomimetic mutant (Ser-to-Asp) at Site III compared to the WT sequence at that site, and this binding was not dependent on the presence of the AMPK phosphate donor pharmacological activator. Furthermore, AICAR increased A subunit ubiquitination as compared to untreated cells.

Conclusions: We propose that V-ATPase A subunit binding to 14-3-3s promotes its ubiquitination and degradation. These pathways are downstream of phosphorylation of the subunit at Ser-384 by AMPK and at Site III by another unidentified kinase. Our results link downregulation of the V-ATPase to metabolic depletion in kidney epithelial cells.

Funding: NIDDK Support

SA-PO936

Albuminuria Enhances Renal NHE3 Expression via the Activation of Mitochondrial Oxidative Stress/RAS Axis

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Background: Renal sodium–hydrogen exchanger 3 (NHE3) plays a known role in the reabsorption of bicarbonate and fluid. As a result, NHE3 is thought to be important in acid base balance and vascular volume homeostasis. The present study was to investigate the role albuminuria in regulating renal NHE3 expression as well as the underlying mechanisms.

Methods: An albumin overload mouse model was established by i.p injection of albumin. The mouse kidney tissues and kidney biopsy specimens from proteinuric patients were analyzed.

Results: Following 12-day albumin overload, we found that albuminuria increased NHE3 expression by 2-fold in mouse kidneys determined by Western blotting and qRT-PCR. Considering the known role of renin-angiotensin system (RAS) in mediating renal sodium and water reabsorption, we examined key components of RAS and found a striking elevation of angiotensinogen (AGT, +2.1 folds), angiotensin converting enzyme (ACE, +3.3 folds), and urinary angiotensin II (Ang II, +70%) output determined by Western blotting or ELISA. In proteinuric patients, we detected a 1.9-fold upregulation of NHE3 and 3-fold increase of ACE by immunohistochemistry in line with a 2-fold increment of urinary Ang II excretion. To further investigate the role of RAS in upregulating NHE3, we performed primary cultures of renal tubular cells and observed that albumin overload directly enhanced NHE3 accompanied by stimulated AGT/ACE/Ang II cascade, which was entirely abolished by ACE inhibitor captopril, indicating a key role of RAS in mediating albuminuria effect on NHE3 upregulation. More interestingly, albumin overload significantly induced mitochondrial oxidative stress evidenced by reduced mitochondrial superoxide dismutase (SOD2, -60%) and elevated ROS production. Notably, a SOD2 mimic (MnTBAP) completely normalized NHE3 upregulation and activated AGT/ACE/Ang II cascade in mice with albumin overload.

Conclusions: These results suggest that albuminuria is of vital importance in upregulating renal NHE3 expression in proteinuric patients via mitochondrial oxidative stress-initiated stimulation of AGT/ACE/Ang II cascade.

Funding: Government Support - Non-U.S.

SA-PO937

ATP6v1b1 Haploinsufficiency Lead to a Mild Incomplete Renal Tubular Acidosis (RTA) in Mice

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Background: Mutations in ATP6v1b1 gene in man is considered as an autosomal recessive disease and lead to distal RTA by dysfunction of the B1 subunit of H-ATPase in type A intercalated cells. In some transgenic mouse model of RTA, it also lead to increase in ammonia and alkaline urine pH.

Methods: Here we investigated on littermate mice whether ATP6v1b1+/- mice also develop acid-base disturbances during an acute and chronic acid challenge performed by 0.2 M HCl added to powdered standard food.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**Results:** ATP6v1b1+/- (WT) and +/- (HEt) mice exhibited no difference in their blood and urine parameters under baseline conditions. During the acid challenge, while ATP6v1b1+/- (KO) developed alkaline pH and low ammonia with hypercalciuria, HEt mice showed no difference in their urine data over the whole acid load compared to WT mice. However, even though, HEt mice did not exhibit low blood pH, as KO mice, they had a lower bicarbonatemia, higher chloremia and lower pcO2 compared to WT mice at the end of the acid challenge. Both KO and HEt mice drank more than WT mice over the acid load with a tendency to urinate more. After 4 days of acid load, subcellular localization of the α4 and β2 subunits of H-ATPase were not different within the 3 strains of mice and WT and HEt mice exhibited the same localization of β1 subunit. However, western blot analysis of B1 and B2 expression in renal membrane fractions revealed a 2-fold decrease of B1 and B2 protein expression in HEt mice compared to WT mice and no difference in the expression of B2 protein in KO mice compared to WT mice while B1 protein was totally absent from KO kidneys.

**Conclusions:** In conclusion, β1 HEt mice developed a mild incomplete RTA during an acid challenge, undetectable regarding urine parameters. The RTA is partly compensated by the respiration and an increase in water consumption. 2) B2 subunit does not compensate for the decrease in B1 expression both in HEt kidney tissues and seems to be inhibited by acid load.

**Funding:** Government Support - Non-U.S.

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**SA-PO938**

**Bedside Rule (pCO2=HCO3+15) Is Reliable in Predicting Respiratory Response in Metabolic Acidosis with Bicarbonate Levels of More than 7 meq/L.** Mohammad Kazem Fallahzadeh, Michael Emmett. *Dept of Internal Medicine, Baylor Univ Medical Center, Dallas, TX.*

**Background:** There is controversy about the reliability of the bedside rule (pCO2=HCO3+15) in prediction of respiratory response in metabolic acidosis. The aim of our study was to compare the accuracy of the bedside rule with Winter’s equation in predicting respiratory response in metabolic acidosis.

**Methods:** We extracted the measured bicarbonate and pCO2 levels of 382 patients with metabolic acidosis from the previously published articles evaluating the respiratory response to metabolic acidosis. We calculated the predicted levels of CO2 by bedside rule and Winter’s equation for each patient. Then we compared the accuracy of these formulas in predicting the respiratory response to metabolic acidosis.

**Results:** As demonstrated in the figure 1, the values calculated by bedside equation (pCO2=HCO3+15) appear to be a reliable predictor of respiratory response in HCO3 levels of more than 7 meq/L, as compared with the line of best fit and Winter’s equation.

**Conclusions:** Our results show that bedside rule (pCO2=HCO3+15) is reliable in predicting respiratory response in metabolic acidosis with HCO3 levels of more than 7 meq/L.

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**SA-PO939**

**TSS-Seq Analysis of Low pH-Induced Gene Transcripts in the Intercalated Cells of the Collecting Ducts.** Yuichiro Izumi,1 Koji Eguchi,1 Terumasa Takahashi,1 Hideki Inoue,1 Tokuma Kikuzoe,1 Hiroshi Nonoguchi,2 Masashi Mukoyama,1 1Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Japan, 2Dept of Internal Medicine and Education & Research Center, Kusasato Univ Medical Center, Japan.

**Background:** Metabolic acidosis is caused by acute and chronic kidney disease due to the decrease of acid excretion in the intercalated cells of the collecting duct in the kidney. Although the effect of acidosis on renal function has been examined in vivo, direct effect of low pH on the intercalated cells has not been investigated.

**Methods:** We employed Transcription Start Site-sequencing (TSS-Seq) to provide low pH-induced gene transcripts in rat intercalated cell line (IN-IC cells). Two biological replicates were used for the analysis. Cells were grown in a FBS-free DMEM/F12 overnight and incubated in an isotonic solution for 24h in which pH was adjusted either to 7.4 or 7.0, then total RNA was extracted. CDNA library for CAGE (Cap Analysis Gene Expression) was prepared and sequenced. Deep sequencing was performed on Illumina HiSeq2500 sequencer. TopHat 2 software was used to map TSS-Seq reads. RECLU was used to identify differentially expressed transcripts. Gene Ontology (GO) analysis was carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID).

**Results:** Biological Processes and Molecular Functions showed 9 clusters of the GO terms with high enrichment score (> 1.5) among expressed transcripts were upidentified. 261 transcripts were upregulated and 17 were downregulated. Among them, 225 upregulated and 13 downregulated transcripts were corresponded to known protein products. GO analysis of the intercalated cells showed high enrichment score (>1.5) were upregulated. TSS-Seq analysis for IN-IC cells at pH 7.4 and 7.0 were performed. 1952 genes were upregulated at pH 7.0 compared to pH 7.4. 1768 genes were downregulated at pH 7.4 compared to pH 7.0.

**Conclusions:** The results suggest that metabolic acidosis could regulate the function of intercalated cells and further exacerbate the renal fibrosis.

**Funding:** Government Support - Non-U.S.

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**SA-PO940**

**Narrowing the Gap Between the Anion Gap and the Strong Ion Gap.** Kenrick Boren,1 Andrew L. Lundquist,2 *Nephrology, St. Elisabeth Hospital, Willemstad, Curacao, Netherlands Antilles; 2MGH Div of Nephrology, Massachusetts General Hospital, Boston, MA.*

**Background:** Despite its importance in understanding acid-base pathophysiology, many physicians do not understand the concept of the strong anion gap. The core of the Stewart-acid-base approach is the ‘strong ion gap’ (SIG). The concept of SIG is similar to the AG, but the main difference is that Stewart uses more strong ions and the contribution of albumin and phosphate are adjusted for the pH. Because SIG gives a more precise picture of the acid-base disturbances, one may postulate that it provides a more accurate analysis of acid-base disturbances. The exact differences, however, are not established. This paper will give insight into the difference between the anion gap and the strong anion gap and provide an adjusted formula for the anion gap to replace the need for the strong anion gap.

**Methods:** The change of the strong ion gap (SIG) and the albumin-corrected anion gap (AG) were calculated at a wide range of albumin, phosphate and pH levels.

**Results:** At a low albumin level of 1 to 3 g/dl and decreased pH from 6.9 to 7.3, the contribution difference of albumin in AG and SIG will be maximally -0.97 to 0.51 mEq/L. In metabolic alkalosis (pH up to 7.6) and hypochloremia (1 to 3 g/dl), the AG differs less than 2 mEq/L with SIG. There is a linear relationship of the serum phosphate and the ionomic contribution of SIG: at a pH of 6.9, the phosphate_SIG is 1.66 times higher and at a pH of 7.6, 1.86 higher. In metabolic alkalosis and moderate hyperphosphatemia, the ionomic contribution to the anion gap will increase, but less than 1 mEq/L.

**Conclusions:** SIG and AG are almost identical across a wide range of values, particularly when albumin and phosphate levels are low. The pH adjusted serum phosphate level in the SIG is about 1.76 higher, with a confidence interval of 0.5 mEq/L. The anion gap will be more precise and incorporate the major components of the SIG when using the equation: [Na+] - [CT] . [HCO3]- - 2.5 [albumin, in g/dl] - 1.76 [phosphate], with an arbitrarily set reference range of 1+/-5 mEq/L.

**Funding:** Government Support - Non-U.S.

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**SA-PO941**

**V-ATPase in Luminal Membrane of Renal Proximal Tubule Requires B2 Subunit and CLC-5 for Its Full Functional Activity.** Nobuhiko Sato,1 Motonobu Nakamura,1 Atsushi Suzuki,1 Masashi Suzuki,1 George Seki,2 Shoko Horita.1 *Nephrology, The Univ of Tokyo Hospital, Tokyo, Japan; 2Izu City Hospital, Shizuoka, Japan.*

**Background:** Using an isolated rat proximal tubule (PT) primary culture system, we have previously shown that the activity of basolateral Na/HCO3 co-transporter (NBCe1) was preserved for 36 hours. Furthermore, gene silencing with siRNA enabled us to identify the signaling pathways involved in insulin-mediated NBCe1 stimulation (Nakamura M, Kidney Int, 2015). However, it remains unknown whether this technique is applicable to analysis of PT luminal transporters.

**Methods:** Freshly isolated mouse PT was attached to a glass coverslip with Cell-Tak glue and the lumen was exposed with a broken glass capillary. BCECF was used to measure intracellular pH (pHi). While the cariporide-insensitive luminal NHE activity was determined by the rates of pH decrease in response to Na removal, the cariporide-sensitive V-ATPase activity in Na-free solution was determined by the rates of pHi decrease in response to Na removal, the bafilomycin-sensitive V-ATPase activity was determined by the rates of pHi recovery in Na-free solution. These experiments were also performed after PTs were cultured overnight in the presence of siRNA against V-ATPase B2 subunit or CLC-5.

**Results:** The luminal NHE activity was at least partially preserved in isolated PT primary cultures (0.89 +/- 0.08 vs in intact system). The hypotonically (210 mOsm)-induced V-ATPase activity was also preserved in PT primary culture (0.50 +/- 0.05 vs 0.32 +/- 0.04 pH unit/min). Overnight treatment with siRNA against B2 subunit or CLC-5 largely suppressed the V-ATPase activity by 81% and 70%, respectively, without affecting the luminal NHE activity. We also confirmed that the Na-free solution, which V-ATPase activity was preserved, was depleted in heK293 cells not only decreased endosomal pH as estimated by ratiometric VAMP2-pHluorin but also induced the plasma membrane V-ATPase activity stimulated by hypotonicity (0.01+/-0.01 vs 0.59+/-0.07 pH unit/min).

**Conclusions:** The V-ATPase activity in the PT is suppressed by CLC-5 and the B2 subunit is involved in this process.
Conclusions: These data revealed for the first time to our knowledge that the luminal V-ATPase in PT is partial and CLC-5 for its full functional activity. The requirement of CLC-5 may be a common feature of mammalian V-ATPase, either expressed in endosome or plasma membrane.

Funding: Government Support - Non-U.S.

SA-PO942

The Mechanistic Target of Rapamycin Regulates Solute Transport in Renal Tubules Nasir A. Shah, Davide Pietro Cina, Tuncer Onay, Vera Eremia, Chengjin Li, Aline Martin, Vashpal S. Kanwar, Susan E. Quaggin, M. Health Services North Queensland, James Cook Univ, Townsville, Queensland, Australia; Medicine, Div of Nephrology, Northwestern Univ, Chicago, IL; Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, ON, Canada; Pathology, Northwestern Univ, Chicago, IL, Canada.

Background: Inhibitors of the mechanistic target of rapamycin (MTOR inhibitors) belong to a family of drugs with potent immunosuppressive, anti-angiogenic and anti-proliferative properties. Despite their clinical potential, their use in humans has been hampered by a significant incidence of proteinuria and electrolyte disturbances. Although some studies suggest MTOR may play a role in regulating renal solute transporter expression and function, the exact mechanisms underlying these changes are largely unknown.

Methods: In this study we examine the contribution of MTOR inhibition in the renal tubules to the development of proteinuria and electrolyte disturbances by generating an inducible Pax8敲出, tubule-specific Mtor knockout mouse (Mtor Pax8-iKO).

Results: Loss of Mtor in the renal tubular epithelium resulted in increased 24-hour urine volume, diminished urine osmolality, and renal failure. Despite elevated 24-hour urine albumin, Ca, and Mg, Mtor Pax8-iKO mice were both hypercalcemic and hypergammaglobulinemic. Histologically, Mtor Pax8-iKO mice exhibited generalized tubular atrophy with focal cysitolic dilations of the distal and cortical collecting tubules, and interstitial fibrosis. Immunohistochemistry showed decreased expression of aquaporin-2 (Aqp2), Calbindin D 28k (Cbd1), and the sodium-potassium-chloride cotransporter (Nkcc2).

Conclusions: Taken together, our results suggest that MTOR is a key player in maintaining electrolyte balance by modifying the expression, and function of solute transporters in the renal tubular epithelium.

SA-PO943

High Mobility Group Box 1 (HMGB1) Inhibits HCO3 Absorption in Medullary Thick Ascending Limb (MTAL) Through Receptor for Advanced Glycation End Products (RAGE)-Rho-Rock1-Mediated Inhibition of Basolateral Na+/H+ Exchange Bruns A. Watts, Thampi George, David W. Good.

Background: HMGB1 is a damage-associated molecule that is released extracellularly in response to infection or injury and plays a role in mediating kidney dysfunction in sepsis and sterile inflammatory disorders. Recently we showed that basolateral HMGB1 inhibits HCO3 absorption in perfused rat MTALs through a RAGE-dependent pathway additive to TLR4-ERK-mediated inhibition by LPS. Here we examined signaling and transport mechanisms involved in inhibition by HMGB1.

Results: Inhibition of HCO3 absorption by HMGB1 was eliminated by the Rho-associated kinase (ROCK) inhibitor Y27632 and associated kinase (ROCK) inhibitor Y27632 and by a specific inhibitor of Rho, the direct activator of ROCK1 by HMGB1 was eliminated by the RAGE antagonist FPS-ZM1 and by inhibition of Rho. Activation of ROCK1 by HMGB1 was eliminated by the RAGE antagonist FPS-ZM1 and by inhibition of Rho. Addition of a direct Rho activator reduced basal HCO3 absorption rate and prevented inhibition by HMGB1. The ROCK and ROCK inhibitors had no effect on inhibition by bath LPS. The Rho-ROCK1 pathway regulates NHE1 and we have shown that inhibition of NHE1 decreases MTAL HCO3 absorption secondary through cytoskeleton-dependent inhibition of apical NHE3. Inhibition of HCO3 absorption by HMGB1 was eliminated by bath amiloride, 0 Na body/day) or vehicle for a week. To further examine the effect of HMGB1 on the regulation of HCO3 in the intercalated cells, in vivo experiments have shown that metabolic acidosis and hypokalemia, that change plasma aldosterone level, increases and decreases the expression of Rhcg, respectively. Direct effect of aldosterone on the regulation of Rhcg has not been examined.

Methods: We examined the effect of aldosterone on the regulation of Rhcg. Membrane fraction of the whole kidney was extracted from mice that were continuously administrated aldosterone (10

Conclusions: The results suggest that aldosterone regulates membrane accumulation of Rhcg possibly through the activation of Sgk1.

Funding: Veterans Administration Support

SA-PO944

Identification of IQGAP-1 as a Pendrin-Binding Protein in the Kidney Jie Xu, Sharon L. Barone, Kamary A. Zahedi, Manoouche Salemi, Center on Genetics of Transport and Epithelial Biology, Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; Research Services, VA Medical Center, Cincinnati, OH.

Background: Networks of interacting proteins are crucial for all levels of cellular function. The Slc26 family of anion transporters [Slc26a3 (DRA), Slc26a5 (prosthen), Slc26a6 (PAT-1), and Slc26a9 (PAT-2)] form multi-protein complexes with cytoskeleton, anchoring proteins, PDZ adaptor proteins, CTR and/or protein kinases, which impart regulatory signals on these isoforms. No information is available on proteins that interact with pendrin (Slc26a4).

Methods: A yeast two hybrid system was employed to screen a mouse kidney cDNA library with a pendrin C-terminal fragment as bait. A total of 6 x 107 interacting clones were identified, out of which 14 clones were confirmed to be positive when screened for β-gal expression. Plasmids from these clones were purified and their interaction with pendrin was confirmed.

Results: Our experiments identified IQGAP-1 as a pendrin C-terminus binding partner. IQGAP-1 is a scaffolding protein that binds and/or stabilizes ezrin, CDC42 and RAC1, and interacts with cytoskeletal and cell adhesion molecules. The kidney, IQGAP-1 is strongly expressed in the DCT, CNT, CCD and podocytes. IQGAP-1 has also been shown to control tight junction formation through recruitment of claudin. Our results indicate that IQGAP-1 co-localizes with pendrin on the apical membrane of B-intercalated cells. IQGAP-1 is also detected on the basolateral membrane of A-intercalated cells in CCD. Functional studies in HEK293 cells demonstrated that the co-transfection of IQGAP-1 and pendrin increased pendrin-mediated Cl/HCO3 exchange activity by more than 60%. Confocal microscopy showed more abundant plasma membrane expression of pendrin in the presence of IQGAP-1.

Conclusions: These studies demonstrate the interaction of IQGAP-1 and pendrin in B-intercalated cells, as well as the stimulatory role of IQGAP-1 on pendrin activity. We propose that pendrin interaction with IQGAP-1 is important in the regulation of CCD function and physiology, and that disruption of this interaction contributes to altered pendrin trafficking and/or activity in pathophysiologic states.

Funding: Veterans Administration Support

SA-PO945

Regulation of Rheg by Aldosterone in Intercalated Cells of the Collecting Ducts Koji Esguchi, Yuichiro Izumi, Terumasa Nakagawa, Yushi Nakayama, Hideki Inoue, Yutaka Kikazoe, Takashige Kuwabara, Masashi Mukoyama.

Background: Acid-base balance is regulated by aldosterone which stimulates acid secretion in the intercalated cells of the collecting ducts of the kidney. Rhesus blood group C glycoprotein (Rheg) is an ammonia transporter which cooperates with H+/ATPase to secrete H+ in the intercalated cells. In vivo experiments have shown that metabolic acidosis and hypokalemia, that change plasma aldosterone level, increases and decreases the expression of Rheg, respectively. Different expression of aldosterone on the regulation of Rheg has not been examined.

Methods: We examined the effect of aldosterone on the regulation of Rheg. Membrane fraction of the whole kidney was extracted from mice that were continuously administrated aldosterone (10

Conclusions: The results show that aldosterone regulates membrane accumulation of Rheg possibly through the activation of Sgk1.

Funding: Government Support - Non-U.S.

SA-PO946

Role of Adenylyl Cyclase 6 in Regulation of Urinary pH Soren Brandt Poulsen, Robert A. Fenton, Timo Rieg, Dept of Medicine, UCSF, La Jolla, CA; VA/DHS, San Diego, CA; Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark.

Background: Adenylyl cyclase isoform 6 (AC6) is expressed in all renal tubular segments and catalyzes the synthesis of cAMP. We have previously reported that AC6 knockout (AC6–/–) mice have an urinary correction defect, a mild diuretic response, and secondary hyperparathyroidism. A recent study (Am J Physiol Renal Physiol. 2012;303(6):F812-20) determined that cAMP can increase pendrin protein (Cl:

Conclusions: The results suggest that AC6-mediated cAMP formation was important for urinary pH regulation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: AC6 wild-type (WT) and AC6-/- mice (n=6 genotype) were challenged with NaHCO₃ in their drinking water for a period of 8 days. As daily fluid intake is doubled in AC6-/- mice, the NaHCO₃ was reduced by 50% in this genotype (0.14 mol/l vs. 0.28 mol/l in WT). Urine was collected; blood was collected under baseline conditions and at the end of the 8 days experimental period. Mice were euthanized, one kidney processed for Western blotting (pendrin, H+-ATPase B1 subunit positive cells/mm² (WT: 322±2 vs. AC6-/-: 28±2) in the renal cortex was not different between genotypes.

Conclusions: Our results imply a role for AC6 in expression of pendrin and H+-ATPase B1 subunit and subsequently regulation of urinary pH. The increase in urinary pH in AC6-/- mice can only be achieved, or is the consequence of, higher pendrin abundance; however, this effect is independent of pendrin distribution changes. Further studies are needed to determine the signals causing baseline differences in urinary pH.

Funding: NIDDK Support, Private Foundation Support

SA-PO947


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Background: There is no clear consensus on the definition of acute kidney injury (AKI) and delay in development of DGF in deceased donor kidneys. In this study, we determine the discriminative and predictive ability of the Kidney Injury: Improving Global Outcomes (KDIGO) compared to the Acute Kidney Injury Network (AKIN) criteria for the prediction of the development of delayed graft function (DGF) and allograft outcome in deceased donor kidney transplantation (DDKT).

Methods: We analyzed 285 kidney transplant recipients who took kidney from 228 deceased donors. We calculated the AKI stage of deceased donor according to the AKIN and KDIGO criteria and compared the predictability for the development of DGF and the change of allograft function.

Results: For 2 classification systems, DGF developed more frequently in the AKI group than non-AKI group (P<.05) and allograft function assessed by the Modification of Diet in Renal Disease (MDRD) equation showed a significantly deteriorating pattern at 2 weeks and 1, 3, 6, 12 months after kidney transplantation compared to that in the non-AKI group (P<.05, comparison at each time point). In the Receiver-Operating Characteristic (ROC) curve analysis, the KDIGO criteria showed better prognostic accuracy of the prediction of the development of DGF compared to the AKIN criteria (area under the curve = 0.72 versus 0.62, P<.05).

Conclusions: In DDKT, the KDIGO criteria may be more useful for predicting the development of DGF compared to the AKIN criteria.

SA-PO948

Impact of Cold Ischemia Time on Graft Failure and Death

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Background: Patient and graft survival post kidney transplant (KT) are influenced by an interaction of multiple factors, including organ quality, preservation and cold ischemia time (CIT). Several small studies have suggested that even small increases in CIT adversely impact patient and graft outcomes. In this analysis we assess the impact of increasing CIT on patient and graft survival in the US.

Methods: We identified 75,660 first-time adult KT recipients, who received a deceased donor (DD) kidney from 2000-2011 in SRTR. Pearson’s chi-square tests of independence and logistic regression models were performed to test association between CIT and mortality, graft failure. Cox proportional hazard analyses, adjusting for donor factors (age, gender, serum creatinine, cause of death), recipient factors (age, dialysis duration, PRA status, HLA mismatch), machine perfusion, and specified effect measure modifiers, were performed to estimate the hazard of either event occurring given CIT.

Results: 60.7% of our cohort was black and 31.4% were black. Mean age was 52.2±10.3 years and average CIT was 18.2±9.2 hours. By univariate analysis, CIT was associated with an increase in risk of both death-censored graft failure and mortality (both HR=1.006; p<.0001). Adjusting for covariates and effect measure modifiers, the relationship between CIT and recipient mortality risk and death-censored graft failure were both attenuated (HR=1.000; p=0.9692 and HR=0.997; p=0.7479, respectively) suggesting that each additional hour of CIT did not significantly increase the risk of graft failure or death.

Conclusions: Our results suggest that increases in CIT do not adversely impact patient and allograft outcomes following DDKT and should not be used to decline organ offers.

SA-PO949

Impact of Hypothermic Machine Perfusion on Outcomes following Kidney Transplantation


Background: Patient and allograft outcomes following deceased donor kidney transplantation (DDKT) are thought to be influenced by the intrinsic quality of the organ at procurement and any superimposed subsequent injury that occurs during cold preservation (CP). Hypothermic machine perfusion (HMP) is used in an attempt to decrease injury from CP especially for organs that have extended periods of cold ischemia. We analyzed the impact of complete, partial or no HMP use during CP on patient and graft survival following DDKT.

Methods: We identified 75,660 first-time adult renal transplant recipients, who received a DD kidney from 2000-2011 in SRTR. Pearson’s chi-square tests of independence and Kruskal-Wallis tests were performed to test for association between HMP and mortality, graft failure, and delayed graft function (DGF). Cox analyses, adjusting for donor factors (age, gender, creatinine, cause of death), recipient factors (age, dialysis duration, PRA, HLA mismatch), CP time, and specified effect measure modifiers, were performed to estimate the hazard of either graft failure, or DGF occurring given HMP.

Results: On unadjusted analyses, compared to no HMP use, kidneys that received HMP for some or all of their CP time were less likely to experience DGF (OR=0.82, p=0.001 & OR=0.77, p=0.001) but more likely to experience allograft failure (HR=1.19, p=0.001 & HR=1.20, p=0.001, figure 1). On multivariable analyses, the use of HMP was associated with a lower incidence of DGF (OR=0.70, p=0.001 & OR=0.59, p<0.001) but continued to be associated with a higher risk of allograft failure even after adjusting for CIT and the lower DGF (HR=1.11, p=0.023 & HR=1.26, p=0.002).

Conclusions: HMP improves short term outcomes by lowering rates of DGF but is associated with reduced long-term allograft survival.

SA-PO950

The Impact of Remote Ischaemic Preconditioning (RIPC) on the Inflammatory Response following Live Donor Kidney Transplantation

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Background: Ischaemia reperfusion injury (IR) at transplantation contributes to organ damage that limits allograft longevity. Animal studies have demonstrated a reduction in proinflammatory cytokines following RIPC, which may contribute to protective effects. REPAIR demonstrated a trend towards improved live donor kidney function following RIPC. We investigated the effects of RIPC on serum and urinary cytokines in this study.

Methods: 406 adult live donor/recipient pairs were recruited. Pairs were randomised using a factorial design to either: sham RIPC, early RIPC (immediately pre-surgery), late RIPC (24 hours pre-surgery) or dual RIPC. Donor and recipient received the same interventions (active or sham RIPC). Serum from donor and recipient and urine from recipients were analysed at baseline and on day 2 for pro-inflammatory cytokines IL-1β, IL-6, IFN-γ and TNFα, using multiplex ELISA. All analyses were conducted using linear regression adjusted for baseline (pre-treatment) values of the cytokine and indicator variables for early and late treatment group. Cytokine values were log transformed before analysis to account for skewed distribution.

Results: There was no difference in the expression of serum cytokines in donor serum or recipient serum and urine between baseline pre-surgery and day 2 post surgery.

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SA-PO952

Low Expression of the Messenger RNA TLRs 2-4,9 from Peripheral Blood Mononuclear Cells of the Kidney Recipients May Indicate Previous Delayed Graft Function

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Background: The Toll-like receptors (TLR) 2-4,9 are engaged in the pathogenesis of acute renal injury. Earlier studies demonstrated that 24 hrs. after transplantation (KT), the expression of the messenger of mRNA (mRNA) TLR4 of peripheral blood mononuclear cells (PBMC) from patients (pts) with delayed graft function (DGFi) was lower than in recipients of kidneys without DGF (DGFi). The aim of study was to examine whether the reduced expression of TLR2-4,9 mRNA is a more permanent phenomenon associated with DGF.

Methods: Each of the 151 KT pts was more than 1 month after KT (from 1 to 128 months). Within this group: in 117 pts blood sample was taken for more than 3 months after KT, 45 pts experienced DGF, 13 DGFi pts was HBCaB positive (DGF+HBCaB). Control group (Con.) included 38 healthy volunteers. TLR2-4,9 mRNA expression (expr.) from PBMC was assessed by polymerase chain reaction (real-time PCR) and analyzed in terms of DGF and clinical course.

Results: KT DGF+ pts had generally lower TLR2-4,9 mRNA expr. than KT DGF- pts (TLR2: p=0.06; TLR3: p=0.02; TLR4: p=0.07; TLR 9, p=0.027) TLR3 mRNA of DGF+HBCaB pts was: lower (p=0.046) than DGF+HBCaB, lower (p=0.013) than DGF-ATN- and lower (p=0.008) than Con. TLR9 mRNA of DGF+HBCaB was lower (p=0.002) than Con. In multiple regression analysis low expr. of TLR mRNA 2-4,9 was associated with the occurrence of DGF in the past.

Conclusions: Lower than typical expression of TLR 2-4,9 mRNA seems to be a potential feature of peripheral blood mononuclear cells of the recipient of the transplanted kidney who experienced delayed graft function. Hepatitis B seems may be associated with additional decline of TLR3 and TLR9 mRNA expression. TLR3,4,9 mRNA expression could potentially be used an indicator of the likelihood of delayed graft function.

Funding: Clinical Revenue Support

SA-PO953

BB3, a Hepatocyte Growth Factor-Like Small Molecule, Improves Outcome in Kidney Transplant Recipients with Delayed Graft Function

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Background: Duration of delayed graft function (DGF) portends poor short- and long-term renal function and graft survival. We studied the safety and efficacy of BB3, a small molecule with HGF-like activities, dosed starting 24 hr post-transplant (Tx) in patients with reduced urine output (UO) in a double-blind Phase 2 study.

Methods: Patients presenting ≥50 cc urine/hr over 6-8 h post-Tx were randomized (2:1) to BB3 (2 mg/kg IV QD X 3 d) or placebo (PBO). An interim analysis was performed on 12 BB3- and 7 PBO-treated patients.

Results: BB3 was safe and well-tolerated. BB3 reduced the median time to produce 1.2L UO/24 hr from > 28 d to 7.5 d, increased the % of patients reaching this UO within 28 d from 43% to 83%, increased cumulative UO (figure), decreased median duration of dialysis (figure), decreased % on-dialysis days during Days 7-28 (14.2% to 7.1%) and during Days 14-28 (10.9% to 3.6%), reduced median SCR, reduced BUN, and shortened median hospital stay (7 d to 5.5 d). BB3 reduced serum CRP and NGAL.

Conclusions: BB3 administered ~24 hours post-Tx significantly reduced severity of DGF in patients presenting with reduced UO. Confirmation of these results in a Phase 3 trial may translate to improved long-term outcome, decreased Tx costs, increased use of marginal organs, and a shorter waitlist.

Funding: NIDDK Support, Pharmaceutical Company Support - Angion Biomedica Corp.

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852A
SA-P0954

DSA Monitoring and Treatment in Kidney Transplant Recipients
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Background: The development of DSA monitoring is a new technique to detect antibodies in kidney transplant recipients. We previously showed that patients who developed de novo DSA (dnDSA) suffer a 35% graft loss. Because of this we have developed a protocol for treating patients that have developed dnDSA post kidney transplantation.

Methods: Since the implementation of this treatment protocol on September 12, 2014, there have been 9 patients that have developed dnDSA after renal transplantation.

Results: Four of the patients that developed dnDSA were in the low risk category and in 5 of them the DSA has cleared. The 4th patient has a DSA against DP1 with an MFI of 1587 that has remained stable. All of these patients have a GFR>45 cc/min. Three patients were in the intermediate risk category. One of them has a creatinine of 3, BK viremia and he has a DSA against A1 with an MFI of 3150 which has been stable.

Conclusions: Since the implementation of this treatment protocol on September 12, 2014, there have been 9 patients that have developed dnDSA after renal transplantation. This preliminary data shows that treatment for dnDSA with this protocol seems to successfully treat the antibodies.

SA-P0956

Low Level Class I or II Donor HLA-Specific Antibodies Do Not Correlate with the Concurrent Presence of Antibody Mediated Injury on Biopsy
Chelsea Estrada,1 Catherine Miranda,2 Hesecuk Suh,2 Frank Darras,2 Edward P. Nord,3 Mersema Abate.1 Nephrology and Transplantation, Stony Brook Medicine, New York.

Background: Pre-transplant and de novo donor HLA-specific antibodies (DSA) have been identified as risk factors for adverse outcomes in renal transplantation, causing antibody-mediated graft injury and acute antibody mediated rejection (ABMR) and transplant glomerulopathy (TG). With improved detection techniques, DSA recognition is increasing but there is no consensus on the definition of DSA positivity. While low level pre-transplant DSA has been associated with the future occurrence of ABMR, low level DSA on the day of indication biopsy is of unclear significance.

Methods: All sera were tested for DSA using single antigen beads with Luminex technology on the day of indication renal transplant biopsy from 7/1/2015 - 5/21/2015. DSA level >500 mfi were considered negative, between 500-1500 mfi low level and >1500 mfi high level. Acute ABMR and TG histology met Banff 2013 criteria. In this cohort, induction was with alemtuzumab and rapid steroid withdrawal, and maintenance immunosuppression was with tacrolimus and mycophenolate mofetil. Chi square analysis was used to assess the association between low and high levels of DSA and biopsy findings of antibody mediated injury.

Results: Fifty-three consecutive indication kidney transplant biopsies were performed from 7/1/2014 - 5/21/2015. Of these 12 had evidence of ABMR (2 acute, 8 TG and 2 both). Six of the 8 patients with TG alone did not have DSA. At the time of biopsy, 12 class I (6 low and 6 high level) and 13 class II (3 low and 10 high level) were detected.

Conclusions: 1. The presence of high level class II DSA was significantly associated with the concurrent biopsy finding of antibody mediated injury. 2. Of greater significance, the presence of class I DSA or low level class II DSA did not correlate with pathologic findings.

SA-P0957

Characteristics of Kidney Transplant Candidates with and without Antibody against Angiotensin II Type I Receptor (AT1R-Ab)
Mary Carinelle Philogene1, S.M. Bagnasco,2 Annette M. Jackson,2 Mary S. LeTellier,1 Andrea A. Zachary.1 1Medicine, Johns Hopkins Univ, Baltimore, MD; 2Pathology, Johns Hopkins Univ, Baltimore, MD.

Background: In this study we sought to determine whether baseline characteristics of kidney transplant candidates when correlated with presence of AT1R-Ab are predictive of transplant outcomes.

Methods: 122 renal transplant recipients were tested for presence of AT1R-Ab using quantitative ELISA (CellTrend GmbH, Germany). Patient demographics were obtained from the hospital electronic record under an approved IRB.

Results: Patients were categorized according to AT1R-Ab levels: positive (>17 Units/ml (30%); borderline 10-17 Units/ml (34%), negative <10 Units/ml (36%). There were fewer females (31% versus 61%, 55%) and African Americans (14% versus 24%, 16%) in the AT1R-Ab >17 Units/ml group compared to the other two groups. The presence of AT1R-Ab has been associated with development of inflammation and fibrosis; therefore, we examined AT1R-Ab among patients categorized by the following diseases: IgA nephropathy, glomerulosclerosis, lupus nephritis, FSGS, and membranoproliferative glomerulonephritis. We found no correlation between these diseases and AT1R-Ab levels (38%, 29% and 30%, respectively; p=0.7). We also found no association with diagnosis of hypertension and AT1R-Ab levels (16%, 17%, 18%). The most significant difference between the three groups was a higher percentage of positive patients among those who received more than one kidney transplant (78%, 22%, 45%; p=0.001). Post transplantation, sixty-one patients were biopsied to investigate graft dysfunction. There were more patients in the borderline and positive AT1R-Ab groups who were evaluated for graft dysfunction compared to the negative group (65%, 54% versus 34%) although this did not reach statistical significance.

Conclusions: The only pre-transplant characteristic linked to presence of AT1R-Ab in patients who are being evaluated for kidney transplantation is the incidence of previous transplant.

Funding: Clinical Revenue Support

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853A
SA-PO958

Effect of B-Cell Activating Factor (BAFF) Inhibition (LY2127399; Tabalumab) on Highly Sensitized Patients with End Stage Renal Disease awaiting Transplantation Muhammad Ahmad Muftiua, Wendy Komocsi, Milagros D. Samaniego-Picota, Eric Nantz, Jayne Hague, Melissa D. Anderson, Benita K. Book, Nancy G. Higgins, Tim E. Taber. Nephrology, Univ of Texas Medical Branch, Galveston, TX; Transplant Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; 3Bio-Medicines, Eli Lilly and Company, Indianapolis, IN; 4Nephrology, Univ of Michigan Health System, Ann Arbor, MI.

Background: B cell activation factor (BAFF) is critical in B-cell maturation. Inhibition of BAFF represents an appealing target for desensitization of highly sensitized end stage kidney disease patients.

Methods: We conducted a Phase 2a, single-arm, open-label exploratory study investigating the effect of tabalumab (BAFF inhibitor) in ESRD patients with cPRAs ≥50%. The treatment period had a total duration of 24 weeks. Eighteen patients received tabalumab, at a dose of 240-mg subcutaneous (SC) at Week 0 followed by 120-mg SC at 4-week intervals for 5 more months. Patients were then followed for an additional 52 weeks. Blood samples were analyzed for HLA antibodies, BAFF levels, serum immunoglobulins, T and B cell subsets at specified time intervals during the treatment and follow-up periods. Pre and post treatment tonsil and bone marrow biopsies were also performed.

Results: Significant reductions in cPRAs were observed at week 16 (p=0.043) and at week 36 (p=0.004), however the absolute reductions were small (<5%). Overall factor effect at week 76 compared to baseline was significant (p=0.04). Mean BAFF levels increased during treatment, reflecting binding to tabalumab and decreased in the follow-up period remaining slightly above baseline at week 76. Expected changes in B cell subsets and reductions in immunoglobulins were observed. Two tabalumab-related serious adverse events occurred (pneumonia and worsening of peripheral neuropathy) while the most common other adverse events were injection-site pain and hypotension. Three patients received a matched donor cadaveric transplant during the study follow up.

Conclusions: BAFF inhibition resulted in statistically significant, but not clinically meaningful reduction in the cPRA from baseline.

Funding: Pharmaceutical Company Support - Eli Lilly

SA-PO959


Background: Pre- and post-transplant DSA increases the risk for acute rejection, humoral rejection and graft loss. Every year a 5% of patients will develop DSA but other patients turn negative. It is unclear how the behavior of pre-transplant DSA under immunosuppression and their clinical impact. This study evaluate the relationship between de novo DSA and the outcome of kidney transplantation, and whether the development of these antibodies is related to pre-transplant DSA status.

Methods: Prospective cohort study. From Jun/2004-Dec/2014 a total of 519 kidney transplant were performed. For analysis we include 412 with DSA determination plus those with positive Flow-Crossmatch (in DSA-positive cases). We classified the patients in 7 groups transfusions were performed. For analysis we include 412 with DSA determination plus these antibodies is related to pre-transplant DSA status.

Results: From 412 patients, 58 patients (14.1%) had pre-transplant DSA. Patients with Pos/Pos or Pos/De Novo DSA had higher and earlier AR and AMR rate, followed by Neg/De Novo-VARIABLE and Neg/De Novo, as you can see in the figure A) and B) respectively. For graft loss only those with Pos/De Novo was higher than Neg/Neg (Figure C). Interestingly, those who are Pos/Neg had similar outcomes than Neg/Neg.

Conclusions: Staying with the same DSA or developing De Novo-DSA after transplantation, regardless what the pretransplant condition was, were associated with development of AR, AMR, and graft loss.

Funding: Pharmaceutical Company Support - Eli Lilly

SA-PO960

Course of Anti-HLA Antibodies After Induction Therapy with Rituximab in Renal Transplantation Luuk Hilbrands, Wil Allesbe, Martijn W.F. Van den hoogen, Irma Joosten, Marjoke C. Baas, Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Laboratory Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands; 3Nephrology, Erasmus Medical Center, Rotterdam, Netherlands.

Background: B-cell depletion protocols have shown to reduce donor-specific antibodies against HLA (DSA) and chronic antibody mediated rejection. We aimed to study the effects of rituximab as a single-agent induction therapy on the titers of pre-existent or de novo DSA and non-DSA after renal transplantation and relate this to rejection free and overall graft survival.

Methods: We collected sera in participants of a prospective double-blind randomized study on the efficacy and safety of the prophylactic use of one dose of rituximab, added to standard immunosuppressive treatment (prednisolone, tacrolimus and mycophenolate mofetil) in comparison with standard immunosuppressive treatment alone in renal transplantation (www.clinicaltrials.gov, NCT016565331).

Results: 280 patients were included (142 received placebo, 138 rituximab). Anti-HLA antibodies (Ab) were determined in serum taken pre-transplant and 12 and 24 months after transplantation. Serum was analysed pre-transplant and at 12 months from 126 placebo and 119 rituximab treated patients. Pre-existent anti-HLA Ab were present in 24/126 (19.0%) patients in the placebo group and in 20/119 (16.8%) patients in the rituximab group (P=0.05). In the placebo and rituximab treated patients HLA class I Ab disappeared in 55.6% and 50% and HLA class II Ab in 23.5% and 57%, respectively (P=0.06). At 12 months, 11 (8.7%) placebo treated patients and 4 (3.4%) rituximab treated patients (NS) developed de novo HLA Ab. 10/245 (4.1%) had de novo HLA class I Ab: 6 (4.8%) and 4 (3.4%) in the placebo and rituximab treated patients, respectively (NS). 12/245 (4.9%) had de novo HLA class II Ab: 9 (7.1%) in the placebo group and 3 (2.5%) in the rituximab group (P=0.09).

Conclusions: Induction therapy with rituximab compared to placebo does not significantly influence the course of anti-HLA Ab at 12 months, however it possibly decreases the levels of pre-existent class II anti-HLA Ab and inhibits the formation of de novo class II anti-HLA Ab.

Funding: Pharmaceutical Company Support - Roche, Astellas

SA-PO961


Background: We conducted a multicenter prospective clinical study in ABO-incompatible kidney transplantation (ABO-KT) without splenectomy (UMIN000006635). To evaluate the benefit of desensitization with rituximab (R), we investigated the data of this study from the time course change of anti-A/B antibody (ab) titer and sequential pathological findings.

Methods: Desensitization protocol included low dose MMF and steroid started 28 days before and CNI started a few days before surgery. R 375 mg/m2 was administered at day -14 and day -1. Minimum 2 sessions of plasma exchange were done for anti-A/B ab removal before transplant, and basiliximab was administered on day 0 and day 4. Anti-A/B
ab titer and eGFR were sequentially evaluated, 0 hr, 1 hr and protocol biopsies (4 weeks after transplant) were also sequentially performed as possible. Pathological specimens were centrally diagnosed by 3 pathologists.

Results: 18 pts received AB0i-KT. One-year pts and graft survival were both 100%. The desensitization with R was well tolerated. Average anti-A/B or IgG titer at baseline was 150x increased to 19.72x immediately before surgery, maintaining until the end of the study. In pts whose sequential pathological specimen available showed positive C4d deposition in 1/3 at 1 hr and 11/16(69%) at protocol biopsy. No pts developed AMR related to anti-A/B abs except for one who experienced AMR with anti-HLA ab (Banff07 type II). Her anti-A/B abs titers were slightly higher than the others (4x-32x). Pathological findings included arteriosclerosis in 8, nephrocalcinosis in 1, IF/TA (grade 1) in 1 and suspicious CNI acute nephrotoxicity in 1. Two pts showed C4d+ without other pathological signs. Conclusions: In this series, anti-A/B ab titers were successfully decreased and no AMR occurred other than 1 caused by anti-HLA ab, whereas C4d deposition was detected in 69% of pts by protocol biopsy. Our desensitization protocol was confirmed both pathologically and clinically and safely effective for AB0i-KT.


SA-PO962
Post-Transplant BAFF Levels Do Not Predict the Development of Anti-HLA Antibody in Kidney Transplant Recipients

Byung H. Chung, MD, PhD, 1,2 Seong K. Ha, MD, PhD, 1,3 Issac B. Lee, MD, PhD, 1,2 Michael D. Kang, MD, PhD, 1,2

Background: Pre-transplant BAFF levels are associated with the development of de novo anti-HLA antibodies and also antibody mediated rejection post-transplant. However, the clinical significance of BAFF values at allograft rejection has not been determined. In this study, we investigated the clinical significance of pre- and post-transplant BAFF levels measured when indicated biopsy was done.

Methods: In 130 kidney transplant (KT) recipients who required allograft biopsy due to an increase in serum creatinine, we checked for anti-HLA antibodies using Lumines single antigen assay, and measured BAFF levels using ELISA kits. In 78 of these patients we also measured pre-transplant BAFF and anti-HLA antibody levels. We investigated the relationship between pre-transplant, post-transplant and delta BAFF levels and the occurrence of anti-HLA antibodies.

Results: Pre-transplant BAFF levels showed significant association with pre-transplant sensitization, represented by positive PRA, high PRA, and presence of HLA-DSA. They also showed positive association with early rejection (rejection within 6 months from KT). Post-transplant BAFF levels showed significant association with pre-transplant sensitization, but did not show association with anti-HLA antibodies and positive donor-specific antibodies at the time of biopsy. We did not find any association between post-transplant BAFF levels and cumulative allograft survival, allograft biopsy results, Banff scores and microvascular inflammation scores.

Conclusions: In conclusion, pre-transplant BAFF levels are associated with pre-transplant sensitization and are useful in predicting allograft rejection. But post-transplant BAFF levels measured at the time of indicated biopsy are not associated with the appearance of de novo HLA-DSA, allograft rejection, biopsy findings and other allograft outcomes.

SA-PO963
Effectiveness of Bortezomib (BT) in the Treatment of Antibody Mediated Rejection Among Pediatric Kidney Transplant Recipients (pKTx)

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Sarah J. Zirulbils,1 Donna J. Claeys,2 Issac A. Ashoor,2 Ashton Chen,1 Sara E. Janideska,1 Raed Bou Matar,1 Jaron Misurac,2 Katherine Twombley,1 Priya Verghese1,2 Pediatric Nephrology, Univ of Minnesota; 1Cincinnati Children’s Hospital; 1Children’s Hospital New Orleans; 1Wake Forest Univ; 2Rush Univ; 2Cleveland Clinic; 1Indiana Univ; 1Medical Univ of South Carolina.

Background: AMR has a poor prognosis despite a number of therapeutic options. BT is increasingly being utilized in adults but there are limited data on its safety and efficacy in pKTx with AMR.

Methods: Multicenter retrospective case series including all pKTx who received BT for biopsy proven AMR, from 2008-2015, at 8 centers within Midwest Pediatric Nephrology Consortium. Results: Twenty-four pKTx from 8 centers were treated with BT for AMR. In addition to BT, 75% were treated with rituximab, 79.2% with plasmapheresis and 91.7% with IVIG. 62.5% were males, 45.8% were white, and 41.7% were African American. Two-thirds were deceased donor recipients, and mean age at transplant was 11.1 years (SD 5.19). Obstructive uropathy and dysplasia comprised 50% of the underlying diseases. At the time of transplant, 82.2% of patients had 0.0% panel reactive antibodies. Mean estimated GFR (eGFR) prior to AMR was 49.6 (SD 12.1). Prevalence of donor specific antibodies (DSA) and changes in eGFR are shown in table 1.

Conclusions: Even though limited by small patient numbers, this trial suggests efficacy of IA in the treatment of late ABMR.

SA-PO965
Pre-Transplant Phospholipase A2 Receptor Autoantibody Concentration Is Associated with Recurrence of Membranous Nephropathy Post-Kidney Transplantation

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Background: Idiopathic membranous nephropathy (mN) has been associated with anti-phospholipase A2 receptor autoantibody (PLA2R-Ab) both in the native kidneys as well as in the setting of recurrence (mN) post-kidney transplant (txp). Previous studies that have assessed pre-txp PLA2R-Ab for the prediction of mN have yielded variable results. Many of these studies have been limited by the use of variable immunosuppressive protocols among patients, different ELISA assays as well as method of diagnoses (surveillance vs indication biopsies).

Results: 40 renal tx recipients diagnosed as biopsy confirmed mABMR at a mean time of 70±40 months after tx were included. Patients were randomly assigned to PE (n=16) or DFPP (n=19) or IA with protein A (n=5). The studies were similar regarding age, gender, donor type, eGFR at randomization and post-tx follow-up time. Donor specific antibody (DSA) was positive in 62.5% of PE, 73.6% of DFPP and 100% of IA groups (p=0.25), and C4d was positive in 75%, 68% and 60% (p=0.79), respectively. All patients received 2 g/kg IVIG and Rituximab 375 mg/m².

Results: Tubulointerstitial scar rate (civt) (p=0.81), microcirculation inflammation (g+pc) (p=0.38) and transplant glomerulopathy (g) (p=0.21) scores were similar. However, the mean total inflammation (ti) score of IA group (2.60±0.55) was significantly higher than PE (1.69±0.70) and DFPP (1.79±0.71). The rates of graft loss were as follows; PE; 13/16 (81.3%), DFPP; 10/19 (52.6%) and IA; 1/5 (20%) (p=0.03). The graft survival was significantly higher for IA than PE (p=0.01). There was a tendency of better graft survival in DFPP compared to PE group (p=0.07). Kaplan-Meier survival analysis revealed better overall survival for IA than for PE and DFPP (p=0.03).

Conclusions: Even though limited by small patient numbers, this trial suggests efficiency of IA in the treatment of late ABMR.
Methods: Sixteen consecutive txp patients with a history of IMN were tested for pre-txp PLA2R-Ab. ELISA titers (Euroimmun, NJ, USA) >14 RU/ml were considered positive, as per manufacturer instructions. All patients received similar post-transplant immunosuppression. A receiver operating characteristic (ROC) analysis was performed after combining data from Quintana et al. (n=21; Transplantation Feb 2015) to determine a PLA2R-Ab concentration which could predict rMN.

Results: Six (out of 16; 37%) patients had biopsy-proven rMN at a median of 3.2 years post-txp. Of these, 5/6 (83%) had a positive PLA2R-Ab pre-txp with a median of 82 RU/ml (range=31-1500). The only patient who had rMN with a negative PLA2R-Ab was later diagnosed with nodular sclerosing Hodgkin’s lymphoma 100% (n=1) patients with no evidence of rMN (median follow-up=5 years) had negative PLA2R-Ab though one patient did have a borderline titer of 13.8 RU/ml. Patients with rMN were treated with rituximab and had an improvement in proteinuria from a median of 6g/d to 0.6g/d. Among the patients with rMN and positive PLA2R-Ab, titers fell to a median of 4 RU/ml at most recent follow-up.

In a combined ROC analysis (n=37) a pre-txp PLA2R Ab>29 RU/ml predicted rMN with an AUC of 0.78 vs. T1/T2 0.82, Z statistic 1.94. In the test set, 12 of 16 txp patients had biopsy-proven rMN at a median of 3.8 years post-txp. Of these, 10/12 (83%) had a positive PLA2R-Ab pre-txp with a median of 59 RU/ml (range=29-293). Patients with rMN had a higher IL10:TNFα ratio. Thus T1 TrBs represent the B subset over the next 5 years (ROC AUC 0.82, P<0.001) and was independently associated with allograft deterioration (HR 26.6, 95% CI 3.1-227.3, P<0.003). In both the test and validation sets, T1/T2 ratio was a much stronger predictor of graft deterioration than traditional markers like eGFR (test set, eGFR ROC AUC 0.76 vs. T1/T2 ratio 0.84, Z statistic 0.97; validation set, eGFR ROC AUC 0.64 vs. T1/T2 ratio 0.82, Z statistic 1.92), or the detection of DSA (test set, DSA ROC AUC 0.68 vs. T1/T2 ratio 0.84, Z statistic 3.2; validation set, DSA ROC AUC 0.66 vs. T1/T2 ratio 0.82, Z statistic 2.35).

Conclusions: Pre-transplant PLA2R-Ab could be a useful tool for the prediction of rMN. Patients with rMN in the absence of PLA2R-Ab should be screened for occult malignancy.

SA-PO966 Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio Predict Acute Allograft Rejection
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Background: Currently, allograft biopsy is gold standard for diagnosing rejection however there is intense interest in identifying non-invasive biomarkers. The goal of this study is to determine whether the neutrophil-to-lymphocyte ratio (NLR) or the platelet-to-lymphocyte ratio (PLR) correlate with acute allograft rejection.

Methods: This single center retrospective case-control study examined all kidney transplant biopsies conducted at Einstein Medical Center from Jan 2013 through Dec 2014. Biopsies were stratified for rejection (acute cellular, borderline, negative). The NLR and PLR were calculated from routine laboratory studies obtained at various time points preceding the biopsy.

Results: Of the 102 “for cause” biopsies, 37.3% showed clear evidence of acute rejection and 18.6% were borderline. NLR and PLR obtained within the week prior to the biopsy showed a significant reduction in acute rejection (P<0.05) and the NLR in PLR preceded the biopsy by 2-4 weeks suggesting a rejection prodome. Interestingly, NLR at the time of boarderline biopsy with acute cellular rejection. This reduction in NLR and PLR preceded the biopsy by 2-4 weeks. A follow-up (ROC AUC 0.84, P<0.001). In a multivariate Cox model, T1/T2 ratio was independently associated with allograft deterioration (HR 4.8 95% CI 1.3-17.8, P=0.02). T1/T2 ratio was examined 2 years post-transplant in a prospective validation set of 97 stable patients derived from a steroid avoidance RCT comparing alemtuzumab (n=51) vs. cyclosporine (n=46). A T1/T2 ratio >1.1 was a strong predictor of graft deterioration over the next 5 years (ROC AUC 0.82, P<0.001) and was independently associated with allograft deterioration (HR 26.6, 95% CI 3.1-227.3, P<0.003). In both the test and validation sets, T1/T2 ratio was a much stronger predictor of graft deterioration than traditional markers like eGFR (test set, eGFR ROC AUC 0.76 vs. T1/T2 ratio 0.84, Z statistic 0.97; validation set, eGFR ROC AUC 0.64 vs. T1/T2 ratio 0.82, Z statistic 1.92), or the detection of DSA (test set, DSA ROC AUC 0.68 vs. T1/T2 ratio 0.84, Z statistic 3.2; validation set, DSA ROC AUC 0.66 vs. T1/T2 ratio 0.82, Z statistic 2.35).

Conclusions: We demonstrate a distinct subset of TrB (T1) characterized by an anti-inflammatory cytokine profile. A decrease in T1-T2 ratio (due to selective loss of T1 cells) is a strong prognostic biomarker for subsequent renal allograft deterioration.

Funding: Private Foundation Support

SA-PO968 The Pre-Transplant Ratio of T Regulatory Cells to Effector/Memory CDB+ T Cells Is Correlated with the Development of Acute Rejection
Kentarou Sugisaki, QiZhi Tang, Sang-Mo Kang, Surgery, Medical Center, Univ of California, San Francisco, San Francisco, CA.

Background: Acute rejection (AR) or renal allografts are a major predictor for the development of chronic allograft nephropathy (CAN) and subsequent graft loss. Although clinical risk factors for the development of AR have been identified, few techniques exist to individually stratify patients for the risk of AR and provide a rational basis for the tailoring of immunosuppression regimens. Over the past two decades, regulatory T cells (Treg) have been identified and subsequently shown to be critical to the prevention of autoimmunity as well as the prevention on organ allograft rejection in numerous models. In parallel, the identification of various T lymphocyte subsets has been greatly refined, allowing a more precise quantitation and correlation with outcomes.

Methods: We hypothesized that Treg abundance pre-transplant could predict for the development of acute rejection in patients undergoing de novo renal transplantation. We prospectively enrolled 16 renal transplant patients undergoing first transplant from August 2013 to March 2014. We excluded patients undergoing second transplants, desensitization protocols, or involved in other clinical trials. Venous blood samples from all recipients at transplant date were isolated the peripheral blood mononuclear cells (PBMCs) and stored. We analyzed the samples in batches and normalized cell surface and intracellular staining using a standard control, using a NAVIOS flow cytometer (Beckman Coulter). All recipients were followed for a minimum of 1 year for the development of biopsy proven rejection.

Results: 12 recipients experienced AR. The pre-transplant ratio of Treg/EM CD8 T cells may identify patients at increased risk of AR and should encourage larger scale studies to validate and quantify the magnitude of risk as well as to assess covariables.

Conclusions: Our data suggests that the pre-transplant ratio of Treg/EM CD8 T cells may identify patients at increased risk of AR and should encourage larger scale studies to validate and quantify the magnitude of risk as well as to assess covariables.

SA-PO969 The Association of Th17 Cell Phenotype with Chronic Allograft Dysfunction in Kidney Transplant Recipients Byung Ha Chune, Hyunsoo Kim, Chul Woo Yang. Internal Medicine, Seoul St. Mary’s Hospital, Seoul, Korea.

Background: The purpose of this study is to determine the significance of the Th17 cell pathway in the progression of chronic allograft dysfunction.

Methods: We investigated the expression of T cell phenotype in long-term stable kidney transplant recipients (KTRs)(LTS, n=67), chronic allograft dysfunction group (CAD, n=52), and also in three control groups (early stable KTRs (ES, n=28), end stage renal dis. reduced (ESRD, n=45), and healthy control (HC, n=26)).

Results: The percentage of Th17 cells out of CD4+ T cells and the proportion of IL-17 producing cells out of effector memory T cells showed a significant increase in the CAD group compared to the LTS group and other control groups (P = 0.06). In addition, The percentage of CCR4+CCR6+CD4+ T cells and IL-17 producing cells out of CCR4+CCR6+CD4+ T cells was higher in the CAD group than in the LTS group (P=0.05). However, the percentage of Th1, Th2, and regulatory T cells did not differ significantly between the CAD and LTS groups (P > 0.05). Also, the serum level of IL-17, IL-33, and RAGE, and the expression of IL-1beta, RAGE, and HMGB1 mRNA showed an increase in the CAD group compared to the LTS group. Lastly, IL-17 induced acute and chronic injury in the human proximal renal tubular epithelial cell line in a dose-dependent manner.

Conclusions: In conclusion, we found the activation of the Th17 cell pathway in patients with chronic allograft dysfunction. The results of this study suggest that Th17 pathway may have a role in the progression of chronic allograft injury.

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Underline represents presenting author.
SA-PO970

Quantitative Characterization of T Cell Repertoires in Kidney Transplant Patients

Patients: Hussein Alachak,1 Martin B. Mutonga,1 Taigo Kato,1 Sowjanya Kalluri,1 Vikas Vujinjii,2 Yusuke Nakamura,2 Nada Alachkar,2 University of Chicago; 2Johns Hopkins Univ; 2Kendall Medical Center.

Background: Acute and chronic T cell mediated rejection remains a major cause of kidney graft failure. Despite the significant decrease in early acute rejection due to current potent immunosuppressions, long-term graft survival remains unsatisfactory. Thus, characterization of the T cell repertoire and the kinetic of the expanded clones in transplant (Tx) patients may shed a light on our understanding of the T cells’ role in graft rejection.

Methods: We collected blood and urine samples from (46) patients before Tx, and at sequential time points post Tx and at time of T cell mediated rejection. We utilized next generation sequencing approach to characterize T cell receptor (TCR) repertoire. Sequencing using the illumina miSeq was performed on DNA synthesized from RNA extracted from patients’ samples. This approach enables to track each expanded TCR clone in the graft at 3 months post Tx, back to their first appearance in blood and urine samples obtained pre or 1 month post Tx. We also measured the RNA expression levels of CD8, CD4, FOXP3, Granzyme and Perforin in blood samples (N=43).

Results: Only patients with acute T cell mediated rejection (n=2) had TCR repertoires defined by the top 10 TCR clones appeared at any time point in blood, showed significant expansion in blood at 3 month post Tx compared with that at 1 month post Tx (P<0.01 and 0.02). CD8, FOXP3, Granzyme and perforin RNA levels were significantly higher in samples obtained from patients with rejection compared to that in patients with no rejection (P<0.02).

Fig 4: Pattern of changes in TCR frequencies in blood of kidney transplant patients.

Conclusions: Our study provides valuable comprehensive longitudinal analyses that define the kinetics of each TCR beta clone, and the changes in diversity of CD3. This approach allows for identification of the expanded T cell clones that are possibly associated with graft rejection.

SA-PO971

Critical Appraisal of the New Banff Criteria for Chronic Antibody-Mediated Rejection in the Real Life Setting

Isabelle Houde, Isabelle Côté, Molsen Agharazii, Sacha A. De Serres. Renal Div, Queen’s Univ Health Centre; Laval Univ, Quebec City, QC, Canada.

Background: Significant changes in the criteria for chronic active antibody-mediated rejection (CAABMR) were made at the 2013 meeting, which is of major concern for clinical management. Here we compared the 2007 vs. 2013 criteria with regards to clinical outcomes.

Methods: Single-center, observational retrospective study of all patients who received an indication biopsy between January 2006 and October 2014, during which EM evaluation, ptc scoring and C4d scoring by IH and IF was routinely performed. Patients were included if they met criterion 1 for CAABMR: score ≥1/0, cgib=0 or severe peritubular capillary basement membrane multilayering. GN, immune deposits, HC+ status or suspicion of TTP-HUS were excluded. The endpoint was a composite of doubling of serum creatinine and death-censored graft loss.

Results: 123 patients were included. 18% met the full 2007 criteria, whereas an additional 18% fulfilled the full 2013 criteria. Only 25% of patients met the 2007 criterion #2-C4d, in contrast to 82% for the 2013 criterion #2-microvascular injury (MVI): 67% vs. C4d-positive and 55% were g’p’tc positive, with substantial overlap. 45 patients experienced the endpoint at a median of 22mo post-biopsy. Overall, only a 2013 diagnosis of CAABMR was associated with the endpoint (adjusted HR=2.5 [1.2-5.2] for 2013 vs. HR=1.6 [0.7-3.8] for 2007 diagnosis). Adjusted Cox modelling revealed that the 2013 criterion #2-MVI was more strongly associated with the endpoint than the 2007 criterion #2-C4d (HR=4.0 [1.1-14.1] vs. HR=2.2 [1.03-5.3]). When the 2013 criterion #2 was dissected by component, the C4d-component was significant (HR=2.5 [1.1-5.4]), but not the g’p’tc (HR=1.2 [0.5-2.3]).

Conclusions: Compared to the 2007 criteria, applying the 2013 criteria here doubled the proportion of patients with CAABMR. Importantly, it improved the association with clinical outcomes.

SA-PO972

Tissue Expression of Aquaporine 2 Is Correlated to Urine Output and Allograft Function in Sensitized Kidney Transplant Patients

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Background: Salt and water disturbances often occur during acute kidney allograft dysfunction contributing to graft failure, but this condition has still been poorly investigated in the setting of alloreactivity. We evaluated the tissue expression of aquaporins (AQPI, AQP2) and of the epithelial sodium channel (ENAC) in kidney allograft biopsies from transplant patients with high immunological risk.

Methods: Eighty-six kidney transplant biopsies from thirty-three sensitized patients were divided into three groups according to the clinical context a possible pathological correlates as follows: time-zero biopsy (ENAC and ENA I) in the setting of acute rejection (P<0.02). Our findings can partially confirm previous experimental data showing downregulation of AQP1 expression after ischemia-reperfusion injury and during rejection. AQP2 downregulation seems to be rejection-independent occurring during deteriorating or poor kidney graft function.

SA-PO973

The Utility of Protocol Biopsy in Renal Recipients: Meta Analysis and Systematic Review


Background: To evaluate the value of protocol biopsy in patients after renal transplantation.

Methods: Searches were applied to the following electronic database: Medline, Embase Database, Cochrane Library. Randomized controlled trails evaluating the value of protocol biopsy for renal allograft recipients were included. Data were extracted independently by two reviewer. The risk of bias of included studies was assessed by the Cochrane collaboration’s tool for assessing risk of bias.

Results: 5 RCTs were included. Long term graft loss was significantly reduced (RR 0.40; 95% CI 0.25 to 0.65, P<0.001) (figure 1) by protocol biopsy after renal transplantation.

Protocol biopsy may reduce the long term serum creatinine (WMD 38.21, 95% CI 54.83 to 21.60, P<0.00001). For renal recipients whose basal immunosuppression is CNI (tacrolimus or cyclosporine), protocol biopsy can significantly improve the long term eGFR (SM 0.78, 95% CI 0.51 to 1.05, P<0.00001). However, for those whose basal immunosuppression is tacrolimus, this effect is not notable. Protocol biopsy seems to have no significant beneficial effect of reducing clinical acute rejection episodes.

Conclusions: Treatment of subclinical rejection detected by protocol biopsy can significantly improve the graft survival and may improve the allograft function.

SA-PO974

Longitudinal Biopsy Findings Among Children, Adolescents, and Young Adult Renal Transplant Recipients from a Southeastern USA Cohort

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Background: Longitudinal procedure history in children, adolescent, and young adult renal transplant recipients needs to be characterized based on their primary cause of end-stage renal disease (ESRD). It is known that pediatric patients are a high risk group for transplant failure. Elucidating potential factors for transplant failure in this group is important for protecting valuable transplants and limiting their use.

Methods: Clinical, demographic and pathological records of patients who received a renal transplant at age ≤30 years of age and who underwent transplant biopsies between 2000 and 2014 at the UNC Hospitals were analyzed. This cohort was classified based on

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Underline represents presenting author.

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the primary cause of ESRD as either glomerular or non-glomerular. Demographics, number of biopsies (total and adjusted for graft years), and transplant failure (rates and cause) were compared between the two groups.

Results: We enrolled 179 patients; 105 (58.7%) were male; 67 (38%) African American, 92 (51%) Caucasian, and 20 (11%) other race. Their mean age at transplant was 18.7 ± 8.2 years and 98 (55%) had a glomerular cause of ESRD. This cohort underwent a total of 505 graft biopsies. Comparing patients with glomerular vs. non-glomerular conditions, we found no statistical differences in renal biopsy findings regarding number of biopsies and biopsies per year for failed transplants (p=0.702), current functioning grafts (p=0.090); mean number of biopsies (3.0 ± 1.9) was higher in the glomerular group, but not significant (p=0.430); mean number of biopsies per year for failed transplants (p<0.001), current functioning grafts (p=0.090); time to a failed transplant (p=0.476); or age at time of transplant (p=0.136).

Conclusions: In this single institution cohort of children, adolescents and young adults, we found no statistical differences in renal biopsy findings regarding number of biopsies and transplant failure. This high risk age group shows no different longitudinal graft survival based on primary cause of ESRD. More analysis will follow.

Funding: Private Foundation Support

SA-PO975

Prospective Study of Risk Factors and Impact of Subclinical Rejection (SCR) and Acute Clinical Rejection (ACR) in Renal Transplant Recipients Rajil B. Mehta,1 Puneet Sood,1 Arvind Cherukuri,2 Shan Shan Chen,2 Chethan M. Putterajappa,1 Christine Wu,1 Nirav A. Shah,1 Parmjeet S. Randhawa,2 Sundaram Harirhan,1 1Starzl Transplantation Inst, Univ of Pittsburgh Medical Center, Pittsburgh, PA; 2Dept of Pathology, Univ of Pittsburgh Medical Center, Pittsburgh, PA.

Background: The long term outcomes of subclinical rejection (SCR) remain unclear. The current study evaluated the risk factors for SCR at 3 months and followed up renal function up to 1 year in pts with SCR, ACR and no rejection.

Methods: We prospectively followed 340 pts who underwent an ABO compatible kidney transplant between Jan 2013 and Sep 2014. Eight pts were excluded. All patients received induction therapy with either thymoglobulin (95%) or Basiliximab for induction, CNI/MPA for maintenance therapy and rapid steroid withdrawal by day 7. Protocol biopsies were performed 3 months post transplant. Based on this, they were divided into 4 groups. Grp 1 - pts with SCR, Grp 2 - pts with normal biopsy; Grp 3 - pts with ACR; Grp 4 - pts without biopsy. Banff classification was followed for biopsy grading. Steroids, thymoglobulin and PPP/IVIG were used as indicated for the treatment of rejection.

Results:

<table>
<thead>
<tr>
<th>Grp 1 (SCR)</th>
<th>Grp 2 (Normal Bio)</th>
<th>Grp 3 (ACR)</th>
<th>Grp 4 (No Bio)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50±3/16</td>
<td>52±3/15</td>
<td>48±1/15</td>
<td>55±5/12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>28/16</td>
<td>100/59</td>
<td>15/18</td>
<td>52/44</td>
</tr>
<tr>
<td>Race (W/C)</td>
<td>34/10</td>
<td>126/33</td>
<td>25/8</td>
<td>80/16</td>
</tr>
<tr>
<td>CIT (mins)</td>
<td>474±327</td>
<td>409±386</td>
<td>396±316</td>
<td>510±380</td>
</tr>
<tr>
<td>DGF (Y/N)</td>
<td>13/31</td>
<td>17/142</td>
<td>5/28</td>
<td>21/75</td>
</tr>
<tr>
<td>HLA mm</td>
<td>4.1±1.5</td>
<td>3.9±1.7</td>
<td>4.25±2</td>
<td>3.96±1.8</td>
</tr>
<tr>
<td>HLA DR mm</td>
<td>1.23±0.7</td>
<td>1.12±0.7</td>
<td>1.41±0.7</td>
<td>1.31±0.8</td>
</tr>
<tr>
<td>DSA (Y/N)</td>
<td>11/27</td>
<td>23/109</td>
<td>9/24</td>
<td>13/73</td>
</tr>
<tr>
<td>PRA I</td>
<td>6.7±17</td>
<td>6.5±19</td>
<td>7.9±19</td>
<td>14±37</td>
</tr>
<tr>
<td>PRA II</td>
<td>10.8±26</td>
<td>14.0±29</td>
<td>7.1±22</td>
<td>12.6±27</td>
</tr>
<tr>
<td>Cr 3m</td>
<td>1.52±0.40</td>
<td>1.42±0.5</td>
<td>1.69±0.48</td>
<td>1.33±0.46</td>
</tr>
<tr>
<td>Cr 6m</td>
<td>1.52±0.5</td>
<td>1.46±0.5</td>
<td>1.54±0.37</td>
<td>1.26±0.42</td>
</tr>
<tr>
<td>Cr 1yr</td>
<td>1.6±0.46</td>
<td>1.5±0.77</td>
<td>1.66±0.48</td>
<td>1.38±0.63</td>
</tr>
<tr>
<td>Banff Gr (Bort/IA or &lt;)</td>
<td>25/75</td>
<td>NA</td>
<td>27/73</td>
<td>NA</td>
</tr>
</tbody>
</table>

Conclusions: 1. Incidence of SCR and ACR around 3 mths was 18.6% and 9.9% respectively. 2. Significant risk variables for SCR/ACR were female recipients and DGF 3. No difference in renal function was noted between the groups at 1 year.

Funding: Pharmaceutical Company Support - Dutch Kidney Foundation

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SA-PO976

Histopathological Changes and Graft Survival of Long-Term Kidney Allograft in Alport Syndrome: A Single-Center Experience in Japan

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Background: Patients with Alport syndrome (AS) commonly develop progressive kidney dysfunction due to a hereditary type IV collagen deficiency, which results in an abnormality in the glomerular basement membrane (GBM). Recurrent glomerulonephritis does not occur in transplanted kidneys, and the allograft survival rate in these patients is similar to that in patients with other renal diseases. Several studies have shown that the type IV collagen of the GBM originates from the recipient’s bone marrow–derived cells. Therefore, we postulated that recurrent glomerulonephritis could occur locally and should influence the long-term allograft survival. In this study, we investigated graft survival and histopathological changes in renal allograft recipients with AS, focusing particularly on whether the expression of GBM type IV collagen is altered.

Methods: We collected data on the clinical characteristics of 19 renal allograft recipients who had been diagnosed with AS. All data were obtained from a database at the Department of Urology, Tokyo Women’s Medical University. Graft survival was evaluated using the Kaplan–Meier method and compared with a control group (n = 18). We assessed the double staining of α2 and α5 using frozen specimens obtained from long-term allograft survival samples.

Results: The graft survival rate was not statistically different between patients with AS and controls (log-rank p = 0.2240). Immunoreactivity to α5 antibody in four patients exhibiting long-term allograft survival showed strong linear positivity and no GBM abnormalities. In the case of chronic active antibody-mediated rejection, the immunoreactivity to α2 antibodies increased in the mesangium and subendothelial space.

Conclusions: These results suggest that the GBM type IV collagen structure was histopathologically maintained for the long term after kidney transplantation, indicating better graft survival in patients with AS.

Funding: National Institute of Health (NIH)

Allograft in Alport Syndrome: A Single-Center Experience in Japan

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Background: Acute Tubular Necrosis (ATN) is a common cause of Delayed Graft Function (DGF) after renal transplantation (RTX). Currently no histological model is available to predict renal outcome. Recovery of ATN is the result of the balance between regeneration and repair. In this study we evaluated the predictive value of immunohistochemical parameters of renal damage and regeneration and compared these to an accepted clinical prediction model for cadaveric renal transplantation.

Methods: We included 25 patients that underwent cadaveric RTX with DGF caused by ATN only, as shown in a renal biopsy 1 week after RTX. Biopsies were evaluated for histological tubular damage (atrophy, edema, casts, vacuolization), DNA damage (γH2AX staining) and apoptosis (cC3 staining). Regeneration was assessed by staining for stem cell marker CD133 and proliferation marker Ki67. Clinical parameters for renal outcome were collected as previously described in the Deceased Donor Score (DDS). The relation between these parameters and renal outcome, defined as eGFR at 6 months, was assessed using regression or one-way ANOVA. A correct analysis for regenerative markers was performed to eliminate potential confounding by the amount of renal damage.

Results: The histological damage score significantly predicted renal outcome (R=-0.52 P=0.01), whereas the DDS only tended to correlate with renal outcome (F:3.12 P: R=0.05). Neither staining for DNA damage, nor for apoptosis could predict renal outcome (R=-0.24 P=0.91 and R=-0.16 P=0.44 respectively). In addition, the investigated parameters for regeneration (CD133 and Ki67) did not predict renal outcome (R=-0.25 P=0.23 and R=-0.10 P=0.63 respectively), also not after correction for renal damage.

Conclusions: We are the first to show that histological parameters can predict renal outcome of post transplantation ATN. Importantly, our histological damage score correlated better with renal outcome than the DDS. Despite the crucial role of regeneration in recovery after ATN, no relation was found between stem cell marker CD133, proliferation marker Ki67 and renal outcome.

Funding: Private Foundation Support - Dutch Kidney Foundation

The Netherlands Institute for Regenerative Medicine
SA-PO978
Histological Assessments from Kidney Transplant Biopsies: An Explorative Post Hoc Analysis of ZEUS 5 Year Data

Background: Analysis of pathologists’ assessments and histological data allow for deeper insight on patient outcome when combined with investigators final clinical diagnoses. Here we present 5 year data from de novo kidney transplant (KTx) recipients after conversion to an everolimus(EVR) based regimen and withdrawal of CNI therapy vs. continued CNI regimen.

Methods: Post hoc analysis of histological and pathologists’ assessments from ZEUS, a prospective, open-label, controlled, multi-center study. At mo 4.5 post Tx, 300 KTx patients (pts) were randomized to either EVR + enetic coated-mycophenolate sodium (EC-MPS, n=154) or cyclosporine (CsA) + EC-MPS (n=146). After 12mo interventional study, observational follow-up (FU) on pts safety and efficacy was performed until mo60 post Tx. As per study protocol, graft core biopsies were indicated by suspected rejection episode. Biopsies were read and interpreted by local pathologists.

Results: Total number (n) and mean n of biopsies per patient performed are overall similar in both groups until mo60. Nr of pts with at least one rejection (as per final clinical diagnosis) was slightly higher in CNI group vs EVR group. Nr of pts with BPAR was higher in the EVR group especially due to mild, early acute rejections (mostly BANFF IA and IB). Nr of pts with histological evidence of chronic sclerosing allograft nephropathy was similar in both groups (both 10%). CAD staining positivity was found slightly higher in the EVR group (11% EVR vs 7% CNI), however, pts with evidence of antibody mediated rejection was higher in the CNI group (2% EVR vs 4% CNI), same for CNI-induced toxicity lesions (16% EVR vs 23% CNI).

Conclusions: Data from histological assessments together with investigator reported final clinical pts outcome show that an EVR-based regimen with early elimination of CNI-therapy is as safe and efficacious as standard CNI-therapy offering the opportunity to reduce cumulative CNI-induced toxicities on the allograft.

Funding: Pharmaceutical Company Support - Novartis Pharma GmbH

SA-PO979
Endothelial Microvesicles as a Biomarker of Antibody-Mediated Endothelial Injury

Results: We have shown that W6/32 antibody binds HMEC-1 cells and activates endothelial production of endothelial microvesicles (in vitro). In vivo, we showed that antibody binding and subsequent complement activation on the production of endothelial microvesicles in vivo and to explore endothelial microvesicles in patients with suspected antibody-mediated rejection (AMR) as a potential biomarker of AMR in renal transplant recipients.

Methods: We have developed an in vitro model of AMR using immortalized human endothelial cells (HMEC-1) and a monoclonal murine antibody against human HLA class I molecules (W6/32). We analyzed antibody binding and complement deposition with immunohistochemistry and flow cytometry. Microvesicle analysis was performed using flow cytometry.

Results: We have shown that W6/32 antibody binds HMEC-1 cells and activates the classical complement pathway upon exposure to normal human serum. This leads to deposition of complement split products on the cell surface (analogous to C4d deposition in biopsies from patients with AMR) and increased release of endothelial microvesicles. Furthermore, anti-HLA antibody (W6/32), C3, and C4 were deposited on the surface of the microvesicles.

Conclusions: Our results suggest that AMR will lead to an increase in production of microvesicles by the renal endothelium, and AMR-associated microvesicles will have surface-bound IgG and C4d. We have obtained human plasma samples from renal transplant recipients with AMR and healthy controls, and we are currently examining the potential of endothelial microvesicles as a biomarker of AMR.

Funding: NIDDK Support

SA-PO980
Dual Leukocyte/Endothelial Stain for Assessment of Endocapillary Inflammation in the Renal Allograft

Results: We hypothesized that sterile leukocyturia could reflect an increased intragraft immune activity and investigated gene expression profiles of transplant kidney biopsies of patients with sterile leukocyturia comparing to patients without leukocyturia.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We identified 15 normal transplant kidney biopsies without leukocyturia (Group 1) and 33 biopsies with non-specific/interstitial tubular atrophy (IFTA) for gene expression profiling. Of the 33 biopsies with IFTA, 24 patients had no sterile leukocyturia (Group 2) and 9 patients had sterile leukocyturia (Group 3). Biopsies with a diagnosis of acute or chronic rejection, recurrent or de novo glomerular disease, or polycoma nephropathy were excluded. Leukocyturia was defined by the presence of sterile leukocyturia (>10^3/µl) without bacterial growth in urine culture. The urinalysis was done within 1 month before or after the biopsy. The gene expression profiles were studied by Affymetrix HuGene 1.0 ST expression arrays.

Results: There was no association in terms of age, race, and sex, type of transplant, previous history of transplantation or acute rejection, donor characteristics, panel reactive antibody levels and immunosuppressive treatment between the Groups 2 and 3. Both groups also had similar acute and chronic Banff allograft injury scores. There was no statistically significant difference in gene expression profiles between the Group 1 and 2. Where c3 and c12 showed 40.9% and 30.1% respectively. Group 3 biopsies were compared to the Group 1 and 2 biopsies, significantly increased gene transcripts associated with cytotoxic and regulatory T cells, and macrophages (P-value for significance <0.05). There was a trend towards increased interferon-gamma and rejection associated transcripts but no statistically significant difference in expression of B-cell or natural killer cell associated transcripts.

Conclusions: The biopsies of the patients with sterile leukocyturia showed increased expression of gene transcripts associated with T cells indicating heightened intra-graft immune activity. Those patients might require close monitoring of their allograft function.

SA-PO983
Elevated Glomerular Mechano-Growth Factor and Vascular Endothelial Growth Factor in Chronic Allograft Nephropathy Is Associated with Activation of Erk1/2

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Background: We previously identified increased GLUT1 glucose transporter, Mechano-Growth Factor (MFG) and Vascular Endothelial Growth Factor (VEGF) in human Chronic Allograft Nephropathy (CAN) kidneys which demonstrate glomerulosclerosis. Here we investigated a glomerular signaling pathway, Erk1/2, with potential to mediate effects of MFG and VEGF on extracellular matrix (ECM) genes. We employed IHC with specific antibodies to assess protein expression for MGF, VEGF and phospho-Erk1/2 (active Erk1/2) in human CAN kidneys vs Normal Control kidneys.

Methods: This study involving examination of archived renal biopsy samples was approved by the Institutional IRB. N = 6 for each group of renal transplant - and native kidney specimens. Immunolabeling of human CAN and Normal Control paraffin-embedded kidney sections was performed for assessment of selected proteins with specific antibodies, by use of immunoperoxidase staining. Scoring of glomerular immunolabeling for individual proteins was 0 – 4+ and was standardized. Data was normalized to open glomerular tuft area. P < 0.05 was considered significant in statistical analysis.

Results: Glomerular MGF protein was increased 3.9-fold in CAN kidneys vs Normal Control kidneys, P < 0.001. Glomerular VEGF was elevated 3.0-fold in CAN vs Normal Control kidneys, P < 0.001. Both of these growth factors have potential to signal via Erk1/2 to ECM expression. Glomerular Erk1/2 activation (i.e. phospho – Erk1/2) was examined and found to be increased 4.3-fold in CAN vs Control, P < 0.0001.

Conclusions: Human CAN, characterized by excessive glomerular MGF and VEGF expression, involved enhanced activation of Erk1/2 in the glomeruli. This provides a mechanism by which these glucose-responsive growth factors may induce glomerular ECM production and glomerulosclerosis. Therefore, MGF and VEGF activation of Erk1/2 may contribute to progressive glomerulosclerosis and renal failure in CAN.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

SA-PO984
Microarray Analysis of Interstitial Fibrosis/Tubular Atrophy in Kidney Transplant Recipients Using Formalin-Fixed, Paraffin-Embedded Renal Biopsy Tissue

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Background: Interstitial fibrosis/tubular atrophy (IFTA) is a common and complex cause of diminution in renal function after kidney transplantation. Early identification of progressive IFTA (pIFTA) may lead to alternative therapies that may attenuate irreversible injury. In this study, we used formalin-fixed, paraffin-embedded (FFPE) renal biopsy specimens with microarrays to conduct differential gene expression studies to identify predictors of IFTA in kidney transplant recipients.

Methods: We identified 22 individuals with multiple protocol biopsies within the first 3 years after transplant. Glomeruli and blood vessels were removed using laser capture microdissection and the remaining tissue was used for mRNA extraction. Affymetrix Expression Arrays were used following standardized protocols. IFTA was defined by histological image masking in Histolab to quantify the cortical interstitial fraction. pIFTA was defined as a 0.5% absolute increase in the interstitial fraction per month between serial biopsies. Data analysis was conducted using R 3.0.2 and Bioconductor 2.22. Significance was defined as an unadjusted p < 0.05.

Results: Of the 22 subjects in this study, 9 had pIFTA while the remaining 13 were considered stable IFTA (sIFTA). At baseline, the eGFR was 60.5 ± 58.5 mL/min/1.73m² (p = 0.79) and log(Urine Albumin) was 3.44 vs. 3.17 (p = 0.72) for the sIFTA and pIFTA groups, respectively. The baseline fibrosis was higher in the sIFTA group (18%) compared to the pIFTA group (13%; p = 0.04). Using linear modeling, 3 of the 10 differentially expressed genes were clustered at baseline with the differential expression of multiple genes prior to phenotypic changes. Prospective investigation of these genes is needed to determine if these are predictive of pIFTA.

Funding: Private Foundation Support

SA-PO985
Pathological Analysis for Transplant Nephrectomy – 124 Consecutive Cases in a Single Center Study Over 10 Years

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Background: Transplant nephrectomy (TNx) is performed for several indications. This study evaluates in depth histological analysis of TNx specimen.

Methods: We identified all cases at the Royal London Hospital between 2004 and 2014. The indication for TNx was divided into four groups: 47 cases with acute graft loss without significant blood flow (AGL), 44 cases of suspected ongoing rejection or graft intolerance syndrome (Rej/GIS); 24 cases with infection (INF); and 9 miscellaneous reasons (MIS). We examined the histological changes in detail and specifically looked at the artery, vein and ureter.

Results: AGL was less likely to have tubulointerstitial changes, but 74.5% had necrosis. In the AGL group, the majority of cases scored zero for t, i, c1 and c2. Neutrophil rich arteritis at renal and small arteries was observed in 29.8% and 19.2%. Venous thrombosis was found in 63.7%. All cases in the Rej/GIS group showed c3 and c12 and 40.9% showed t3 and c3. Glomerulitis was observed in 52.3% and eg was detected in 75.1%. Arteritis of small and renal arteries was detected in 70.5% and 59.1%. C4d expression was present in 54.1%. Nearly 70% showed ureteric inflammation. Variable cellular infiltrate comprising monocytes, plasma cells and eosinophil were seen in all cases. In the INF group, 66.7% (t1-3) and 79.2% (i1-3) were observed, and c3 and c13 were detected in 66.7%. Glomerulitis was rare although allograft nephropathy was detected in 62.5%. All cases had intimal thickening of small and renal arteries but arteritis was unusual. Lymphocyte and plasma cell were common at interstitium and 73% of all plasma cell, neutrophil and eosinophil rarely appeared at vascular lesions. In the MIS group, histological changes were minor, t13, i1-3, arteritis and venuitis were not detected.

Conclusions: The histological changes were similar and specific within the TNx groups but different between the groups. A failed graft often showed substantial immunological response. In depth histological analysis may aid management of subsequent grafts.

SA-PO986
MIrnAs as Novel Biomarkers for Transplanted Patient's Evolution

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Background: Transplanted patients evolution and outcome is dependent on many factors including allograft function, vascular homeostasis and immunogenicity. Up to this moment, apart from creatinine renal biopsy, there are no quantitative and accurate biomarkers to predict the evolution of the allograft and the receptor, that would enable clinicians to improve the transplanted patient’s management. Our group has validated a combination of serum miRNAs as accurate biomarkers for AKI from ischemic aetiology, including: miR-127, miR-101, miR-210, miR-146a, miR-26b, miR-29a, miR-10a, miR-93 and miR-27a. Here we have determined the expression of these miRNA in serum from kidney donors and recipients and correlate this expression with clinical parameters of allograft evolution, including ATN development, delayed graft function, rejection and vascular complications.

Methods: For this purpose, serum sample from brain death donors and receptors along post-transplantation period (6h, 1, 2, 3, 4, 5, 6 and 7days and 1,3, 6 months) in 30 transplanted patients form our Hospital. After RNA extraction from serum, the combination of miRNAs has been determined by qRT-PCR and correlation with clinical data has been established using SPSS.

Results: The expression of these 10 miRNAs in serum samples from donors did not exhibit significant differences among them. This combination neither correlate with immediate delay graft function because NTA or immunological rejection. However, some of the miRNAs correlate with long term evolution of transplanted patients in terms of non-rejection and graft function and they also discriminate patients with also exhibited renal vascular alterations.

Conclusions: In summary we have identified miRNAs that correlates with long term evolution of transplanted patients. These information could be useful for improve transplant care that is different in the context of personalized patient handling.

Funding: Other NIH Support - Fundación Mutua Madrileña

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

860A
Plasma MicroRNA 17 Host Gene Protein Level Cluster and Tumor Necrosis Factor-Alpha (TNF-α) in Patients with Renal Transplantation: Relation to Allograft Function and Survival
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**Background:** Chronic allograft dysfunction (CAD) remains the leading cause of late graft loss after kidney transplantation. MicroRNAs (miRs) are small (19-25 nucleotides) noncoding RNAs that regulate gene expression of diverse biological processes. The polycistronic miR-17-92 cluster is comprised of six miRs and its primary transcript may also encode for a polypeptide of 70 amino acids designated as the miR-17 host gene (MIR17HG) protein. So the aim of this work was to evaluate the plasma levels of MIR17HG protein and TNF-α levels in patients with renal transplantation in relation to allograft function and survival.

**Methods:** This study included 45 subjects; they were divided into three groups each 15, renal transplant patients with stable renal function (Group I), with CAD (Group II) and healthy subjects as controls (Group III). Quantitative determination of plasma levels of MIR17HG protein and TNF-α were performed using enzyme linked immunosassay (ELISA). Blood urea, serum creatinine and estimated glomerular filtration rate (eGFR), urinary albumin/urinary creatinine ratio and C-reactive protein (CRP) were done. Resistive index (RI) was calculated. Renal biopsy was done in patients with CAD.

**Results:** MIR17HG protein and TNF-α levels were significantly higher in renal transplant especially patients with CAD than the controls. In patients with renal transplantation TNF-α level were positively correlated with each other and with serum creatinine, urinary albumin/creatinine ratio and CRP and was negatively correlated with eGFR. The degree of fibrosis in renal biopsy was positively correlated with MIR17HG protein, TNF-α and resistive index (P<0.05).

**Conclusions:** MIR17HG protein and TNF-α plasma levels can be served as circulating biomarkers for early detection of renal allograft dysfunction and follow up of patients with renal transplantation. They can act as a pro-fibrotic factor and denoting ongoing inflammation in the pathogenesis of CAD.

**SA-PO988**

**Polymorphisms of IL17 and CXCL9 Genes, but Not AIF1 Gene, Affect Early Kidney Allograft Function After Transplantation**
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**Background:** Kidney transplantation outcome is determined by immunological and non-immunological factors, both the donor and the recipient dependent. There are reports suggesting that AIF1, IL17 and CXCL9 genes polymorphisms might influence the post-transplant immune response, and thus kidney function. Therefore the aim of this study was analysis of association between 8 AIF1, IL17 and CXCL9 genes polymorphisms and creatinine concentrations up to 1 year after transplantation.

**Methods:** The study enrolled 269 Caucasian renal transplant recipients (165 males, 104 females, mean age 47.63 ± 12.96 years). Blood samples were collected for genetic analysis and creatinine concentrations evaluation 1, 3, 6, and 12 months after kidney transplantation. The analysis regarded rs2269475, rs2373162 and rs2259571 within AIF1 gene, rs2275913 within IL17 gene, rs2397084, rs1146553 and rs763780 within IL17F gene and rs7137326 within CXCL9 gene. Genotyping was performed using RT-PCR and PCR-RFLP methods.

**Results:** Creatinine concentrations 1, 3, 6 and 12 months after transplantation differed between the rs2275913 within IL17A gene promoter polymorphism genotypes and were higher among GG homozygotes (GG vs. GA+AA; p=0.03, p=0.08, p=0.06 and p=0.03 respectively). In regard to rs2297084 IL17F gene polymorphism, creatinine concentrations differed between the genotypes 1, 2 and 6 months after transplantation and were higher among TT homozygotes (TT vs. CC p=0.02, p=0.02 and p=0.09 respectively). Creatinine concentrations 3, 6 and 12 months after transplantation differed between the rs7137326 within CXCL9 gene polymorphism genotypes and were higher among GG homozygotes (GG vs. GA+AA p=0.07, p=0.048 and p=0.02 respectively). There were no significant differences between the studied AIF1 gene polymorphisms genotypes.

**Conclusions:** Polymorphisms of IL17 and CXCL9 genes, but not AIF1 gene, affect early kidney function after transplantation. These preliminary results indicate that there is a need of genome-wide association studies scanning on genes implicated in the immune response after transplantation.

**SA-PO987**

**Noninvasive Diagnostic and Predictive Value in Renal Transplant Recipients by Measurement of Urine BCA-1**
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**Background:** To investigate the relationship between early-stage renal acute rejection and the level of BCA-1 in urine, explore the diagnostic value and noninvasive monitoring on early acute rejection after transplantation by measurement of urine BCA-1.

**Methods:** 145 patients were enrolled between January 2006 and October 2009, including 49 with biopsy-proved acute rejection, 58 patients with stable renal function and no abnormal histological findings, 9 patients with biopsy-proven acute tubular necrosis (ATN), 29 patients with acute humoral rejection (AMR) and 29 patients with acute cellular rejection (ACR). We measured plasma and urine BCA-1 in 77 patients with underwent KTP. The concentration of BCA-1 was analyzed by enzyme linked immunosorbent assay (ELISA). According to allograft status, Groups are divided stable, long-term good survival, immune tolerance, acute cellular rejection (ACR), acute antibody-mediated rejection (AMR) and chronic AMR.

**Results:** Plasma BCA-1 was not significantly different between all groups according to allograft status (p>0.424). Whereas, urine ESM-1 was significantly different between groups according to allograft status (p<0.001). Urine ESM-1 was higher in both ACR and AMR as well as chronic AMR than stable status. Patients with acute AMR showed significantly higher level of urine ESM-1 compared with patients with ACR (p=0.05). Area under the curve (AUC) for differentiating acute AMR from ACR was 0.744 (p=0.01).

**Conclusions:** Urine ESM-1 may reflect endothelial injury of allograft and it could be used to differentiate the patient with acute AMR from ACR.
SA-PO992
B Cell Attracting Chemokine 1 in Urine Is a Biomarker of Acute Hemural Rejection
Weshan Peng, Jianhua Chen. Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.

Background: Presently, there are no noninvasive approaches which can be directly applied to clinical diagnosis of acute rejection (AR) or distinguish type of rejection in renal transplant recipients. The aim of this study was to construct diagnostic models of biomarkers in acute rejection patients with AR or AHR in renal transplant recipients.

Methods: Concentration of nine biomarkers in urine of 81 patients with AR and 167 patients with stable renal function (No-AR) was determined by ELISA technique. Firstly, by discriminant analysis, we screened a number of biomarkers to construct the diagnostic models for AR and AHR. Secondly, another 102 patients with No-AR and AR patients were analysed to test the accuracy of the diagnostic model.

Results: Four biomarkers were selected to set up the diagnostic model of AR or No-AR. Based on the model of AR, 84.3% patients were correctly diagnosed. Two biomarkers were selected to set up the diagnostic model of AHR. Based on the two model of AR, 100% patients with No-AR and 96.3% patients with AR were correctly diagnosed. Only B cell attracting chemokine 1 (BCA-1) was selected for the diagnostic model for AHR or acute cellular rejection (ACR). Rejection type of 81.5% patients with AR were correctly classified. Another 102 patients tested the accuracy of the diagnostic models. Diagnostic accuracy of AR or No-AR and AHR or ACR were 100% and 95.4% respectively.

Conclusions: Urinary BCA-1 was a valuable biomarker for determining AHR. These diagnostic models might directly identify AR and types of AR.

Funding: Government Support - Non-U.S.

SA-PO993
*FDG-PET/CT Imaging in Suspected Acute Renal Allograft Rejection
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Background: The diagnosis procedure for kidney transplant recipients (KTR) with suspected acute rejection (AR) relies on needle biopsy. Still, noninvasive tests to predict nonrejection would be useful to save selected patients from undergoing inessential biopsy. AR is associated with a recruitment of activated leucocytes to the transplant, which are characterized by a high metabolic activity and an increased uptake of glucose analog, 18F-fluoro-deoxy-glucose (*FDG). Thus, *FDG-PET-positron emission tomography coupled with computed tomography (PET/CT) may help noninvasively distinguish nonrejection from AR.

Methods: From January 2013 to February 2015, we prospectively performed 32 *FDG-PET/CT in 31 adult KTR with suspected AR who underwent a biopsy. Biopsies were categorized as "normal", "borderline", "AR" or "others" according to Banff classification. PET/CT imaging was performed within 20 ± 18 minutes after i.v. administration of 3.2 ± 0.2 MBq/kg of *FDG, before any modification of immunosuppression. The mean standard uptake values (SUV) of both upper and lower renal poles were measured, with no threshold activity.

Results: Biopsies were diagnosed as "normal", "borderline", "AR" or "others" in 8, 10, 8 and 6 (including 3 polyoma-BK nephropathies) cases. AR was antibody-mediated in 1 case, whereas Type I, II and III cellular AR were found in 5, 1 and 1 cases, respectively. Mean SUV reached 1.5 ± 0.3, 2.9 ± 0.8, 2.2 ± 1.2 in each category. Mean SUV of biopsy-proven AR was significantly higher than "normal" cases (p<0.01). No difference was found between "normal" vs. "borderline", or between "AR" vs. "others" histopathology. Still, a positive correlation between mean SUV and acute composite (g1+ v1+t+p1) score of AR was found with a coefficient of 0.70 (p<0.001). Sensitivity and specificity of *FDG-PET/CT in detecting pathological biopsies were respectively 92.3 and 36.8, with a mean SUV threshold at 1.4.

Conclusions: *FDG-PET/CT imaging may help discriminate nonrejection, thereby avoiding unnecessary transplant biopsy in KTR with suspected AR.

Funding: Government Support - Non-U.S.

SA-PO994
High Renmant-Like Particle-Cholesterol Is A Risk Factor of Worsening Graft Function in Japanese Kidney Transplant Recipients
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Background: Many factors cause dyslipidemia after kidney transplantation. Low density lipoprotein cholesterol (LDL-C) has been focused to reduce cardiovascular disease(CVD), but residual risk factors such as triglyceride(TG), remnants or small dense LDL-C are also important to reduce CVD. We investigated whether residual risk factors affected graft function in kidney transplant recipients.

Methods: This study is a retrospective cohort study at a single center. Three hundred and seventy seven kidney transplant recipients (male 223) in more than 6 months after transplantation were enrolled. TG, Remnant-like particle-cholesterol (RLP-C), non-high density lipoprotein cholesterol(HDL-C), LDL-C/apoB, eGFR(estimated glomerular filtration rate), Urine protein/day (UP), Body Mass Index (BMI) and other parameters at baseline were measured and we studied the association of residual risk factors with kidney fuction. DeGFR meant the difference between eGFR at baseline and eGFR 1year after transplantation (eGFR 1y). Data are shown as mean ± SD or median (interquartile).

Results: Patients’ characteristics of this study is showed below.

SA-PO995
The Modification of Erythrocyte Membrane Fatty Acid Contents According to Kidney Transplantation: Prospective Study
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Background: Modifications of erythrocyte membrane fatty acid (FA) contents may affect on cellular function or transmembrane receptors. The high erythrocyte membrane oleic acid contents are related with acute coronary syndrome. It is known that transplanted recipients have lower cardiovascular event than dialysis patients. Therefore, we prospectively evaluated whether erythrocyte membrane FA contents were modified after kidney transplantation (KTP).

Methods: We recruited 22 kidney transplanted recipients from September 2011 through May 2014. Blood samples were obtained just before KTP and at 6 months after KTP. The Modification of Erythrocyte Membrane Fatty Acid Contents According to Kidney Transplantation: Prospective Study Young Ki Son,1 Sung Hyun Son,2 Dongyeol Lee,1 Hansae Kim,1 Eu Geon Jeong,1 Su Mi Lee,1 Yun Jung Oh,1 Won Suk An,1 Seong Eun Kim,1,2

Conclusions: High RLP-C is a risk factor of worsening graft function in Japanese kidney transplant recipients.

SA-PO996
The Modification of Erythrocyte Membrane Fatty Acid Contents According to Kidney Transplantation: Prospective Study
Young Ki Son,1 Sung Hyun Son,2 Dongyeol Lee,1 Hansae Kim,1 Eu Geon Jeong,1 Su Mi Lee,1 Yun Jung Oh,1 Won Suk An,1 Seong Eun Kim,1,2 1Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; 2Dept of Internal Medicine, BHS Han Seo Hospital, Busan, Republic of Korea; 3Dept of Internal Medicine, Bong Seng Memorial Hospital, Busan, Republic of Korea; 4Dept of Internal Medicine, Cheju Halla General Hospital, Cheju, Republic of Korea.

Background: Modifications of erythrocyte membrane fatty acid (FA) contents may affect on cellular function or transmembrane receptors. The high erythrocyte membrane oleic acid contents are related with acute coronary syndrome. It is known that transplanted recipients have lower cardiovascular event than dialysis patients. Therefore, we prospectively evaluated whether erythrocyte membrane FA contents were modified after kidney transplantation (KTP).

Results: DeGFR were associated with worsening graft function. These changes of erythrocyte membrane FA contents may effect on cellular function or transmembrane receptors. The high erythrocyte membrane oleic acid contents are related with acute coronary syndrome. It is known that transplanted recipients have lower cardiovascular event than dialysis patients. Therefore, we prospectively evaluated whether erythrocyte membrane FA contents were modified after kidney transplantation (KTP).

Methods: We recruited 22 kidney transplanted recipients from September 2011 through May 2014. Blood samples were obtained just before KTP and at 6 months after KTP. The Modification of Erythrocyte Membrane Fatty Acid Contents According to Kidney Transplantation: Prospective Study Young Ki Son,1 Sung Hyun Son,2 Dongyeol Lee,1 Hansae Kim,1 Eu Geon Jeong,1 Su Mi Lee,1 Yun Jung Oh,1 Won Suk An,1 Seong Eun Kim,1,2

Conclusions: High RLP-C is a risk factor of worsening graft function in Japanese kidney transplant recipients.
SA-PO996

Diffusion Impairment Measured by Functional MRI Correlates with Allograft Fibrosis After Kidney Transplantation in Patients with Delayed Graft Function

Jan H. Bresen1, Abdelaразаг Ahmad Khalifa1, Faikah Gueler1, Frank Lehner1, Wilfried Gwinner2, Dagmar Hartung1, Hermann G. Haller1, Katja Hueper1, Inst for Pathology, Hannover Medical School, Hannover, Germany; 2Inst for Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Germany; 3Clinic for General, Abdominal and Transplant Surgery, Hannover Medical School, Hannover, Germany.

Background: Functional MRI parameters derived from diffusion weighted (DWI) and diffusion tensor imaging (DTI) correlate with renal fibrosis and cell infiltration in experimental studies. Aim of this study was to investigate these non-invasive techniques in patients with delayed graft function (DGF) and to correlate diffusion parameters with renal function and renal histology of allograft biopsies.

Methods: 33 patients with initial graft function between day 4 and 11 after kidney transplantation and 31 patients with DGF were examined on a 1.5 Tesla MRI. DTI and DWI sequences were acquired and apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated. Kidney biopsies were available in 26 patients and analysed for acute rejection (Banff), amount of fibrosis, inflammatory infiltrates, and tubular injury as well as edema.

Results: ADC was significantly reduced in patients with DGF compared to patients with initial function. Similarly, FA positively correlated with renal function (r=0.573 and r=0.53, p<0.001) and negatively with the amount of renal fibrosis. Diffusion parameters in DGF patients did not discriminate between acute rejection and tubular injury. Histological evaluation of the allograft biopsies did not reveal any significant differences between DGF or initial function in the following parameters: leukocyte infiltration (CD4, CD8, CD15, CD20, CD68), CD31 positive peritubular capillaries or edema (intertubular distance).

Conclusions: Functional MRI with diffusion techniques detects allograft dysfunction early after kidney transplantation correlating with allograft fibrosis. Biopsy is needed to verify rejection.

Funding: Government Support - Non-U.S.

SA-PO997

Identification of Common Biological Mechanisms of Fibrosis in Transplanted and Native Kidneys with Chronic Diseases

Konrad S. Famulski, Jeffery M. Venner, Jeff Reese, Philip F. Halloran. Unv of Alberta, Edmonton, AB, Canada.

Background: In both primary kidney diseases and in transplants fibrosis is caused by chronic progressive diseases. Hence, we hypothesised that fibrosis has fundamental common biological pathways in native and transplanted kidneys.

Methods: We studied the molecular associations with fibrosis in 703 kidney transplant indication biopsies (bx) 3 days to 35 years post-transplant. The number of bx with fibrosis increased with time post-transplant and most bx with ci>1 (74%) were attributable to time-dependent diseases (ABMR, GN, TG).

Results: By microarrays we compared bx with ci<1 to those with little or no fibrosis (ci<1) and determined the association strength of transcripts (p-value) for ci>1. First we focused on transcripts previously associated with fibrosis: immunoglobulin, mast cells and AKI-associated transcripts. Strongest associations with ci>1 were for immunoglobulin and mast cell transcripts, but not for AKI transcripts. Because time of bx post-transplant is highly correlated with ci, we repeated the comparison of ci<1 vs. ci>1 after correcting for time. This resulted in a massive reduction in association strength for the immunoglobulin and mast bx transcripts (from 10e-27 to 10e-9). However, AKI transcripts were now more strongly associated with fibrosis (from 10e-9 to 10e-18). Thus time correction emphasised the injury-repair response at expense of inflammation. We then analyzed the fibrosis associated transcripts in native kidneys (CKD). 75% of CKD transcripts overlapped with our transcripts.

Funding: This study was supported by the Canadian Institutes of Health Research (CIHR) Fellowship to KSF.

SA-PO998

DNA Double Strand Breaks Induced Collagen Type V1 Secretion of Glomerular Endothelial Cells in Renal Allografts

Yuki Matsui1, Norifumi Hayashi, Junko Imura, Keiji Fujimoto, Hiroki Adachi, Hiduki Yamaya, Hitoshi Yokoyama. Nephrology, Kanazawa Medical Univ, Uchinada, Japan.

Background: The relationship between DNA injury and glomerular fibrosis in renal allografts remains unclear.

Methods: We examined renal allograft specimens from 35 patients in which DNA double-strand breaks and glomerular fibrosis were detected by phospho-histone H2A.X (γ-H2AX) expression and collagen (COL) types III, IV, and V accumulation. We also examined the in vitro relationship between DNA damage and COL accumulation by mitomycin C (MMC)-induced DNA damage in human glomerular endothelial cells (HRGEc).

Results: The γ-H2AX and COL type V1, which mainly accumulated in the subendothelial and mesangial regions, were positively correlated with the duration of the post-replant transplant (RT) period (r=0.691, p<0.01; r=0.760 p<0.01, respectively). In multiple regression analysis, the duration of the post-RT period and cg in the Banff’07 classification were identified as significant predictors of COL type V1 accumulation (β value=0.699 p<0.001; 5.558, p=0.035, respectively) and γ-H2AX expression in the glomerular capillaries (β value 0.700 p<0.001; 2.031, p<0.01, respectively). In addition, the γ-H2AX-positive area was also identified as a predictor of glomerular accumulation of COL type V1 (β value=0.439, p=0.028). In the immunochemistry examination, γ-H2AX was detected in most cells after 24 hours’ MMC treatment, whereas γ-H2AX expression had been detected before the MMC treatment. Although COL type V1 was detected around the nuclei of the HRGEc before the MMC treatment, it was not present there after the MMC treatment. COL type V1 was detected in the cytoplasm of the HRGEc, which was secreted into the supernatant after MMC stimulation with γ-H2AX expression. The number of γ-H2AX (+) COL type V1 (+) cells was inversely associated with the number of γ-H2AX (+) COL type V1 (+) cells (r=0.655, p<0.001) during 24 hours’ MMC treatment.

Conclusions: Our findings suggested that over the long term RT may induce DNA double-strand breaks and HRGEc-secreted COL type V1 accumulation in the glomerular capillaries, which might progress to intractable glomerular fibrosis.
Factors Associated with Referral, Evaluation and Listing for Kidney Transplant: A Survey of Dialysis Patients

**Background:** Kidney transplant (KT) is the treatment of choice for most patients with end-stage renal disease (ESRD). Disparities in referral, evaluation, listing and transplantation have been documented. We studied factors associated with the likelihood of referral, evaluation and listing for KT.

**Methods:** We sent 1,283 flyers to dialysis units. Of 2,536 interested participants, 2,472 completed the survey (97.4%). We assessed associations for KT referral, listing and acceptance.

**Results:** Eighty-five percent of participants reported no euvolemia. A total of 467 participants, 401 of whom had been referred, 361 had been evaluated and 201 were listed. Having received 3 or more correct out of 6, respectively. (OR:1.44; CI:1.17mg/dl, respectively. Trough tacrolimus levels were maintained between 5 and 7ng/ml.

**Conclusions:** Early short-term low dose IM reduced renal cortical interstitial fibrosis in deceased donor KT patients. The role of long term IM in the prevention of interstitial fibrosis in renal allograft warrants further studies.

Factors Associated with Referral, Evaluation and Listing...
Kidney Transplant Referral Among Incident Georgia Dialysis Patients with and without Systemic Lupus Erythematosus: The RaDIANT Community Study
Laura Plantinga, Rachel E. Patzer, Sung S. Lim, Cristina Drenkard, Stephen O. Pastan. Emory Univ, Atlanta, GA.

Background: Although providers often wait to transplant patients with systemic lupus erythematosus (SLE), shorter overall times to transplant are generally associated with more favorable transplant outcomes in SLE patients. We examined whether referral for evaluation—the first step in the often-years-long process of kidney transplantation—is delayed in dialysis patients with SLE, relative to other dialysis patients.

Methods: United States Renal Data System data on a cohort of 18,419 incident (1/1/05-9/30/12) adult (18-69 years) dialysis patients were included. A referral was defined as provider-assigned cause of ESRD. Logistic regression and Cox proportional hazards models were used to examine the associations of assigned cause and patient characteristics with preemptive referral (referral prior to the start of dialysis) and time from start of dialysis to referral [censored for death or last date of follow-up (9/30/12)], respectively.

Results: Of the 352 dialysis patients with SLE, 43 (12.2%) were preemptively referred—50% more often than other ESRD patients [1573/18,067 (8.7%); OR=1.9 (95% CI, 1.6-2.2)] but not as often as those referred within the first 2 years of dialysis [1573/18,067 (8.7%); OR=1.1 (95% CI, 0.9-1.3)]. Among the 17,293 dialysis patients not preemptively referred, SLE patients were referred at twice the rate of other dialysis patients in crude analyses [HR=1.9 (95% CI, 1.6-2.2)] but not after adjustment for [HR=1.1 (95% CI, 0.9-1.2)]. Among SLE patients, black vs. white race was associated with lower likelihood of preemptive referral [OR=0.5 (95% CI, 0.2-1.2)] but higher rates of referral after dialysis start [HR=1.8 (95% CI, 1.1-2.9)]. Male vs. female sex was associated with higher rates of referral on dialysis [HR=1.6 (1.2-2.2)].

Conclusions: Referrals for kidney transplant evaluation do not appear to be delayed among dialysis patients with SLE, relative to other dialysis patients of similar age. Efforts to increase kidney transplant access in SLE patients should focus on potential race and sex disparities in referral as well as potential delays in other steps of the kidney transplant process.

Funding: Other NIH Support - NIMHD

Association of Kidney Transplantation Referral with Other Indicators of Quality Care Among Incident Georgia Dialysis Patients: The RaDIANT Community Study
Laura Plantinga, Stephen O. Pastan, Jenna Krischer, Eric M. Gibney, Laura L. Mulloy, Rachel E. Patzer. Emory Univ, Atlanta, GA; Southeastern Kidney Council, Inc., Raleigh, NC; Piedmont Transplant Inst, Atlanta, GA; Georgia Regents Univ, Augusta, GA.

Background: Dialysis facility referral rates for patients for kidney transplant is a potential indicator of quality care. We examined whether referral within a year of dialysis start (1-year referral) was associated with other quality indicators among incident Georgia dialysis patients.

Methods: We examined a cohort of 14,120 incident (7/1/05-9/30/11; follow-up through 9/30/12) adult (18-69 years) dialysis patients using United States Renal Data System data linked to concurrent referral data from all three adult Georgia kidney transplant centers. Multilevel, multivariable logistic regression was used to examine the association of 1-year referral with dichotomous quality indicators [pre-ESRD nephrology care, dialysis modality, permanent vascular access in place at dialysis start (HD patients only), pre-ESRD erythropoietin use, and transplant information at dialysis start], with adjustment for demographic and clinical variables and accounting for variation across clinics.

Results: Overall, 1-year referral was 24.8% and was higher among patients with other indicators of quality care: 26.0% vs. 23.8%, with vs. without pre-ESRD care (P=0.005); 27.8% vs. 24.6%, PD vs. HD (P=0.03); 28.3% vs. 22.9%, with vs. without a permanent vascular access in place at HD start (P=0.001); and 27.2% vs. 16.5%, informed vs. not informed of transplant options at dialysis start (P=0.001). With adjustment, pre-ESRD care [OR=1.34 (95% CI, 1.22-1.47)], permanent vascular access in place at dialysis start [OR=1.54 (95% CI, 1.41-1.70)], and transplant information at dialysis start [OR=1.63 (95% CI, 1.45-1.85)] remained associated with higher 1-year referral.

Conclusions: These findings suggest that patients who receive quality care in multiple domains are more likely to be referred for kidney transplant evaluation within a year of starting dialysis, independent of demographic and clinical characteristics. Interventions to increase transplant access should be targeted to patients whose care fails to meet other quality indicators.

Funding: Other NIH Support - NIMHD

Feasibility and Sustainability of the RaDIANT Community Study Among Georgia Dialysis Facilities
Jennifer C. Gandig, Leighton Sauls, Teri Browne, Laura Plantinga, Laura J. McPherson, Eric M. Gibney, Laura L. Mulloy, Stephen O. Pastan, Rachel E. Patzer. Emory Univ; Southeastern Kidney Council; Univ of South Carolina; Piedmont Hospital, Georgia Regents Univ.

Background: The Southeastern Kidney Transplant Coalition developed the randomized, dialysis facility-level Reducing Disparities In Access to kidney NeTraN (RaDIANT) Community Study to address racial disparities and low rates of kidney transplantation (KTs) in Georgia. We aimed to evaluate the feasibility and sustainability of the RaDIANT intervention activities.

Methods: The 67 dialysis facilities that completed a 12-month intervention as part of the RaDIANT study consisted of 12 recommended activities intended to increase KT referrals, such as education and outreach activities targeting the patient, facility staff, and facility policy level. After the intervention, facility staff were asked to complete a 20-item questionnaire on the helpfulness (Likert scale) of each intervention activity and the likelihood (yes/no) of their facility continuing the activity.

Results: A total of 86 staff (51.2% social workers) at the 67 intervention facilities completed the survey. The median number of the 12 intervention activities completed by dialysis facilities was 9 (range, 0-11). Most facilities reported discussing the benefits of KTs at a staff orientation (86.6%), attending monthly webinars (80.7%), and developing a referral improvement plan (76.3%) to be helpful or very helpful. The median number of prescribed intervention activities the facilities reported they would continue was 2, with the distribution of educational brochures (41.9%), a staff orientation focused on KTs (41.9%), and a patient and family education session (34.9%) among the most commonly cited.

Conclusions: Dialysis facility staff perceived that RaDIANT intervention activities were feasible to implement, with staff education potentially being the most helpful and sustainable component. Sustainability may be limited to intervention components that were the least expensive and time intensive to implement. Additional ongoing support from ESRD Networks may be necessary to sustain increased KT referrals observed in the RaDIANT Community Study.

Funding: Other NIH Support - The RaDIANT Community Study is funded in part by NIMHD Award R24MD008077

Physiosocial Differences Between Living and Deceased Donor Renal Transplant Recipients
Anna Bertram, Selma Pabst, Martina De zwaan, Tanja Zimmermann, Mario Schiffer. 1Clinic for Psychosomatics and Psychotherapy, Hannover Medical School, Hannover; 2Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany.

Background: The specific impact of living donor (LD) as compared to deceased donor (DD) kidney transplants on psychosocial functioning has received surprisingly little attention. The present study aimed to assess whether LD and DD recipients differ in socio-demographic variables, time since transplantation, emotional variables, knowledge about immunosuppressant (IS) intake, and self-reported adherence to IS.

Methods: A questionnaire study was performed among 72 LD and 169 DD recipients who attended the kidney transplant outpatient clinic of Hannover Medical School for a follow-up visit at least 1 year after transplantation. Emotional responses were assessed using the Hospital Anxiety and Depression Scale (HADS) and the Transplant Effect Questionnaire (TEQ). Knowledge about IS intake was examined with the Transplant Patients: Prevalence, Agreement, and Correlates of Adherence. No differences between LD and DD recipients were found for gender, educational level, depression, perceived social support, and allotropic rejection. Feelings of guilt and anxiety may be an important focus for interventions to improve emotional adjustment to transplantation, especially in LD recipients.

Funding: Other NIH Support - NIMHD

Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany.

Physician-Reported Adherence with Immunosuppressants in Renal Transplant Patients: Prevalence, Agreement, and Correlates
Anna Bertram, Selma Pabst, Martina De zwaan, Mario Schiffer. 1Clinic for Psychosomatics and Psychotherapy, Hannover Medical School, Hannover, Germany; 2Nephrology and Hypertensiology, Hannover Medical School, Hannover, Germany.

Background: Assessing adherence to immunosuppressants (IS) is difficult. We investigated (1) the prevalence of non-adherence with IS as estimated by physicians; (2) the agreement between the physicians’ estimated and other adherence measures; (3) the difference between adherent and non-adherent patients according to the physicians’ estimation with regard to socio-demographic variables, transplant-related variables, and psychological factors.

Methods: All kidney transplant patients attending the outpatient clinic for a follow-up visit from 11/2014 to 02/2015 were screened; 238 patients met inclusion criteria. Adherence with IS was assessed with several measures: 4-item Baseline Assessment of Adherence to:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO1010
The Difficult Road for Native Americans in Kidney Transplantation: Decreased Access and Reduced Long-Term Survival
Sarah Stith,1 Kristina Piorkowski,2 Fidel Barrantes.2
Economics, Univ of New Mexico, Albuquerque, NM; 1Presbyterian Transplant Center, Renal Medicine Associates, Albuquerque, NM.

Background: Native Americans (NAs) have disproportionately high rates of end-stage renal disease, yet wait listed NAs have lower rates of kidney transplantation than other racial/ethnic groups and worse long-term post-transplant survival outcomes than whites. This study evaluates these disparities across multiple medical and socioeconomic dimensions.

Methods: Using data from the Organ Procurement and Transplantation Network (OPTN), we evaluated wait list removal reasons and post-transplant survival rates from 3/1/95 to 12/31/12. We use a logistic regression model, controlling for patient, donor, match characteristics, and center and year fixed effects, along with a Blinder-Oaxaca decomposition of the results.

Results: Among registered patients removed from the wait list, NAs were less likely to receive a transplant (odds ratio, 0.71 [95% CI, 0.64-0.80]), and more likely to die on the wait list (1.88 [9.89-3.94], compared to whites. NAs are less likely than whites to survive at least two years (odds ratio, 0.80 [95% CI, 0.70-0.92]) and at least three years (0.81 [0.71-0.94]), but these disparities become statistically insignificant with risk adjustment.

Conclusions: NAs experience higher rates of adverse wait list removal reasons than other racial/ethnic groups. Among NAs who do receive transplants, short term survival outcomes are similar to those of whites, but longer term survival outcomes are lower. The decomposition of our results indicates that the disparity in three-year post-transplant survival between NA and whites is driven primarily by the prevalence of lower quality donors among NA transplants, a greater negative impact from such donor characteristics on survival among NA. NAs also tend to receive transplants at centers associated with worse outcomes and would benefit disproportionately from receiving transplants at better centers.

Funding: Private Foundation Support

SA-PO1011
Estimated GFR for Living Kidney Donor Evaluation
Naya Huang,1 Meredith C. Foster,1 Krista L. Lentine,2 Amit X. Garg,1 Emilio D. Poggio,1 Bertram L. Kasiske,1 Lesley Inker,1 Andrew S. Levey.1
1Div of Nephrology, Tufts Medical Center, Boston, MA; 2Div of Nephrology, Saint Louis Univ, MO.

Background: Using data from the Organ Procurement and Transplantation Network, we compared estimated GFR (eGFR) by race from 3/1/95 to 12/31/12. We use a logistic regression model, controlling for patient, donor, match characteristics, and center and year fixed effects, along with a Blinder-Oaxaca decomposition of the results.

Results: Among registered patients removed from the wait list, NAs were less likely to receive a transplant (odds ratio, 0.71 [95% CI, 0.64-0.80]), and more likely to die on the wait list (1.88 [9.89-3.94], compared to whites. NAs are less likely than whites to survive at least two years (odds ratio, 0.80 [95% CI, 0.70-0.92]) and at least three years (0.81 [0.71-0.94]), but these disparities become statistically insignificant with risk adjustment.

Conclusions: NAs experience higher rates of adverse wait list removal reasons than other racial/ethnic groups. Among NAs who do receive transplants, short term survival outcomes are similar to those of whites, but longer term survival outcomes are lower. The decomposition of our results indicates that the disparity in three-year post-transplant survival between NA and whites is driven primarily by the prevalence of lower quality donors among NA transplants, a greater negative impact from such donor characteristics on survival among NA. NAs also tend to receive transplants at centers associated with worse outcomes and would benefit disproportionately from receiving transplants at better centers.

Funding: Private Foundation Support

SA-PO1012
Change of Physical Activities in Male and Female Recipients in 12 Months After Living Kidney Donor Transplantation
Makoto Tsujita, Transplant Surgery, Nagoya Daini Red Cross Hospital, Japan.

Background: Since renal dysfunction and immunosuppressive drugs cause muscle degeneration, physical activities decrease in CKD, dialysis patients and transplant recipients. In addition, elderly kidney transplant recipients are increasing in Japan, so improving physical activities and increasing muscle strength and volumes are important to prevent fractures and fall accident.

Methods: Consecutive 58 patients (male 33) older than 40 years were enrolled in this study from 2012. Immunosuppression basically contains steroid, cyclosporine or tacrolimus, and mycophenolatefomafen or everolimus. Hypertension, hyperlipidemia, and osteoporosis were treated as needed. Parameters of physical activities such as hand grip, SMI (skeletal muscle index) and Body fat mass using by DEXA (dual-energy x ray absorptiometry) were measured.

Results: 12 months after transplant, more than 20% of male and female recipients increased their muscle strength and volumes. SMI increased by 2% and Body fat mass decreased by 3% in male recipients. In female recipients, muscle strength and volumes increased by 5% and SMI increased by 3%. Body fat mass decreased by 2%.

Conclusions: These results indicate that lifestyle modification and physical activities after transplant can improve muscle strength and volumes in recipients.

Funding: Private Foundation Support

SA-PO1009
Evolution Through 20 Years of the Major Kidney Transplant Program from Living Donor in Mexico
Edgar Solis,1 Luis Alberto Evangelista-Carrillo,1 Enrique Rojas-Campos,2 Benjamin Gomez-Navarro,21 Dept of Nefrología y Trasplantes, IMSS, Guadalajara, Jalisco, Mexico; 2Unidad de Investigación Médica en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico.

Background: According to the National Transplant Center, in 2013 a total of 2707 kidney transplants (KT) were performed in Mexico. Our program performed the highest single center number of transplants with 270 KT, mostly from living donors.

Methods: We use data collected in our registration program at Nephrology and Transplant Unit. All the KT in adult patients performed from January 1994-December 2014 in CMNO were included. We also analyzed the last 909 kidney recipients and their serum creatinine at the end of first year. Successful KT was defined as a Cr <1.5 mg/dl at 1 year following. Grafts lost were defined as Cr >4.0 mg/dl or replacement therapy initiation.

Results: During this period 3643 KT were performed, 3236 from living donors and 407 from cadaver donor. Of living donors, 2786 were from related donor and 450 were from genetically unrelated donors. The mean age of recipient was 28 years; 65% of our recipients were male. The evolution of the program is shown.

Conclusions: Each year we are still growing the number of KT. The age of our recipients is diminishing and age of donors is increasing. Months before KT are also increasingly lately reflecting the great number of ESRD patients. Recipient age, HLA mismatching, induction therapy use and generic drugs can explain the 13.2% of patients with Cr above 1.5 mg/dl.

SA-PO1008
Success rate of KT following 1 year was 86.8%. Only female gender and younger donors were statistically significant associated with successful transplant. Graft lost during the first year was 3.6%. Death was 2.4% during the first year.

Multivariate analysis for successful transplant

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>IC 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient gender</td>
<td>2.56</td>
<td>(1.26-5.13)</td>
<td>0.009</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.03</td>
<td>(1.01-1.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Identical HLA</td>
<td>0.21</td>
<td>(0.12-0.31)</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Conclusions: Each year we are still growing the number of KT. The age of our recipients is diminishing and age of donors is increasing. Months before KT are also increasingly lately reflecting the great number of ESRD patients. Recipient age, HLA mismatching, induction therapy use and generic drugs can explain the 13.2% of patients with Cr above 1.5 mg/dl.
absorptiometry), and Body mass index (BMI) were measured and compared at prior, 6, and 12 months after kidney transplantation. Recipients were encouraged to do daily exercise for 30 to 60 minutes everyday.

**Results:** Mean age (years) were 52.3±10.0 in male, and 53.6±10.4 in female. In male patients, any parameter did not change after transplantation in male patients. In female patients, SMI improved in 12 months (p<0.005), and Hand grip also tended to increase with statistically difference.

**Figure 1 Results of this study for male and female (mean±SD)**

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 33)</th>
<th>6 months after transplantation</th>
<th>12 months after transplantation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m2)</td>
<td>22.6±3.4</td>
<td>21.8±3.2</td>
<td>22.7±3.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>20.4±5.8</td>
<td>20.1±5.4</td>
<td>21.1±5.4</td>
<td>0.59</td>
</tr>
<tr>
<td>SMI (kg/m2)</td>
<td>7.1±1.8</td>
<td>7.0±1.6</td>
<td>7.0±1.6</td>
<td>0.12</td>
</tr>
<tr>
<td>Hand grip (kg)</td>
<td>31.6±9.8</td>
<td>32.0±6.1</td>
<td>32.1±8.2</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Female (n = 25)**

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 25)</th>
<th>6 months after transplantation</th>
<th>12 months after transplantation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m2)</td>
<td>21.3±3.6</td>
<td>20.2±3.7</td>
<td>21.5±4.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>25.4±6.1</td>
<td>27.0±6.8</td>
<td>28.3±7.0</td>
<td>0.05</td>
</tr>
<tr>
<td>SMI (kg/m2)</td>
<td>5.4±1.8</td>
<td>5.5±1.4</td>
<td>5.9±1.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Hand grip (kg)</td>
<td>17.7±5.8</td>
<td>19.2±5.1</td>
<td>21.4±5.5</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Physical activities seemed unchanged after transplantation in more patients than before.

**Conclusions:** In male recipients, physical activities do not seem to recover in 12 months after kidney transplantation. More interventions and more studies are needed to increase physical activities and know the effect of daily exercise clinically.

SA-PO1013

**Search for New Data to Predict Kidney Transplant Outcomes in the Organ Procurement and Transplantation Network Database**

**Background:** The Organ Procurement and Transplantation Network (OPTN) collects data used to monitor transplant program outcomes for quality assurance and regulatory oversight. It is imperative that the variables in the OPTN database used by the Scientific Registry of Transplant Recipients to determine expected outcomes after kidney transplant be reliable, complete, and up-to-date.

**Methods:** We conducted a systematic review to identify risk factors not included in current OPTN data that predict graft failure or mortality after kidney transplant. We searched for studies with publication date between Jan 1 2000-May 1 2015; at least 1000 subjects in one or more risk prediction models; multivariate analysis used to select variables predicting patient or graft survival; inclusion in the multivariate model of at least one risk factor collected before or at the time of transplant that is not already collected by OPTN; and English language. For duplicate publications we selected the most recent. For publications with overlapping but distinct cohorts, we selected the one with the largest cohort. We arbitrarily limited the search to studies including 1000 participants in at least one risk-prediction model. Although a small single-center study may convincingly show that a newly described risk factor predicts outcomes at that center, there are likely major barriers to measuring and collecting this risk factor uniformly at every program in the US.

**Results:** We identified 33 studies that met inclusion criteria: 6 (18%) were single-center, 4 (12%) were multicenter, and 23 (70%) were registry studies. Promising new variables included: myocardial infarction, coronary artery revascularization, atrial fibrillation, congestive heart failure, valvular heart disease, cerebral vascular accident, chronic kidney disease, renal transplant, diabetes, hyperphosphatemia. We also found that 68 patients had hypophosphatemia. Serum iPTH levels were higher in group I (58.4±14 ng/dl) versus group II (138.3±5 ng/dl; p<0.001). In group I, iPTH levels were significantly correlated with eGFR (r value=−0.37, p<0.05). Both serum ALP and iPTH levels showed significant negative correlation with eGFR in groups I and II (p<0.05). In all groups, bone minerals, iPTH and serum Alkaline Phosphatase levels had no statistically significant relation with the immunosuppressant agent used (p<0.05).

**Conclusions:** Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function and transplantation duration.

SA-PO1014

**Prevalence of Mineral and Bone Disorders Among Living Kidney Transplant Recipients**

**Background:**Mineral and bone disorders (MBD), frequent complications of chronic kidney disease (CKD), occur frequently in kidney transplant recipients. Still, it is known about its prevalence and clinical correlates in transplanted patients. Therefore, we conducted a cross-sectional analysis of 504 stable living kidney allograft recipients. Detailed medical history, demographic data and routine laboratory investigations, including s.creatinine, s.corrected Calcium, s.Phosphorus, serum iPTH and s.Alkaline Phosphatase (ALP) were collected. Estimated GFR was calculated using the abbreviated MDRD formula. Patients were stratified into three groups based on duration of kidney transplantation. Group I: 0-6 months to 1 year, group II: from 1 to 5 years and group III: more than 5 years. Correlations were done between bone minerals and all laboratory results. We also analyzed the possible relation between various immunosuppressant drugs and bone minerals, serum iPTH and serum ALP.

**Results:** The mean age was 32±8 years in group I, 45±37 years in group II, and 40±5 years in group III, with no significant difference between the three groups (p>0.05). There was no significant difference between the studied groups as regards laboratory parameters (p>0.05). 115 patients had iPTH levels >170 ng/dl, while 365 patients (72.4%) had iPTH levels >70 ng/dl. Only 24 patients had hypercalcemia, and 34 patients had hyperphosphatemia. We also found that 68 patients had hypophosphatemia. Serum iPTH and iCa levels were higher in group I (58.4±14 ng/dl, 138.3±5 ng/dl) versus group II (138.3±5 ng/dl, 122.6±6 ng/dl) (p<0.001). In group I, iPTH levels were negatively correlated with eGFR (r value=−0.37, p<0.05). Both serum ALP and iPTH levels showed significant negative correlation with eGFR in groups I and II (p<0.05). In all groups, bone minerals, iPTH and serum Alkaline Phosphatase levels had no statistically significant relation with the immunosuppressant agent used (p>0.05).

**Conclusions:** Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function and transplantation duration.

SA-PO1015

**Risk of Adverse Maternal and Fetal Outcomes During Pregnancy in Living Kidney Donors**

**Background:** A frequently asked question by potential kidney donors is risk of nephrectomy on maternal and fetal outcomes in pregnancy. Studies regarding the risks of living kidney donation and pregnancy outcomes are conflicting. The purpose of this study was to determine the risk of adverse maternal and fetal outcomes in donors vs. non-donors.

**Methods:** Using data from an integrated health care delivery system in Utah from 2000 through 2014, a total of 72 women were living kidney donors that became pregnant after kidney donation. Using a pool of 74,105 women who were not donors, we selected 1223 to use for matches for the living kidney donors. These women were matched 1:3 by age and race. Adverse pregnancy outcomes were defined as preterm delivery, delivery via cesarean section, preeclampsia, eclampsia, length of stay in the hospital and low birth weight (<2.5 kg). Logistic regression analysis was used to examine the association between donation and adverse outcomes.

**Results:** Of the living kidney donors, the mean (SD) age and mean (SD) gestational age at delivery was 30.9±5 years and 38.2±2 weeks, respectively. The mean (SD) length of stay in the hospital was 2.7±2.7 days. Six cases (8%) had a history of chronic hypertension. Living kidney donors did not have a higher risk of preterm delivery (OR 1.82, 95% CI 0.87-3.77), preeclampsia/eclampsia (OR 1.11, 95% CI 0.47-2.65), delivery via cesarean section (OR 1.51, 95% CI 1.05-2.16), length of stay = 3 days (OR 1.29, 95% CI 1.03-2.64) or low birth weight (OR 1.94, 95% CI 1.67-4.35) compared to non-donors.

**Conclusions:** Living kidney donation is not associated with a higher risk of adverse outcomes in pregnancy.

**Funding:** NIDDK Support
Disparities in Access to Renal Transplant in Puerto Rican Children

Nélida del Jesús González,1 Sonia M. Caraballo,1 Eduardo J. Santiago-Rodríguez,2,3 Marta P. Suárez-Rivera,1 Melvin A. Bonilla-Feliz.1 1Medical School, Pediatric Nephrology Div, Univ of Puerto Rico; 2Univ Central del Caribe; 3Puerto Rico Clinical and Translational Research Consortium.

Background: Disparities in access to renal transplant have been reported in racial minorities living in US. No data is available from children with ESRD living in Puerto Rico (PR). We describe the pediatric population with ESRD in PR from 2003-2013, the renal transplant rates and possible barriers to receiving a graft.

Methods: Retrospective chart review of patients diagnosed with ESRD in PR from 2003-2013. Incidence, prevalence rates, means/standard deviations (SD), medians/interquartile range (IQR), frequencies and percentages were calculated and compared to national rates.

Results: From 2003-2013 99 patients, male: 52%, age: 13.5yrs (8-16yrs), were diagnosed with ESRD. Congenital anomalies were the primary cause in 40%, and FGCS in 24%. Incidence of ESRD ranged from 3-14 subjects per million population/year, with prevalence per dialysis modality from 7-18 subjects per million population/year. 38% were transplanted in PR (Median age: 14yrs, IQR: 9-16), 23% from living donors. 14.1% received a transplant in the first year (National rate: 38%). 63% of these non-transplanted children had Medicare coverage. None of 9 infants diagnosed with ESRD were transplanted during infancy. 46% of the children who were not transplanted stayed at our unit for a median time of 2 yrs (IQR: 1-3). The rest was transferred to a dialysis unit outside PR (15%) or to an adult facility without being transplanted (39%). 67% of these non-transplanted children were covered by Medicare. The mortality rate during the first year of diagnosis was 3% (National rate: 4%).

Conclusions: Children with ESRD in PR face striking disparities in access to renal transplant. Lack of pediatric transplant surgeons, geographical isolation and minimal living donation are potential barriers. Medicare coverage does not appear to be a factor, as it was similar between transplanted and non-transplanted. Interventions to reduce these inequities are needed.

Post Donation Diabetes and Risk of Death and ESRD


Background: We have previously shown that development of diabetes following live kidney donation does not result in accelerated GFR decline when compared to diabetics with two kidneys. Herein, we report on the development of a risk calculator for new onset DM in donors and address its contribution to mortality and also renal outcomes.

Methods: Donors were followed indefinitely through surveys including development and treatment of diabetes and renal outcomes. Risk factors for post donation diabetes were determined using stepwise proportional hazards regression.

Results: Development of DM was ascertained in 3874 donors with a mean follow-up of 16.1±1.2 years. In total, 279 (7%) developed DM. Pre-donation risk factors for development include older age, BMI, tobacco use, and fasting serum glucose at donation, p<0.01 for all (Table 1a). Diabetes following donation was associated with a nearly 5 fold increase in the non-diabetic group and 36% in adherent adolescents. Only 40% of the adherent group reported elevated distress versus 57% of the non-adherent group. There was a gender bias toward male non-adherence in this group with 100% of the non-adherent population being male. The mean time from transplant of non-adherent groups was 6.1 years versus 3.9 years in the adherent group. These differences were not statistically significant except as above.

Conclusions: Our population’s rate of psychiatric diagnosis was significantly elevated compared to community norms and also correlated with elevated psychosocial distress and non-adherence. Disagreement in parent and adolescent reporting was common regardless of adherence status. Our sample did demonstrate gender differences in non-adherent behavior as well. Interpretation of these results, as well as statistical significance is limited by the small sample size.

Funding: Other NIH Support - This investigation was supported by the Utah Study Design and Biostatistics Center, with funding in part from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant U01TR000105 (formerly UL1RR025764).

The Case against Declining Donors with Impaired Fasting Glucose

Robert N. Foley, Naim S. Issa, Danielle M. Berglund, Arthur J. Mitas, Hassan N. Ibrahim. Univ of Minnesota, Mpls, MN.

Background: The definition of diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have changed over time. IGIF was defined in 1997 by fasting glucose 110-125 mg/dL and in 2003 the definition changed to fasting glucose 100-125 mg/dL. With the introduction of this new definition, many potential donors with fasting blood sugar between 100-110 mg/dL have been denied donation. This is highly relevant as many of these are potential donors to family members with type 2 diabetes mellitus.

Methods: We assessed the risk of death, new onset diabetes, hypertension, proteinuria, and reduced eGFR (<45 or <30 ml/min/1.73m2) in 3738 kidney donors according to fasting blood glucose(FBG) at the time of donation spanning the period between 1963-2013.

Results: 2900 donors had a FBG <100 mg/dL, 550 with 100-109, 205 with 110-125 and 128 donors with FBG > 126 mg/dL. Donors with FBG (100-109 mg/dL) after multivariable adjustment were more likely to die, develop diabetes, proteinuria, hypertension, eGFR <45 ml/min/1.73m2 or eGFR <30ml/min/1.73m2 as compared to those with FBG <100 mg/dL (Table 1). In contrast, those with FBG between 110-125 mg/dL were more likely to become diabetic and hypertensive but not proteinuric or reduced GFR. Those with FBG >126 mg/dL were more likely to die, develop DM and HTN but not suffer any adverse renal consequences.

Conclusions: Excluding potential donors with a fasting glucose (100-109 mg/dL) should be revisited as these donors do well in the long-term.

Funding: Other NIH Support - NIH (5P01 DK013083)
Conclusions: Diabetes can be reasonably predicted in kidney donors using baseline data. Diabetes is a significant contributor to reduced GFR and proteinuria.

Funding: Other NIH Support - NIH (5P01 DK013803)

SA-PO1021

What Kind of Obesity Does Affect Kidney Function? Survey of Kidney Transplant Donors

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Background: Currently obesity is a risk for chronic kidney disease. It is also suggested that sarcopenia is the independent risk factor of hypertension. It is unclear whether obesity and body composition affect to kidney function and other prognosis of donors in our country.

The aim of this study was to investigate the influence of body composition, the findings of graft biopsy and 1-year after clinical outcome.

Methods: This is a retrospective single center study of 60 living kidney transplant donors from 2009 to 2014. Donors are stratified according to Body Mass Index (BMI³25kg/m²) for appearance of muscle on cross-sectional CT images (L3 SMI, Under 38.5cm²/m² for men and 52.4cm²/m² for women are defined as a sarcopenia)(1). We divided donors into four groups; (A) Obesity negative + Sarcopenia negative (ONSN)(B) Obesity positive + Sarcopenia negative (OPSN)(C) Obesity negative + Sarcopenia positive (ONSIP)(D) Obesity positive + Sarcopenia positive (OPSP). We evaluated kidney function at donation, baseline kidney graft biopsy findings and clinical course 1 year-after donation.

Results: Seven patients were ONSP (11.7%), 22 patients ONSN (36.7%), and 4 patients OPSP (6.7%). Visceral fat area ³100 m² (which is defined as central obesity in Japanese criteria) was significantly higher in OPSP group. Sercre at donation was significantly lower in OPSP and ONSP groups. In multivariate analysis of graft biopsies, BMI³25kg/m² was a significant risk for small artery intimal thickenings and interstitial fibrosis/tubular atrophy. On the contrast, OPSP was an independent risk for global sclerosis. In multivariate analysis, central obesity was significantly correlated with 1-year after proteinuria. In addition, OPSP was an independent risk for 1-year after hypertension.

Conclusions: These results indicate obese donor already has a risk for arterial and interstitial damages at transplantation. In addition, central obesity and sarcopenia contribute to the late graft function and hypertension.[Reference] (1) Prado CM et al. Lancet Oncol 2008; 9: 629–635.

SA-PO1022

Living Donor Remaining Function Measured by CKD-EPI Correlates with Remaining Kidney Volume

Asif A. Sharifuddin, Ali Khalil, Muhammad S. Yaqub, Tim E. Taber, Muhammad Ahmad Mujtaba. Medicine/Neph, Indiana Univ.

Background: The aim of our study was to evaluate whether preserved kidney volume correlates with donor renal function at 2-years post-donation using the CKD-EPI eGFR equation.

Methods: Demographics and renal function of living donors who underwent living nephrectomy between January 2008 and November 2012 were reviewed. All donors underwent computed tomography with an estimation of kidney volumes. Preserved Kidney Volume (PKV) was adjusted (ΔPKV) to Body Surface Area.

Results: A total of 208 donors with 2 year follow up data available. Pre-donation eGFR (β Coef. 0.344), age (β Coef. -0.318) and ΔPKV (β Coef. 0.11) were found to be independent predictors of 2yr eGFR (p=0.001). ΔPKV was divided into tertiles (low/middle/high) and a 2 year eGFR of <60ml/min was chosen as a cut off for dichotomous analysis as in Table 1.

<table>
<thead>
<tr>
<th>V ol Tertile</th>
<th>2yr eGFR&lt;60</th>
<th>2yr eGFR&gt; 60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>V ol Tertile 1 (low)</td>
<td>44(47.8%)</td>
<td>24(26.7%)</td>
<td>68(72.7%)</td>
</tr>
<tr>
<td>V ol Tertile 2 (medium)</td>
<td>31(33.7%)</td>
<td>35(38.2%)</td>
<td>66(31.7%)</td>
</tr>
<tr>
<td>V ol Tertile 3 (high)</td>
<td>17(18.5%)</td>
<td>57(61.9%)</td>
<td>74(35.6%)</td>
</tr>
</tbody>
</table>

Mean aPKV (ml/min) 52±6 76±15*

Mean 2yr eGFR was 57±9; 65±16 and 73±17 between the tertile groups (p<0.05). The odds ratio of having a 2yr post-donation eGFR<60 with a cutoff of median ΔPKV of 194ml was 5.8 (95%CI 2.9-11.6; p<0.0001), while that of 2yr post-donation eGFR<60 with a cutoff of < 25th percentile of ΔPKV of 159.9 was 5.6 (95%CI 2.7-11.2; p<0.0001). The odds ratio of having an eGFR<60 if the ΔPKV was above the 75th percentile was 0.13 (95%CI 0.05-0.3) p=0.0001. ROC and AUC for ΔPKV and eGFR (CKD-EPI) of <60 were 0.763 (CI0.69-0.82) p=0.005 as in Figure 1.

Conclusions: Our study is the first to show using CKD-EPI equation that preservation of residual renal function in living donors needs to take into account remaining kidney volume, when selecting kidneys from healthy donors.

SA-PO1023

Assessing Adherence Barriers in Pediatric Kidney Transplant Recipients

Charles D. Varnell,1 Kristin Loiselle,2 Alina Lh Pai,2 Avani Modi,2 David K. Hooper.1 Div of Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Center for Treatment Adherence and Self-Management, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Nonadherence in pediatric kidney transplant recipients(KTRs) is associated with poor outcomes and poses a significant financial cost to society. Patient and family reported barriers to taking medications predict nonadherence, rejection, graft failure, and death. Despite their clinical importance and amenability to intervention, barriers to medication adherence are not routinely assessed in pediatric settings.

Methods: From Jan 2015 - May 2015, barriers to immunosuppressant adherence in KTRs were assessed using a standardized checklist of 14 common barriers. For KTRs<10 y.o. the caregiver completed the assessment. For KTRs>10 y.o. both the patient and caregiver, if present, completed the assessment. Assessments were completed during routine outpatient clinic appointments.

Results: 36 pediatric KTRs [M(SD)age=13.14(6.43)years;56.7%male] and 50 primary caregivers completed a barriers assessment. At least one barrier was reported by 47% of KTRs compared to 42% of caregivers. For KTRs the most frequent barriers were forgetting(22%), hating the taste(13.9%) and running out of medication(8.3%). For caregivers, the most frequently endorsed barriers were forgetting(20%), side effects(6.0%) and patient refuses to take their medication(6.0%). There was excellent concordance(96.2%) in dyads where both KTR and caregiver reported barriers. Assessing for barriers to adherence was easy to perform in practice and required<60 seconds.

Conclusions: Nearly half of all patients report at least one barrier to taking their immunosuppression, and there is generally consistent agreement between patient and caregiver perception of barriers. Standardizing the approach to assessing barriers to immunosuppressant adherence in the clinical setting can quickly produce information that might be missed by the provider. Future research should evaluate the effectiveness of interventions delivered as part of routine medical care to overcome identified barriers and prevent known complications associated with nonadherence.
A Longitudinal Follow-Up of Hispanic Living Kidney Donors

Clarence E. Foster III,1 Pinky J. Patel,1 Hirohito Ichii,1 Madeleine V. Pahl,2 Elani Streja,3 Jonathan R. Lakey,4 Kamary Kalantar-Zadeh,2 1Surgery/ Div of Transplantation, Univ of California, Irvine, Orange, CA; 2Medicine/Nephrology, Univ of California, Irvine, Orange, CA.

Background: This is a long-term follow-up of living kidney donors (LKD) in an ethnically diverse patient population. Hispanics are known to have an increased risk of developing chronic kidney disease, associated with hypertension and obesity. The hypothesis is Hispanic living kidney donors or unclassified living kidney donors would have poorer long-term outcomes secondary to lack of access to health care and secondary to the higher risk factors for developing chronic kidney disease. 

Methods: The objectives: measure obesity, hypertension, diabetes, measure CrCl post-donation and compare to the pre-donation CrCl. LKD were contacted & invited to participate & had a questionnaire about their general health & history and physical. Analysis included a CBC, serum chemistry, a 24-hour urine collection to measure creatinine, protein and albumin. A Patient Data Visit Sheet, RAND 35 Health Questionnaire. The IRB approved this study.

Results:

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Hispanics (N=42)</th>
<th>Non-Hispanics (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) post-donation, range (year)</td>
<td>36 +/- 12 (18 to 55)</td>
<td>32 +/- 11 (18 to 52)</td>
</tr>
<tr>
<td>Pre-donation GFR, ml/min</td>
<td>41 +/- 10 (22 to 55)</td>
<td>0.007</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>U.S. Citizen (%)</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td>Health Insurance (%)</td>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>Years Post-Donation</td>
<td>3.8 (1.1 to 13.5)</td>
<td>3.6 +/- 2.8 (1.2 to 11.8)</td>
</tr>
<tr>
<td>Pre-donation BMI, mean</td>
<td>25.6</td>
<td>27.9</td>
</tr>
<tr>
<td>Pre-donation GFR, ml/ min, mean</td>
<td>122</td>
<td>137</td>
</tr>
<tr>
<td>Pre-donation GFR, ml/ min, mean</td>
<td>104.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Pre- and post-donation systolic and diastolic blood pressures were similar between Hispanics and non-Hispanic LKD. Non-Hispanic LKD had a greater decrease in systolic blood pressure post-donation -4.5 mmHg vs. 6.6 mmHg (p=0.0378). The decrease in CrCl post-donation was the same in Hispanic and Non-Hispanic LKD, 33 ml/min vs. 35 ml/min. None of the LDLK in the study had significant proteinuria or microalbuminuria.

Conclusions: Post living donor kidney donation in our ethnically diverse patients are not at a higher risk for developing obesity, HTN, or CKD. Overall, our LKD feel they have a good overall quality of life including both physical and emotional realms.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals

Post-Kidney Transplant Follow-Up in Native American: An Opportunity for Improvement

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Background: Native Americans have been shown to face decreased access to waitlisting and transplantation. We explore the possibility that Native Americans might face decreased access to high quality post-transplant care, especially in the long-run, due to a decreased general access to healthcare, as is faced by many socioeconomically disadvantaged minority populations.

Methods: Using data from the OPTN, we evaluated the quantity and type of post-transplant care received by Native Americans. We compare Native American populations with other ethnically diverse groups from October 1, 1987 to December 31, 2012 using multivariate regression analysis, controlling for time-invariant factors affecting all patients in a given year (year fixed effects) and time-varying factors associated with a specific transplant center (center fixed effects). (Standard errors are clustered at the center level to account for heteroscedasticity and spatial correlation among patients in a given center).

Results: Statistically significant regression results (p<0.05) indicate that Native Americans are less likely to receive transplant program-based aftercare than other racial/ethnic groups (Black, White, Hispanic and Asian/Pacific Islander), opting instead to see other types of specialists. They also are two percentage points more likely to be lost to follow-up (mean=0.15), one percentage point less likely to participate in an immunosuppression-related research study (mean=0.03), and receive 0.3 fewer follow-up visits (mean=2.2) than whites. They face the lowest number of follow-up visits, the lowest probability of participating in a research study, and the highest probability of being lost to follow-up. They are also 13% points less likely to work post-transplant (mean=0.35) than whites.

Conclusions: The results indicate that Native Americans have reduced access to high quality post-transplant care. Further research will explore how much of the disparity in post-transplant care is related to the high correlation between being Native American and poor and between being Native American and living in a rural area, especially on tribal lands.

Funding: Private Foundation Support

Pre-Procurement Iodinated Contrast Exposure Is Associated with Early and Late Kidney Transplant Outcomes

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Background: Iodinated contrast can cause acute kidney injury. We sought to evaluate the association of iodinated contrast exposure prior to organ procurement in deceased donors with subsequent kidney transplant outcomes.

Methods: Using OPTN data for kidney transplants between May 2000 and December 2012, we performed multivariate regression to model 2 different definitions of delayed graft function.

Results: 122,856 deceased donor kidney transplants were included in the analysis, of which 28% (n=34,428) had received iodinated contrast exposure prior to procurement. Among recipients, 3.7% (n=4,491) experienced delayed graft function. Using OPTN data for kidney transplants between May 2000 and December 2012, we performed multivariate regression to model 2 different definitions of delayed graft function.
function as a function of donor exposure to coronary angiograms, controlling for time- invariant factors affecting all patients in a given year (year fixed effects) and time-varying factors associated with a specific transplant center (center fixed effects with standard errors clustered at the center level to account for heteroskedasticity and spatial correlation among patients in a given center).

Results: Of 93,811 donors listed in study period, 8.5 % (8012) were exposed to coronary angiograms. From this group, 14,628 kidneys were transplanted. Statistically significant regression results (p<0.01) indicate that patients receiving organs from donors who received coronary angiograms are 2% points more likely to receive dialysis within the first 3 months post-transplant (mean=0.24) and are less likely to experience a ≥25% decline in serum creatinine in the first week of transplant (mean=0.56). These patients also face a 61 day shorter average graft survival time and a 1% point lower probability of 6-month post-transplant patient survival. At three years recipients from donors with contrast exposure have 2% decrease in survival rate (P=0.005).

Conclusions: This large database analysis provided statistical power to detect an association between donor exposure to iodinated contrast from coronary angiograms before organ procurement and subsequent adverse early as well as later kidney transplant outcomes. Further research into the effects of deceased-donor management strategies is warranted to expand the organ pool while decreasing adverse transplant outcomes.

Funding: Private Foundation Support

SA-PO1029

One Year Recovery After Kidney Donation: The Medical and Donor Point of View in a Prospective Cohort Study Briançon Serge,1 Lucie Germain,1 Michele Kessler,2 Marie-Alice Macher,3 Marc Soudant,1 Marie Thuong,2 Épidemiologie CIC-EC, CHU de Nancy, Nancy, France;2 Nephrology, CHU de Nancy, Nancy, France;3 Transplantation, Agence de la Biomédecine, Paris, France.

Background: Renal transplantation is the reference treatment for ESRD patients; the living donor kidney has been proven to provide better outcomes to recipients. Recovery of donors has been less studied and understood.

Methods: An exhaustive sample of 500 donors recruited in every French transplantation between October 2009 and January 2012 (T0) were followed at 3 (T1) and 12 months (T2) after surgery. Questionnaires investigating the donation course, quality of life (SF-36 and Euroqol) and recovery were sent back. Medical data were from CRISTAL register. 384 donors participated at 3(85%) and 12months(90%). The exceptional participation rate reflects the high commitment of donors.

Results: Before the donation, the physical health is incredibly high especially for older. On average a 75 year-old donor has the PCS SF36 level of 35 year-old men in the general population Three months after surgery, all outcomes exhibited decreased health indicators. Three quarters of the donors underwent laparoscopy, associated with less pulmonary complications, kidney failure, high blood pressure, persistent physical pain, better postoperative recovery. More than half the donors have at least one complication of which 8% was severe. The appearance of the scar is one of the dissatisfaction of the donor. One year after the donation, over 10 donors, 9 resum work, 3 not at all completely recovered, three still feel physical pain, 4 have not recovered their PCS pre-donation level, and 5 their MCS level. However their status remains better than that of the general population of the same age and sex. Donors are ready to do it again (98.2%) and recommend the donation (96%).

Conclusions: The experience alters neither the initial impetus nor the meaning attributed to the donation. The recommendations are meant to develop the process of laparoscopy: to inform and manage completely pain, to better prepare the donor to the surgical procedure, its risks and aftermath, including professional ones in younger, to perfectly plan the medical follow up with information to referee physicians.

Funding: Government Support - Non-U.S.

SA-PO1030

Discard of Deceased Donor Kidneys in the United States: The Weekend Effect Sumit Mohan,1 Karl F.W. Foley,1 Mariana C. Chiles,1 Geoffrey K. Dube,1 Russell J. Crew,2 Stephen O. Pasma,7 Rachel E. Patzer,2 David J. Cohen,1 Dept. of Medicine, Columbus Univ College of Physicians & Surgeons, New York, NY;2 Dept. of Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: The discard rate of deceased donor kidneys (DDK) has slowly increased over time. The underlying reasons remain unclear. The impact of low resource availability over the weekend is unknown. We aimed to determine the impact of weekends on organ utilization patterns.

Methods: The majority of DDK (80%) are transplanted over the weekend and are procured on either Friday or Saturday (Fri-Sat). Using data from the Scientific Registry of Transplant Recipients (SRTR), we identified and compared all DDK procured on Fri-Sat to those that were procured on other days of the week. Using logistic regression we estimated the adjusted odds of discard for DDK over the weekend.

Results: Among the available kidneys, the Fri-Sat period was associated with lower procurement (89.5 vs 90.2%, p<0.001) and the procured kidneys were older (39.7±17.7 vs 39.1±17.6, p<0.001) and of lower quality (KDRI 1.3±0.49 vs 1.3±0.49, p<0.001). Not only were Fri-Sat DDK were more likely to be discarded (18.6 vs 16.4%, p<0.001), these kidneys were of higher quality than those discarded during the rest of the week (KDRI 1.8±0.57 vs 1.8±0.56, p=0.018). Fri-Sat DDK were more likely to be shared without payback and be transplanted at a large transplant center. After adjusting for KDRI, Fri-Sat DDK were 20% more likely to be discarded than kidneys procured during other times during the week (OR=1.20, p<0.001).

Conclusions: DDK procured on Fri-Sat are more likely to be discarded than at other times. This may be due to the fact that organs are less likely to be shared with large transplant centers. Our results demonstrate the possibility that low resource availability on the weekends adversely impacts organ procurement, acceptance and transplantation.

SA-PO1031

Medication Adherence Barrier Burden Predicts Subsequent Adherence to Dosing Time Schedule in Adolescent Kidney Transplant Recipients in the TAKE-IT Trial Bethany J. Foster,1 Huanqiao Zhao,2 Ahna Lh Pai,2 Nataliya Zelikovskaya,3 Crystal D. Holly,1 Jodi M. Smith,1 Vikas R. Dharnidharka,2 Diane Hebert,2 Lorraine E. Bell,2 Douglas G. Matsell,1 Veronique Phan,2 Susan L. Furrh.2 Pediatrics, McGill Univ;2 TAKE-IT Investigators.

Background: Studies of adherence to timing of medication dosing in high-risk adolescent kidney transplant recipients are lacking.

Methods: We aimed to determine whether the burden of perceived barriers to medication adherence predicted timing adherence (proportion of doses taken ≥1 h before to ≥2 h after the prescribed dosing time) during the subsequent 3 mo., as monitored with a multidose electronic pillbox. We evaluated the 126 participants of TAKE-IT who had electronic adherence data available for the 3-mo. run-in period (no intervention). Participants (11-24 y.; ≥ 3 mo. post-transplant) were followed in 8 centers (Canada and USA). Adherence barriers were assessed at baseline using the Adolescent Medication Barriers Scale (AMBS). A higher score indicates greater barrier burden (possible range 17-85). We used linear regression to estimate the association between baseline AMBS scores (total score and ingestion, disease adaptation, and cognitive/organization subscores) and timing adherence. Models also included sex, age, race, and time since transplant.

Results: 60% were male and 67% were white. Median age at baseline was 15.8 (IQR 14-17.4y). Median time since transplant was 1.1 (0.7-7.5) years. Median timing adherence for the interval was 82.6±32.8. Higher barrier burden (median score 38 (IQR 30-44)) was significantly associated with poorer timing adherence: a 5 unit higher total AMBS score was associated with 2.0% (95% CI 0.4, 3.6) lower timing adherence. A 5 unit higher score was associated with 4.3% (1.2, 7.5) lower timing adherence for the disease adaptation subscale, and with 5.9% (0.2, 11.6) lower timing adherence for the cognitive/organization subscale. Males had 10% (2.9, 17.6) lower timing adherence than females.

Conclusions: Higher burden of perceived barriers was a significant predictor of poorer timing adherence in this longitudinal study. Future analysis of the TAKE-IT data will determine the impact of an intervention targeting individual barriers on timing adherence.

Funding: NIDDK Support
SA-PO1034

Short-Term Outcomes in Individuals with Persistant Asymptomatic Non-Visible Haematuria

Background: National guidelines in the United Kingdom suggest investigation to exclude urological disease and identify glomerular pathology in potential donors with persistent asymptomatic non-visible haematuria (PANVH). There is currently no guidance on how to proceed where abnormal immunohistochemistry (IHC) is found without proliferative glomerular changes or electron dense deposits (EDD).

Methods: Demographic characteristics, renal function and biopsy details were obtained by retrospective case note review of kidney donors in the South West Thames transplant network who had undergone renal biopsy for PANVH between 2008-13. Light microscopy, IHC and electron microscopy (EM) findings were collected and clinical outcomes analysed for donors and recipients.

Results: Twenty four donors with PANVH proceeded to donation. All donors completed their 1st year, only 32 patients (34%) achieved an optimal outcome. This was defined by the following criteria:
- Nephritis, hyperlipidaemia, hypertension, serum creatinine > 1.5
- Kidney transplant glomerulopathy, and no history of AMR or ACR
- Infection (BKV PCR <10,000, CMV PCR<0, no history of PTLD or symptomatic EBV) and cardiovascular (CV) health

Conclusions: Facilitating directed donations will continue as part of our routine practice. Each year approximately one in six of our donor families identified potential recipients, but transplants from these requests remained consistently less than 2% of our annual total. Future studies are planned to evaluate recipient outcomes, assess donor family satisfaction with a recipient known to them, as well as to examine our practice in detail in an effort to standardize the language and timing of the directed donation discussions.

SA-PO1035

Deceased Directed Kidney Donations: A Three-Year Experience at a Single OPO

Background: The UAGA allows for deceased directed organ donations. Our OPO has incorporated the practice of offering the option of directed donations during every donation discussion in response to routine donor family requests. However, facilitating directed donations for donor families remains a controversial topic. Opponents suggest that directing gifts is not only inequitable, but that it may encourage malfeasance in the form of organ solicitation via media or social networks, and worse, lead to patients who promote discrimination. The purpose of this research effort was to identify how many directed kidney requests were received and honored during a three-year period in order to assess the impact on our allocation scheme.

Methods: We analyzed retrospective data from our OPO for three years from 2012-2014. We evaluated the number of directed kidney donation requests in relation to the overall number of donors, as well as the transplant outcomes or reasons for decline when the request was not honored. Relationship of donors to potential recipients was also assessed.

Results: During the three year period, 176 of our 1,056 authorized donors had a potential directed donation. Of these, 80% were directed to patients on the kidney waiting list. However, only 16% of the attempted directed kidney donations resulted in a transplant. The data illuminate that incompatibility/mismatch of potential directed kidney recipients is the most common reason that directed kidneys are not transplanted, despite the fact that directed donations are allocated ahead of highly sensitized patients, mandatory shares, multivisceral combinations, and the like.

Conclusions: Facilitating directed donations will continue as part of our routine practice. Each year approximately one in six of our donor families identified potential recipients, but transplants from these requests remained consistently less than 2% of our annual total. Future studies are planned to evaluate recipient outcomes, assess donor family satisfaction with a recipient known to them, as well as to examine our practice in detail in an effort to standardize the language and timing of the directed donation discussions.

SA-PO1036

Optimal Outcomes in Pediatric Renal Transplant Recipients

Background: Pediatric kidney transplant recipients (pKTRs) experience multiple sequelae of their condition, yet comprehensive assessment of these is lacking in the literature. Our objective was to develop a composite outcome measure for pKTRs that considers the most common comorbidities, and to evaluate a population of pKTRs at specific intervals post-transplant.

Methods: We retrospectively reviewed all KTRs at our center from 10/2008 through 2/2015. An optimal outcome composite measure was created consisting of 14 criteria in four domains: allograft function (CKD stage 3, urine protein/creatinine ratio < 0.5, absence of DSA's), histology (no or mild interstitial fibrosis and tubular atrophy, no transplant glomerulopathy, no history of AMR or ACR), infection (BKV PCR <10,000, CMV PCR<0, no history of PTLD or symptomatic EBV) and cardiovascular (CV) health (triglycerides<500, LDL <130, BP <90th %ile, fasting glucose < 126, and BMI < 85th %ile). Patients were evaluated on these pass/fail criteria at post-transplant yrs 1, 3, 5, and 10. Optimal outcome was defined as passing ³13/14 criteria.

Conclusions: Only 1/3 of pKTRs achieved an optimal outcome at 1 year post-transplant, and this fell to 1/6 of patients by 10 years. Cardiovascular health and graft function were the system and brain death declaration is not mandatory. Andhra Pradesh and Telangana are the two impotheastern states in India, situated on the country’s southern coast. It is India’s fourth largest state by area and fifth largest by population. Government of Andhra Pradesh, considering the shortage of organs and burden of end stage organ failure in the state, has come up with a Government Order called “Jeevandan” to streamline the procedure for facilitating and regulating the cadaver transplantations on an end-to-end basis.

SA-PO1034

Jeevandan: Deceased Donor Transplantation Programme from a Developing Country

Background: In developing country like India the prevalence of end stage organ disease is increasing. Though transplantation has been in practice in India, its been grossly inadequate in terms of actual numbers, due to a shortage of resources and organs. The only solution for the shortage of organs is deceased donor transplantation.

Methods: In India the Human Organs Transplantation Act, was enacted in 1994 with in India the Human Organs Transplantation Act, was enacted in 1994 with the objective of promoting and regulating the transplantation of human organs like kidney, liver and heart - both live as well as cadaver there was no significant increase in cadaver transplantation over the past two decades for various reasons. India follows “opt in” system and brain death declaration is not mandatory. Andhra Pradesh and Telangana are the two impotheastern states in India, situated on the country’s southern coast. It is India’s fourth largest state by area and fifth largest by population. Government of Andhra Pradesh, considering the shortage of organs and burden of end stage organ failure in the state, has come up with a Government Order called “Jeevandan” to streamline the procedure for facilitating and regulating the cadaver transplantations on an end-to-end basis.

Results: There were 129 deceased donations in 2 years. Male were 93 and female 36: female to male ratio being 1: 2.58. The mean age was 41 years (range 8 to 79). Most common Blood group was O in 51 (39.5%) donors followed by B in 39 (30.2%). A positive crossmatch in 22 donors, and ABO in 26 (10.7%). donors. Total 593 organs in 532 recipients were retrieved from 129 deceased donors; 233 kidneys, 126 livers, 7 hearts, 118 heart valves, 103 corneas, 5 lungs and 1 Pancreas. Total deceased donor renal transplantations done during this period were 24.67%. Out of 129 donors, 6.8 % kidneys and 3% livers were not utilized. Mean age of renal recipients was 44.07 years (range 13 to 72). There were 26.8% females and 73.2% males, female to male ratio being 1:2.73. Among deceased donor renal transplant recipients, O blood group was most common, seen in 36.79% followed by B in 32.38%, A in 22.64% and AB in 8.17% patients.

Conclusions: Deceased donor transplantation is the solution for organ shortage and increasing demand of organ requirement.
primary failure modes. Evaluation of all transplant-related outcomes at specified follow-up intervals will allow practitioners to assess the success of kidney transplantation and overall recipient health and focus clinical outcome improvement efforts.

SA-PO1037
Clinical Outcome of Elderly Living Kidney Donors: A Single-Center Study in Japan
Jumpei Hasagawa, Kohei Unagami, Masayoshi Okumii, Kazuya Otomo, Hideki Ishida, Kazumari Tanabe. Urology, Tokyo Women’s Medical Univ, Tokyo, Japan.

Background: Previous studies and current guidelines have suggested that elderly persons can be living kidney donors; however, reports on elderly donors > 70 years old are limited. In order to clarify the donor safety and feasibility, we investigate the clinical outcomes of living kidney donors > 70 years old after nephrectomy.

Methods: We conducted a case-series study of living kidney donations involving 48 donors aged >70 years at the time of transplantation. The kidney donations occurred between 2001 and 2014 at Tokyo Women’s Medical University in Tokyo, Japan. The primary outcomes were survival or end-stage renal disease (ESRD)-free rate and all crude event-free rates, including death, vitro, infection, ESRD, or any adverse event. The secondary outcome was serum creatinine level at the end of the follow-up period.

Results: The 48 cases were followed up for a median of 4 years. The survival rate among the donors was 100% until the fifth year, and only two donors died during follow-up. The ESRD-free rate was 100% during the follow-up period. The overall event-free rate was 100% at 1 year, 85.7% at 3 years, and 75.0% at 5 years. The mean serum creatinine level was 1.18 ± 0.24 mg/dL at the time of hospital discharge and did not increase (1.18 ± 0.24 mg/dL) at the end of follow-up.

Conclusions: Living kidney donation from elderly donors >70 years old appears to be a safe and acceptable option for patients requiring renal-replacement therapy.

SA-PO1038
Immunosuppressive Medication Adherence following Kidney Transplantation at the Military Healthcare System
Dustin J. Little, Matthew Ward, Robert Nee, Christina M. Yuan, Rahul M. Tindle. Walter Reed National Military Medical Center, Bethesda, MD; Uniformed Services Univ of the Health Sciences, Bethesda, MD.

Background: Limitations on the amount and duration of Medicare coverage of immunosuppressive medications (ISM) may contribute to ISM non-adherence and allograft failure. ISM adherence has not been reported in US patients who receive these medications at no cost. We therefore designed a prospective cohort to investigate the incidence of ISM non-adherence in Military Healthcare System (MHS) beneficiaries, who receive lifelong post-transplant ISM at no out-of-pocket cost.

Methods: Adult MHS kidney transplant recipients who provided informed consent completed the Immunosuppressive Therapy Adherence Scale (ITAS) and Beck Depression Inventory-II (BDI-II). Chart reviews were performed to obtain demographic and clinical data. Perfectly adherent subjects (P) (ITAS score of 12/12), were compared to not perfectly adherent subjects (NP; ITAS score £11/12) using Student’s-t test and Fisher’s exact test where appropriate. Exact logistic regression was performed to evaluate for factors associated with P versus NP adherence.

Results: Forty subjects completed survey instruments. 57.5% of subjects were male, 7.2 vs. 13.6 ± (27/39) of subjects reported P adherence. BDI-II scores were significantly lower in P vs. NP adherence. One subject did not complete the ITAS. Mean overall ITAS score was 11.5 ± 2.5.

Conclusions: MHS beneficiaries reported high levels of ISM adherence. Modest increases in BDI score associated with marked reduction in adherence, and subjects with NP adherence were significantly more likely to have DSA. Our results suggest that enhanced ISM coverage as well as education, identification, and treatment of depression should be prioritized for future study in order to improve outcomes following renal transplantation.

Funding: Other U.S. Government Support

SA-PO1039
Clinical Impact of Kidney Donor Follow-Up by Nephrologists
Hee Jin Kwon, Jin Hee Kim, Jee Eun Park, Subin Hwang, Jung Eun Lee, Woosong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh, Hye Ryoun Jang. Nephrology Div, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea.

Background: Compensatory and adaptive mechanisms in the remnant kidney occur immediately after nephrectomy. The adaptability in early postoperative period may affect the renal function of the remaining kidney. Since the introduction of extended criteria living donor selection, the number of marginal donors with risk of new morbidity in recipients is increasing. The aim of this study was to evaluate the clinical impact of kidney donor follow-up by nephrologists at a donor clinic (DC).

Methods: Our study included 427 living kidney donors from January 2010 to December 2014 at Samsung medical center. Nephrologist-run donor clinic was established in January 2013. The study period was divided into pre-DC and post-DC. Primary outcomes were incidence of CKD and renal functional adaptability (%MDRD = post/pre eGFR X100) at 6 months after donation. Secondary outcomes were changes in compliance and incidence of co-morbidities; hyperuricemia and microalbuminuria.

Results: A total of 215 and 172 donors were included in pre-DC and post-DC, respectively. Before donation, age, sex, proportion of hyperuricemia and microalbuminuria were similar. Preoperative eGFR in pre-DC was significantly higher than post-DC (p<0.001). After donation, poor renal adaptation (post-donation eGFR at 6 months < 60% of preoperative eGFR) was less frequent in the post-DC period compared to the pre-DC period (p=0.026). CKD development tended to be higher in pre-DC period. Donors in the post-DC period had shorter mean outpatient clinic visit intervals (p<0.001), more visits within 6 months after donation (p<0.001), earlier detection of de-novo hyperuricemia (p<0.001). The incidence and detection time of microalbuminuria were similar.

Conclusions: After establishment of kidney donor clinic operated by nephrologists, donors tended to show better renal adaptability and earlier diagnosis and treatment of hyperuricemia. In conclusion, donor clinic may be a good strategy for improved renal outcome and detecting potential risk factors of CKD in donors.

SA-PO1040
Predicting Kidney Allograft Half-Life Using a Podometric Approach
Roger C. Wiegins, Abhijit S. Naik, Diane M. Cibrik, Jeffrey B. Hodgin, Farsad Afshinnia, Larysa T.wickman, Milagros D. Samaniego. Dept of Medicine, University of Michigan.

Background: Increasing donor age is a powerful predictor of worse renal allograft outcome. Podocyte depletion is part of the normal aging process (Hodgin, JASN, 2015). Recently we showed that kidney hypertrophy that occurs at time of transition from a 2 kidney 1 kidney state (transplantation), leads to a 20% reduction in podocyte density and a 6-fold increased rate of podocyte detachment associated with transplant glomerulopathy and allograft failure (Yang, JASN, 2014). To test the hypothesis that podocyte depletion could impact allograft half-life we used a model combining age specific podocyte nuclear density decrease and rate of podocyte attrition after transplantation for comparison with actual allograft outcome data.

Methods: Podocyte density was estimated from immediate post perfusion biopsies from living and deceased donors or from non-diseased nephrectomy specimens. Projected allograft life was predicted based on modeling age-specific podocyte density and the observed attrition of podocytes. Observed data were drawn from the OPT/UNOS STAR files as of Sep 2014, using all transplants performed between Oct 1987-June 2013. A “conditional” Kaplan Meier analysis using the “period” method was used to calculate observed half-lives at different donor ages.

Results: The podometric projected average half-life for a 40 year old donor is 15.1 years, similar to the observed average allograft half-life (15.1 years). The projected effect of increasing donor age on allograft half-life from podometric measurements is similar to the observed effect of donor age on allograft half-life at all calculated donor ages (p=NS).

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SA-PO1041
Abstract Withdrawn

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

873A
SA-PO1042
Prediction of Patient Survival After Kidney Transplantation (Tx): Construction, Validation and Evaluation of Decision Models Using Data Mining Approaches
Irina Scheffer,1 Kaixin Hua,2 Dan Simovici,2 Tanja Abeling,1 Hermann G. Haller,1 Wilfried Gwinner.1 1Hannover Medical School, Germany; 2Unite of Massachusetts.
Background: Understanding the risk factors that predispose to death is important to deliver the most appropriate therapy to Tx patients (pts). Aim of this study is to build reliable models to help us identify the relevant risk factors for death using different data mining approaches.
Methods: We analyzed 761 pts transplanted between 2000 and 2007 (follow-up of up to 10 years). Data included biopsy results, clinical & laboratory factors. After conventional statistical feature selection analysis, we built Naive Bayesian (NB), C5.0, RPART and Random Forest (RF) models.
Results: Compared to C5.0 and RPART, NB and RF resulted in models with a higher sensitivity to predict death and a high specificity. Using different partitions for training and test set, NB models had a sensitivity of 62-65% and a specificity of 89-91% to predict death. With RF, sensitivity was 64% and specificity 96%. Because of the imbalance of the outcome groups (13% deceased pts) modeling was repeated with balanced datasets obtained by oversampling. With the balanced data, sensitivity was 82% and specificity 79% with NB. With RF, sensitivity was 83% and specificity of 68%. These models were externally validated with two separate datasets showing sensitivities of 64 and 59% and specificities of 86% and 78% for the NB models and sensitivities of 84 and 61% and specificities of 60 and 65% for the RF models. Highly important variables were recipient age, pre-Tx diabetes mellitus, peripheral arterial and coronary heart disease, cold ischemia time, graft function within the first 6 weeks and annual GFR loss, and post-Tx systolic and diastolic blood pressure, urinary tract infections, and hyperparathyroidism. Modestly important variables included donor age, time on dialysis, HLA DR mismatches, delayed graft function, pre-Tx smoking. The estimated models performed well in predicting death and can be used to identify pts on risk. Moreover, with the identified (modifiable) risk factors pts can be assigned to different treatment strata to offer each patient the optimal therapy. Fundering: Government Support - Non-U.S.
SA-PO1043
The Decline of Dialysis in Northern Ireland
Kathryn E. Larmour. Regional Nephrology Unit, Belfast City Hospital.
Background: The first session of haemodialysis in Northern Ireland (NI) was in 1959 for acute kidney injury. There has been an inexorably rise in the prevalent dialysis population in the province since then, with expansion of dialysis facilities to accommodate ever increasing numbers. However, in addition to inferior outcomes compared to transplantation, there are considerable social and recurrent costs associated with chronic haemodialysis provision. This study considered the impact of an expansion in the living donor (LD) transplant programme on dialysis in NI and the financial implications.
Methods: The prevalence dialysis population from 1999-2014 (inclusive) data were retrieved retrospectively from collected data. The number of LD transplants in NI patients is prospectively recorded. The economic impact of the changes evident in our centre were then evaluated.
Results: In 1999 there were 479 patients in NI receiving maintenance dialysis treatment. This number increased annually until a zenith of 836 in 2009. There were no LD transplants in NI patients until 1999, when 17 transplants were performed annually. There was an expansion of the LD programme thereafter, and for the past four years there have been between 33-60 LD transplants each year (>30 donor related, >20 non-donor related in an initial plateau and then a decline in the prevalent dialysis population [figure 1]. The cost of maintaining a patient with end-stage renal failure on dialysis is £17,500 ($27,000) per patient per year for a patient on peritoneal dialysis and £35,000 ($54,000) per patient per year for a patient on hospital haemodialysis. The first year of care after a kidney transplant costs around £17,000 ($26,000) and £5,000 ($7,500) for every subsequent year. Live donor costs are approximately £9,000 ($14,000). Transplantation results in a cost benefit in the second and subsequent years of £25,800 ($39,500) per annum. The cost benefit of transplantation compared to dialysis over a period of ten years is £241,000 ($370,000).
Conclusions: A proactive approach to living donor transplantation has benefits not only for individual patients but in reducing the prevalent dialysis population and the healthcare costs associated with renal replacement therapy.
SA-PO1044
Pre-existing Donor-Related Diabetic Nephropathy Predicts Poor Allograft Survival
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Background: Diabetic nephropathy (DN) is the most common cause of end stage renal disease in the US, and in the transplant setting may play a role in long-term graft dysfunction. In patients with diabetes, finding features of DN in the immediate for cause post-transplant biopsy may confer increase risk of allograft dysfunction.
Methods: From 2005-2014, 141 biopsies from 120 transplant patients with DN were studied. DN was classified as 1) donor related if present on biopsy –2 yrs from transplant or where no available recipient, 2) recurrent if <2 yrs with history of pre-transplant DN, or 3) de novo in post-transplant diabetes (all >3 yrs). Clinicopathologic parameters were analyzed in 95 patients with adequate clinical history (25 excluded).
Results: Of 95 biopsies with features of DN, 43 were characterized as recurrent, 17 donors and 35 donor-related. Biopsies with donor-related DN were done 0.5 yrs (0 days-3.6 yrs) post-transplant and 6 had delayed graft function. Other non-DN related disease was seen, likely prompting biopsy: acute tubular injury (10/35), antibody mediated rejection (4), acute cellular rejection (1), CNI toxicity (3), AIN (4) and BKV (1). The first biopsy class of DN were: Class 1-3, Class 2a-21, Class 2b-1, Class 3-10. Class 3 DN lesions are associated with higher proteinuria, Cr, and increased vascular sclerosis. 13/35 donors had known diabetes with mean hemoglobin A1c of 8.5% (range 4.7-14.6%). DN was not listed on any pre-implantation biopsy reports. Mean follow-up times were 3.8 yrs for donor related, 7.8 for recurrent, and 10.3 for de novo. Despite shorter follow-up, transplants with donor-derived DN had significantly more failure than recurrent DN (49 v 14%, P<.0008) or de novo DN (49 v 18%, P<.024). Recurrent and de novo DN had similar rates of graft loss (P=.64).
Conclusions: Despite careful screening of transplant kidney donors, donor related DN may be missed on pre-surgical biopsy or not effectively reported and leads to renal dysfunction in the early post-transplant period. Donor related DN is a significant contributor to early allograft loss compared to recurrent or de novo DN and predicts poor long term graft survival.
SA-PO1045
Maternal and Fetal Outcomes in Living Kidney Donors in Korea
Kyung Don Yoo, Hajeong Lee, Jae Yoon Park, Eunjin Bac, Jung Pyo Lee, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim. Seoul National Univ Coll of Medicine.
Background: Mild elevation of blood pressure was detected after unilateral nephrectomy in kidney donors. Consequently, female kidney donors at risk for complications such as gestational hypertension caused concern. However, the impact of kidney donation on maternal and fetal outcomes had not been well established in Asian kidney donors.
Methods: This study included young female kidney donors under 45 years old (YO) at the time of kidney donation in Seoul National University Hospital between 1972 and 2014 (417 female donors). A survey of participants (45YO) was enroled. A survey of previous experiences was performed by medical chart abstraction and telephone poll. We additionally enrolled 3,608 pregnancies were enrolled as non-donor control. The questionnaires were approved by institutional review board in our institute.
Results: We tried to contact all of 417 female kidney donors. The thirty five donors had no experience of pregnancy, and finally we could have got 253 questionnaires of kidney donors. Donors were compared in the three groups according to pregnancy pre-,post-kidney donation group and non-donor control group. The proportion of predonation pregnancies were 82% (170cases, Mean age 38.8 years), and postdonation pregnancies were 14.0% (56cases, Mean age 27.2 years). In the majority of postdonation pregnancy cases were detected in recent years from 2007 to 2014 (72.3%). There were no differences of fetal outcomes such as incidence of prematurity, low-birth weight and fetal death between the groups. Gestational hypertension were no differences between the postdonation group and non-donor control group (5.4% vs. 5.8%). Donors with pregnancy after donation were more likely to have undergone Cesarean section (40.4%) than those with pregnancy before donation (21.9%).
Conclusions: This study revealed that maternal and fetal outcomes had little difference between the kidney donors and normal control. Further research using matched controls should be warranted.
SA-PO1046
Self-Monitoring Renal Function After Transplantation: A Clinical Trial on Safety and Usability
Céline Lianne Van lint,1 Sandra Van dijk,1 Wenxin Wang,2 Mark Neerinckx,2 Ton Rovekamp,2 Ton J. Rabelink,1 Paul J. Van der boog,1 Willelm-Paul Brinkman.2 1Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; 2Faculty of Computer Science, Delft Technical Univ, Delft, Netherlands; 1Dept of Technology in Healthcare, Prevention and Health, TNO, Leiden, Netherlands.
Background: Kidney transplantation requires intensive monitoring which is burdensome for both patient and healthcare. With the availability of an innovative creatinine device, patients are enabled to monitor renal function at home. To investigate safety and usability of self-monitoring during the first year after transplantation an RCT was conducted.
Methods: The intervention group used a Statusensor® Xpress™ to measure creatinine at home during the first year after transplantation. Measurements were registered in a web-based system using a traffic light analogy to support interpretation of creatinine trends. Differences between groups regarding GFR were assessed at baseline (discharge) and at 1 year. Creatinine trends measured at home were compared to clinically relevant increases (10%) measured in the hospital laboratory. A subsample of intervention patients were interviewed on self-monitoring experiences.
Results: In total 119 patients were included (intervention n=64; control n=55). GFR did not differ between groups at baseline, nor at 1 year (72.8 and 71.1 ml/min at 1 year for intervention and control group, respectively). For 34 out of 65 laboratory-based creatinine increases, sufficient home-based creatinine measurements were available for trend comparison. In 76% a similar trend was observed. Self-monitoring enhanced early detection of rejection in 3 out of 5 cases, none were missed. Satisfaction was high: 71% of the interviewed patients (n=26) would have liked to extend self-monitoring creatinine beyond 1 year.
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author. 874A
SA-PO1047

Comparison of Heart Rate Variability in Kidney Transplantation and End-Stage Renal Disease Patients on Dialysis Lee Heeyoung, Internal Medicine, Bong Song Memorial Hospital, Busan, Korea; Internal Medicine, Pusan National Univ Hospital, Busan, Korea.

Background: Heart rate variability (HRV) is a method for evaluation of autonomic nervous system activity by expressing the balance of sympathetic and parasympathetic tone. Some studies of HRV in patients with end-stage renal disease (ESRD) have been performed. However, few have examined kidney transplantation (KT) patients. Therefore, we investigated autonomic nervous system activity by means of HRV in patients with KT due to ESRD.

Methods: We compared the pattern of cardiac sympathetic and parasympathetic activity by time- and frequency-domain analysis of HRV with 24-h Holter monitoring of 23 KT and 56 dialysis patients. Patients underwent KT between January, 2008 and June,2011. Results: The mean ages of KT and dialysis patients were 54.2 ± 12.3 and 53.7 ± 12.6 years, respectively. The KT group showed increased time- and frequency-domain HRV (including HRV index), very low frequency (VLF), means and standard deviations of all normal R-R intervals for all 5-min segments of the entire recording (SDNNi), low frequency (LF), LF in normalized units (LFnorm), and LF to high-frequency power ratio, compared with the dialysis group.

Conclusions: Autonomic tone in patients with KT is higher than that in patients with ESRD on dialysis.

Funding: Private Foundation Support

SA-PO1048

Physical Capacity and Function Are Associated with Body Composition, Cardiovascular Health and Quality of Life in Renal Transplant Recipients Danielle Richle, Jara Hale, Maurice Dungey, Patrick Highton, Emma L. Watson, Alice C. Smith. Leicester Kidney Exercise Team, Dept of Infectious, Immunology and Inflammation, Univ of Leicester, Leicester, United Kingdom.

Background: A renal transplant can transform the life of patients with end stage renal failure but cardiovascular disease remains a major cause of morbidity and mortality. Post-transplant weight gain is common, and physical functioning often fails to improve in line with increased renal function. This study explored associations of physical function and capacity with body composition, cardiovascular status and quality of life (QoL) in renal transplant recipients (RTxs).

Methods: 35 stable RTxs participated (mean age 52 years (range 29-70), 66% male). Self-reported QoL and physical function were measured by EQ-5D and Duke Activity Status Index (DASI) questionnaires. Physical capacity was measured by shuttle walk test (SWT), body composition by DXA, cardiac haemodynamic function by bioimpedance (NICOM), and systemic inflammation by plasma IL-6,ELISA.

Results: SWT, DASI and EQ5D all showed significant correlations with percentage body fat (SWT: r=-0.63, p<0.001; DASI: r=-0.41, p=0.02, EQ5D r=-0.47, p=0.005) and with IL-6 (r=0.34, p=0.05). On the other hand, fat-free mass showed positive correlation with cardiac output (r=0.79) and stroke volume (r=0.81, both p<0.001), and inverse correlation with total peripheral resistance (r=-0.67, p<0.001).

Conclusions: This study shows that in RTxs, poor physical function and capacity is significantly associated with lower QoL and also with higher percentage body fat and systemic inflammation, both of which are important cardiovascular risk factors. An increase in fat-free mass was significantly associated with superior cardiac function. Taken together, these results suggest that weight loss is desirable for those with excess body fat, and that increasing muscle mass is also important. Optimising body composition through appropriate exercise and nutrition may therefore improve physical function and capacity and enhance quality of life, and also reduce the risk of cardiac-related morbidity and mortality in this vulnerable population.

Funding: Private Foundation Support

SA-PO1049


Background: Fertility in women is recovered few months after kidney transplantation. However, pregnancy viability and maternal complications remain unclear.

Methods: We studied data from patients from a kidney transplant center in Brazil from 2001 to 2012. In this retrospective study, we identified all pregnant kidney transplant recipients and collected clinical and laboratory data before pregnancy, every quarter and 12 months after delivery. Each pregnancy was considered a single event.

Results: We included 36 subjects and 53 events were found. The average age was 28±5 years. Pregnancy occurred 4.4±3 years after transplantation. Maintenance immunosuppression before pregnancy was prednisone, tacrolimus and azathioprine in 74% of the cases. The frequency of chronic hypertension was 38%, and 8% had preexisting proteinuria greater than 0.5g, 8 (15%) unintended termination of pregnancy (UTP) were observed in the first quarter and 4 (8%) occurred in the second quarter. Delivery was induced by medical conditions in 41% of cases. 9 (22%) premature births and 7 (17%) very premature births were observed. Two (5%) stillbirths and two (5%) neonatal deaths occurred. Maternal complications were proteinuria de novo (60%), urinary tract infection (23%), preeclampsia (9%) and high blood pressure (9%). During the follow-up period, two (6%) acute rejection and one (2%) graft loss occurred. Average baseline creatinine was compared with third quarter and 12 months follow-up creatinine and significant increase (1.17 vs. 1.46 vs 1.59/mg/dl, p=0.001) was found.

Conclusions: Although the sample is limited, the number of UTP was higher than the general population, with high rates of maternal complications. Besides, diagnosis of preeclampsia may be challenging because of the high frequency of hypertension and preexisting proteinuria. The sustained increase in creatinine suggests higher risk of long-term graft loss. Further research regarding the issue of pregnancy and kidney transplantation is required, in order to improve maternal safety and preserve graft function.

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SA-PO1050

Outcomes of Twin, Triplet and Quadruplet Pregnancies in Kidney Transplant Recipients Serbian Constantinescu, LisaCoscia, Dawn Armenti, Michael J. Moritz. Medicine, Temple Univ School of Medicine, Philadelphia, PA; NationalTransplantation Pregnancy Registry (NTPR), Gift of Life Inst, Philadelphia, PA; Transplantation, Lehigh Valley Health Network, Allentown, PA.

Background: The purpose of this study is to analyze multiple gestation pregnancy outcomes reported to the National Transplantation Pregnancy Registry (NTPR) in 50 kidney transplant recipients.

Methods: Data were collected via questionnaires, telephone interviews, and hospital records.

Results: Of 986 kidney recipients (1802 pregnancy outcomes) participating in the NTPR, there were 50 who reported 52 multiple gestations with 112 pregnancy outcomes (45 sets of twins, 6 sets of triplets, and 1 set of quadruplets). There were 94 live births, 11 miscarriages, 6 stillbirths, and 1 reduction (triplet to twin pregnancy). Pregnancy occurred after 1st kidney transplant in 47, after a 2nd in 4, and after 3rd in 1 recipient; 14 recipients had a prior post-transplant live birth and 2 recipients had 2 multiple birth pregnancies. Use of reproductive assistance was reported for 16 conceptions (medication 5, intrauterine insemination 5, in vitro fertilization 4, and unspecified 2). There were no reports of rejection during pregnancy or postpartum (PP). Mean serum creatinine (mg/dl) was pre-pregnancy 1.4±0.6, during pregnancy 1.4±0.5, and PP 1.4±0.5. There were 4 graft losses within 2 yrs PP. Mean gestational age was 32.1±4.1 wks (range 23-37.4 wks) and mean birthweight was 1680±652 g (range 454-3551 g). There were 11 neonatal deaths including all of the infants in the quadruplet pregnancy. There were 5 birth defects reported: soft cleft palate, hypospadias, unilateral kidney, undescended testicle, and Tetralogy of Fallot. Overall, the majority of the children were reported healthy and developing well at last follow-up.

Conclusions: Female kidney transplant recipients can successfully maintain a pregnancy with multiple gestations. Given the increase in multiple gestations with the use of assisted reproductive techniques and the greater risks to the resulting fetuses, heightened surveillance in the transplant recipient population is warranted.

SA-PO1051

Kidney Transplantation for End-Stage Kidney Disease After Hematopoietic Stem Cell Transplantation

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Background: Hematopoietic stem cell transplantation (HSCT) is associated with various kidney diseases. The safety of kidney transplantation (KT) for end-stage kidney disease (ESKD) after HSCT has not been established. In this retrospective multicenter study, we investigated the immunological background, immunosuppressive regimes, and outcome in the KT patients after HSCT.

Methods: We report our experience with 5 KT patients following HSCT: 4 patients received bone marrow transplantation and 1 received umbilical cord blood transplantation. Median age at the time of HSCT was 29 years old (ranged 13-54 years old), and ESKD developed after 119 months (67-307 months). The median duration of pre-transplant dialysis therapy was 18 months (7-69 months). In one patient, bone marrow and kidney were from the same donor.

Results: Median observational period was 18 (5-60) months. All patients were treated antibody-induction with basiliximab followed by triple immunosuppression consists of tacrolimus, mycophenolate mofetil and methylprednisolone. In one patient with positive complement dependent cytotoxicity cross match, we added rituximab, splenectomy and plasmapheresis. In another one patient who received KT and BMT from the same donor, we temporarily gave immunosuppressive drugs. After KT, only one patient experienced subclinical acute T-cell mediated rejection and bacterial pneumonia, and the other patients have not experienced acute rejection or severe infectious complications.

Conclusions: Pre-existing CKD may have an effect on development of ESRD post-OLT. These effects if generalizable in larger cohorts are important for organ allocation.

SA-PO1052

The Risk Factors of Chronic Kidney Disease Occurrence in Patients Received Liver Transplantation

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Background: Analysis the risk factors of chronic kidney disease (CKD) occurrence in patients with liver transplantation.

Methods: 190 patients received liver transplantation followed up during 2001 to 2013 were analyzed retrospectively. 40 patients developed CKD. The observation items included patients’ gender, age, primary diseases, surgical approach, preoperative complications, laboratory examinations (hemoglobin, albumin, creatinine, glomerular filtration rate), intraoperative blood loss and blood transfusion volume, postoperative complications and average serum calcium concentration (from liver transplantation to the onset of CKD). Clinical data of CKD occurrence group were compared with the non-CKD group. Chi square test, t test, and logistic regression analysis were used.

Results: The incidence of CKD in patients with liver transplantation was 21.1%. Renal pathology included IgA nephropathy, hepatitis B virus associated nephropathy, membranous proliferative glomerulonephritis, focal segmental glomerular sclerosis and cryoglobulinemia associated renal injury. 85.7% patients had tuberculosis interstitial damage. Univariate analysis showed that preoperative renal function, hemoglobin, intraoperative blood loss and transfusion volume, postoperative acute kidney injury, average calcium concentration in serum (from liver transplantation to the onset of CKD) were risk factors of CKD in patients with liver transplantation. Logistic regression analysis showed that preoperative glomerular filtration rate (OR=0.980, P=0.041), hemoglobin (OR=0.972, P=0.034), calcium concentration (OR=1.364, P=0.015) and postoperative hypertension (OR=8.833, P=0.048) were independent risk factors of CKD occurrence.

Conclusions: Although limited by small sample size and low event rate, our analysis suggest that pre-OLT CKD3 may have an effect on development of ESRD post-OLT. These effects if generalizable in larger cohorts are important for organ allocation.

SA-PO1053

Pre-Transplant CKD, but Not AKI, Impacts Survival in Liver Transplant Recipients

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Background: Chronic kidney disease (CKD) stage and duration of RRT pre-liver transplant (OLT) have been associated with increased risk of progression to ESRD in OLT recipients. Currently, allocation of dual organ transplantation (liver/kidney) is limited to CKD stage 4 and/or RRT > 4 weeks. The data regarding the associations of less severe pre-OLT AKI (RRT<4 weeks) and, of CKD stage 3, with ESRD post-OLT is unclear. We examined the renal outcomes of OLT recipients at our center.

Methods: We reviewed charts of OLT recipients at Mount Sinai for clinical, demographic, laboratory and outcome data from the medical record. We utilized multivariable logistic regression for analysis.

Results: We had data on 115 OLT recipients from 2008-14 (mean age 57.7 years, 66% male). 55/115(47%) patients developed AKI pre-transplant, most often from HRS (47%). Pre-existing CKD-3 was present in 26/115 patients. Pre-OLT AKI developed in 23/26 CKD-3 patients. RRT was required in 8/26 CKD-3 patients. Mean eGFR at 1- and 2-year follow-up in the CKD-3 group compared to non-CKD group were 37.4 ± 16.6 vs. 33.3 ± 23.1 (p=0.01) and 59.8 ± 20.8 vs. 62.7 ± 22.3 (p=0.01) respectively. At a mean follow up of 1.4 years post OLT, proportion of patients developing ESRD was higher in CKD vs. non-CKD group (23.1% vs. 2.3%; p=0.01). Although, AKI was a significant predictor of ESRD (adjusted for age, sex, race, diabetes), its effect was attenuated after adjusting for CKD. CKD3 was the strongest predictor of ESRD (aOR 8.34; 95% CI 1.25-55.7; p=0.02) (figure 1). Overall, patient survival at a mean of 2.4 years of follow-up was lower in CKD3 vs. non-CKD groups (76.9% vs. 91%; p=0.08).

SA-PO1054

Can Acute-On-Chronic Liver Failure Classification Predict Post-Liver Transplant and Liver Kidney Transplant Outcomes?

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Background: Recent evidence suggests that acute on chronic failure (ACLF) stratification is more accurate than other methods in predicting short term mortality rates pre-transplant. There is no evidence of ACLF stratification as predictor of post-transplant outcomes. We analyzed if ACLF could predict patient and allograft survival in live liver transplant recipients (LTR) or simultaneous liver kidney transplant recipients (SLKTR) especially if hepatorenal syndrome (HRS) is present.

Methods: A retrospective analysis was performed on 86 adult patients, 77 LTR and 9 SLKTR transplanted in 2013. Patients were classified into different ACLF grades (0-3) based on their pre-transplant parameters:MELD labs ( total bilirubin, serum creatinine, INR), hepatic encephalopathy, ventilator dependence and the presence of shock. Patient and allograft survival, and kidney function (serum creatinine < 1.5 mg/dL) were analyzed at 6 & 12 months post-transplant between LTR and SLKTR. A further analysis between recipients with HRS receiving either LT or SLKT was made. SLKTR received kidney transplants based on current International Club of Ascites (ICA) guidelines.

Results: Demographics of LTR and SLKTR cohorts: mean age of 58 and 59 years; males 63% and 56%; mean MELD of 21 and 33 respectively. Recipients with HRS pre-transplant had mean MELD 38 vs 30 in the LTR and SLKTR groups respectively. 27% of LTR had OLT 0-1; 11% SLKTR had OLT 0-1; 73% of LTR had OLT 2-3; 89% of SLKTR had OLT 2-3. LTR with HRS had 100% with ACLF 2-3; SLKTR with HRS had 83% with ACLF 2-3. One year post transplant outcomes: Patient Survival – 92% LTR, 66.7% SLKTR; 1 year Graft Survival – 89.6% LTR, 66.7% SLKTR; Kidney Function good – 81.8% LTR, 33.3% SLKTR. In patients with HRS both patient and graft survival are 83.3% SLKTR and 75% LTR, but kidney function trended to be better in LTR (50% vs SLKTR 33.4%).

Conclusions: Patient graft survival and kidney function appear to trend better overall in LTR vs. SLKTR. However, HRS patients fared the opposite favoring SLKTR vs LTR.


SA-PO1055

C3 Alone Is Not a Prognostic Indicator of Patient or Graft Survival in Post-Transplant Glomerulonephritis

Background: The prognostic implications of glomerulonephritis in the post-transplant setting are not well characterized.

Methods: We examined patient and graft outcomes in 71 kidney transplant recipients diagnosed with glomerulonephritis(GN). Biopsies were studied by immunofluorescence(IF) for glomerular C3 staining and divided into two categories, C3-positive or C3-negative.

Primary outcomes were graft and patient survival at 3, 12, and 36 months and at last follow-up. Serum creatinine(Cr) at last follow-up was a secondary outcome.

Results: Thirty three(46%) patients were C3-positive and 38(54%) were C3-negative. Mean follow up was 103 months for positive C3 and 117 months for negative C3 groups. There were no significant differences among groups by age, gender, type of donor, or prevalence of hypertension, diabetes, and hepatitis B or C. A total of 57% of C3-positive patients had a functioning graft at 36 months post-transplant, compared to 75.1% of C3-negative (p=0.16). A total of 88.2% of C3 positive patients were alive at 36 months post-transplant, compared to 85.7% of C3 negative (p=0.9). The mean serum Cr for C3 positive patients at 36 months was 1.59mg/dl compared to 1.71mg/dl for C3 negative (p=0.55). There were no significant differences in graft and patient survival between two groups.

Conclusions: There was no significant difference in patient or graft survival, or in serum Cr between patients with GN and C3-positive IF compared to patients with C3-negative IF. This suggests that the presence of C3 alone is not a prognostic indicator of patient or graft survival in post-transplant GN.

SA-PO1057

Does Hepatitis B Virus Impact the Outcomes in Kidney Transplant Recipients? Analysis by Phases of Infection

Background: In kidney transplant recipients (KTRs) with hepatitis B virus (HBV) infection, immunosuppression may increase the risk for the progression of liver disease. HBV may contribute to allograft disease and anti-HBV therapy can have nephrotoxic potential. The aim of this study is to evaluate the impact of different phases of HBV infection on the outcomes in KTRs.

Methods: Using OPTN/UNOS database, we selected adult KTRs from 2001 - 2011 who received peri-operative antibody induction followed by calcineurine inhibition/mycophenolate mofetil maintenance along with/without steroids. The cohort was divided into 4 groups based on the presence/absence of hepatitis B surface antigen(HBsAg) and core antibody(HBcAb) at the time of transplantation: HBsAg+/HBcAb-(acute infection); HBsAg+/HBcAb+(developing immune response); HBsAg-/HBcAb+(resolving infection) and HBsAg-/HBcAb-(HBV naive). Graft and patient survival were compared among the groups as shown in the table by using multivariate Cox model. Donor, recipient and transplant related confounders including lamivudine therapy were adjusted in the model.

Results: Adjusted graft and patient survival comparisons are shown in the table.

SA-PO1056

Pretransplant Hepatitis B Virus Infection Increased Risk of Death After Kidney Transplantation: A Multicenter Cohort Study in Korea

Background: The incidence of antiviral prophylaxis for rituximab (RIT)-associated hepatitis B virus (HBV) reactivation in patients with malignant lymphoma has been reported. However, the effect of single-dose RIT on HBV reactivation in kidney transplant recipients with hepatitis B surface antigen-negative (HBsAg-) and hepatitis B core antigen antibody-positive(HBcAb+) results is unclear, and there is no evidence for the necessity of prophylaxis in those patients.

Methods: From 2001 through 2014, 1021 patients underwent kidney transplantation (KTx) at Kyoto University and Tokyo Women’s Medical University, of whom 76 (7.4%) had HBsAg-/HBcAb+ results. Those patients showed hepatitis C virus (HCV)-RNA-negative, hepatitis B surface antibody-positive (HBsAb+), and HBV-DNA-negative. A RIT dose of 200mg/body was administered to 49 patients, and 45 patients did not receive prophylaxis. We monitored HBV-DNA and alanine transaminase levels every 1-3 months after KTx. HBV reactivation was defined as an elevation of serum HBV-DNA level ≥2.1 log copies/mL.

Results: HBV reactivation was found in 1 of 45 patients (2.2%) without prophylaxis. In the patient with HBV reactivation, serum HBV-DNA was detected at 6 weeks after KTx, and the minimum and maximum HBV-DNA levels were 2.1 and 2.6 log copies/mL, respectively. Although the patient was not treated with antiviral therapy, the HBV-DNA disappeared at 8 months after KTx. HBV reactivation was not found in the patients without RIT, and in the 4 patients who received both RIT and prophylaxis. Four (8.9%) of the 45 patients developed acute rejection, and 1 patient (2.2%) died of sepsis during the observation period.

Conclusions: The incidence of RIT-associated HBV reactivation in the HBsAg-/HBcAb+ patients without prophylaxis was less than 5%, suggesting that low-dose RIT might be associated with low incidence of HBV reactivation. However, sequential monitoring of HBV-DNA is necessary to prevent severe de novo hepatitis.
SA-PO1059
Direct Acting Antiviral Agents for HCV-Infected Patients Transplanted with a Kidney from a HCV Positive Donor

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Background: The availability of direct acting antivirals (DAAs) has changed the treatment of hepatitis C virus (HCV) infection. The decision to treat a HCV (+) patient (pt) before or after transplant has important ramifications. The current study reports outcomes in HCV-infected pts who received a kidney from a HCV (+) donor followed by early post-transplant treatment with DAAs.

Methods: HCV RNA (+) pts on the waiting list were consented to receive a kidney from a HCV (+) donor. Immunosuppression (IS) included thymoglobulin and sirolimus followed by maintenance IS with tacrolimus and mycophenolate mofetil. At 3 months post-transplant sofosbuvir combined with either ledipasvir, simeprevir and/or ribavirin for 12 or 24 weeks was initiated.

Results: Ten pts have started DAA therapy (5 others pending): 6 blacks and 4 hispanics with a mean age of 49.4 yrs. No pts were HIV or HBV co-infected. All pts were treatment naive, genoype 1 and non-cirrhotic. Median wait time was 30 days after consenting to accept a HCV (+) kidney. Viral clearance rates are shown in figure 1.

Conclusions: Treatment of HCV with pegylated interferon during dialysis results in some improvement of patients and graft survival following transplantation as compared to untreated patients. There is also trend of decrease in serious infection in treated patients. Sepsis and liver failure are two most common cause of mortality in untreated patients.

SA-PO1060
Impact of Treatment of HCV Infection on Renal Transplant Outcome
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Background: Impact of HCV treatment on post renal transplant outcome has not been reported adequately. This retrospective study was done to evaluate impact of HCV treatment on the post renal transplant outcome.

Methods: Adult patients on dialysis with HCV infection treated with pegylated interferon and subjected to renal transplant (RT) formed the study group. Untreated patients subjected to RT during same period served as controls. Primary end points were patient’s and graft survival and secondary end points were serious infections and NODAT. Factors which affect the outcome like age, gender, diabetes as basic disease, diabetes vintage, HBV co-infection, HCV genotype, viral load, liver biopsy grade and stage, induction and baseline immunosuppression were considered for analysis.

Results: At the time of study, 2010 RT were done in department of which 133 had HCV infection. 30 were treated with 68% SVR and 103 were untreated. In untreated group, there were more males (92% vs 77%), less dialysis number (137 Vs 211), less HBV co-infection (0.9% Vs 10%), less use of Tacrolimus (13.6% Vs 30%). There was no difference in terms of age, diabetes, HCV genotype, viral load, liver biopsy grade and stage, use of induction, Mycophenolate mofetil and duration of follow-up in two groups. With mean follow-ups of 59 ± 22 months (range 12-105), there was no statistically significant difference in term of acute rejection (23% vs 15%), NODAT (10% vs 16.7%) and overall serious infections (23% vs. 15%) between two groups. However, there were 11 deaths in untreated group (8 sepsis related, 3 liver failure and 1 coronary artery disease) while only one death related to sepsis in treated group. Patients survival (97% vs 89%) and graft survival (97% vs 84%) was significantly better (p<0.05) in treated group as compared to untreated group.

Conclusions: Treatment of HCV with pegylated interferon during dialysis results in some improvement of patients and graft survival following transplantation as compared to untreated patients. There is also trend of decrease in serious infection in treated patients. Sepsis and liver failure are two most common cause of mortality in untreated patients.

SA-PO1061
Prospective Study of Urinary Tract Infection in Renal Allograft Recipients in India: Single Center Study
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Background: Urinary tract infection (UTI) is common in renal transplant (RT) and in addition to morbidity, presumed to affects graft outcome also. Still it is least studied infection in RT. There is no data from India. We looked for incidence, risk factors and pattern of UTI in first 6 months after RT and its impact on graft function.

Methods: All RT between Dec 2013 and March 2015 were followed with urine exam and C/S at day 3, 7, 14, 21, 28 and then every two week till 3 months then monthly for another 3 months. Patients with asymptomatic bacteriuria (ASB) were randomized into treatment and no treatment group. Treatment was done for 7-10 days as per C/S. Study was approved by institute review board and informed consent was taken from each subject.

Results: During the study period 180 RT were done, (4 died, 2 nephrectomy, 1 graft failed, 4 lost to FU); 169 were analysed. Mean age of patients was 31.4 ± 10.4 (14-56) yrs and 51.6% were males. Diabetes was in 3.5%, renal stone in 3.5% and 3.5% had history of pre-RT recurrent UTI. All were on tacrolimus, MMF and steroid. 53% received induction. None got anti-reflux surgery. All were on cotrimoxazol for 6 months. 49 (29%) pts had at least one episode of UTI; 23 symptomatic and 26 ASB. Most common UTI was seen at 21 days followed by 14 days post surgery. 50-60% of these were symptomatic. Following RT, with time, frequency of UTI went on decreasing. Of the 84 UTI episodes, 97 (56%) were caused by E.coli followed by Klebsiella (16.7%), Enterococci (12%) and Pseudomonas (8.3%). Of the patients who had UTI, there were more females (33% vs. 13%), more stone disease (8.2% vs. 1.7%) and more post-operative surgical complications (24.5% vs. 11.7%). Of the 26 ASB, 11 were treated and 15 untreated. Of the 15 untreated ASB, none developed symptomatic UTI or rejection. There was no difference in serum creatinine between treated and untreated ASB on last follow-up.

Conclusions: In conclusion, symptomatic UTI in RT is our setting is seen in 13.6% patients, mostly in first month with E.coli as causative organism in half of patient. Untreated symptomatic UTI does not affect graft outcome and does not lead to symptomatic UTI.

SA-PO1062
High Dose Steroid Therapy in BK Viremia Adversely Affected Long Term Graft Function in Kidney Transplantation
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Background: High dose steroid therapy has been tried for the management of confusing cases of BK nephropathy (mixed cellular rejection). However, the eventual fate of renal allograft after steroid therapy in the long term is still unknown. Therefore we investigated the graft survival and the change of BK viral load after steroid therapy in patients with BK viremia.

Methods: The study population comprised 144 kidney transplant recipients with BK viremia (serum BK viral load>1x10^4 copies/mL) consecutively detected at least two times, followed by steroid pulse treatment between July 2004 and March 2013. Patients were divided into two groups based on the amount of steroid: low dose (steroid 0-2g) or high dose (steroid>2g).

Results: A total of 123 patients belonged to low dose group and 21 patients were in high dose group. There were no differences in baseline characteristics, including age, gender, and the rates of biopsy-proven BK nephropathy and acute rejection. Serum BK viral loads at the time of steroid pulse therapy were 5.38±1.10 log copies/mL in low dose group and 6.00±0.98 in high dose group (p=0.054). They were changed into 5.22±1.05 and 6.14±1.45 in each group one month after steroid treatment (p=0.03) and 4.92±1.25 and 5.86±1.74 at two months (p=0.133), respectively. From three months to one year, BK viral loads were not different from each group. Kaplan Meier analyses demonstrated that the incidences of further 50% decline in renal function assessed by estimated GFR and graft failure were significantly higher in the high dose group (p=0.004 and p=0.04, respectively). In multivariate regression analysis, high dose steroid treatment (p=0.002, HR 6.91, 95% CI 2.25-20.99) and log serum BK viral load at two months after high dose steroid administration (p=0.027, HR 1.72, 95% CI 1.06-2.78) were important risk factors of further 50% decline in renal function.

Conclusions: In kidney transplant recipients with BK viremia, high dose steroid therapy induced BK viral activation and subsequently resulted in poor long term graft function and early graft failure.
SA-PO1063

Donor Seroreactivity Strongly Correlates with Recipient BKV-Viremia and Nephropathy
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Background: Incidence and severity of reactivating latent infections in kidney transplant (KTx) recipients are difficult to predict. In case of BK polyomavirus (BKV) induced nephropathy, donor origin of infection is likely. Since BKV-seroreactivity reflects BKV-reactivity, we hypothesized that donor BKV-seroreactivity correlates with infectivity and predicts BKV infection of recipients.

Methods: In a retrospective cohort of 407 living donor-recipient pairs transplanted between 2003 and 2013 at LUMC, pre-KTx sera from donors and recipients were tested for presence and intensity of BKV IgG-seroreponses. Measured seroresponses were compared with recipient BKV-loads (viremia) determined post-KTxs and compared with other potential risk factors for BKV-infection.

Results: Within one year after KTx, BKV-viremia was observed in 27% of recipients. Baseline BKV-seroreprevalece among donors (96%) and recipients (95%) was high and not correlated with viremia. However, a strong association was observed between the strength of donor BKV-seroreactivity and occurrence of both viremia and PVAN (p=0.001). Baseline recipient BKV-seroreactivity as such was not associated. The hazard ratio of viremia was almost 10-fold higher in recipients of high compared to low seroreactive donors. In multivariate analysis, donor seroreactivity was the strongest baseline factor associated with viremia and nephropathy post-KTx (p=0.001), outcompeting other described risk factors.

Conclusions: The strong association between donor BKV-seropositive status and recipient BKV-infection points directly to the donated kidney as the source of BKV-induced disease and possibly reflects the BKV allograft load. Our findings warrant further research into the usefulness of BKV-serological testing prior to transplantation.

Funding: Private Foundation Support

SA-PO1064

The Role of BK Viral Subtypes in BK Viral Infection After Renal Transplantation
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Background: Risk factors for developing BK virus (BKV) infection after renal transplantation are unresolved, including the role of BKV subtypes.

Methods: We report on 146 patients with viral replication in urine tested by quantitative PCR (Cephid-Affigene Kit) before transplantation (29 donors and 11 recipients, spontaneous replication in urine) and after transplantation (106 infected recipients, routine recipient BKV testing). Genotyping of BKV DNA subtypes was performed. Patients were divided into three groups: group 1, donor BKV subtype Ib-2; group 2, donor BKV subtype Ib-3, non subtype Ib-2; group 3, patients with BKV-negative post-transplant BKV nephropathy or high viremia of >10000 copies/mL (n=32, group 1) were compared to post-transplant recipients with viremia alone or with low viremia of <10000 copies/mL (n=43, group 2) and with donors and recipients before transplantation (n=40, group 3).

Results: BKV subtype Ib-1 was seen in 14/16 (10%), subtype Ib-2 in 92/162 (63%), subtype II in 9/164 (6%), subtype III in 1/166 (2%), and subtype IV in 30/164 (21%) of all patients. Thus, subtype Ib-2 was the first and subtype IV the second in frequency of subtyping infected patients. Comparing the 3 groups (group 3), there was no stat. sign. difference in the prevalence of subtype Ib-1 (8 vs 15 % in 10%); subtype Ib-2 (60 vs 70 vs 60%); subtype II (3 vs 7 vs 10%); subtype III (2 vs 0 vs 5%); and subtype IV (27 vs 12 vs 20%). However, after transplantation, subgroup IV had a trend to be less prevalent in patients with viremia/ low viremia (group 2) compared to patients with BKV nephropathy or high viremia of >10000 copies/mL (group 1) (5/34 vs 17/60, p=0.054).

Conclusions: BKV subtype Ib-2 is the most frequent subtype in all patients of the three groups. In the situation after renal transplantation, patients being infected with BKV subtype IV could be more likely to develop BKV nephropathy or high viremia than patients being infected with other subtypes. This has to be investigated in larger patient groups.

SA-PO1065

Inflammation and Reconstitution Injury in Resolving Polyomavirus Nephropathy: Good or Bad? Insights from a Protocol Biopsy Based Prospective Study
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Background: Polyomavirus nephropathy (PVN) has been extensively studied at time of disease onset and in index biopsies. In contrast, little is known about acute and chronic changes occurring during PVN resolution under low dose maintenance immunosuppression. Aim: Enhance understanding of resolving PVN.

Methods: From 1/2009-9/2014 823 adult renal transplants with an 8.5% incidence of PVN (n=37) were prospectively followed at UNC. UNC PVN patients were monitored with the urinary PV-Haufen test and protocol biopsies collected 9-37 patients when the test turned from positive to negative as marker for PVN resolution. Histology in index PVN (n=9) versus post-PVN (n=12) biopsies (n=9) was compared; clinical, treatment and long-term outcome data were obtained from electronic medical records.

Results: Serum creatinine and Banff scores at time of PVN index biopsy and follow-up protocol biopsy in Table 1.

Index biopsy: 5/9 cases with PVN grade 1 and 4/9 grade 2. Treatment: reduction tacrolimus and/or MMF. Protocol biopsy (median 6 weeks post index, range: 4-60): 5/9 cases with PVN, 4/9 reduction in minimal PVN; 1/9 requiring MPGN; 3/9 acute ABMR or Banft type 2 definitive rejection. Anti-rejection therapy 6/9 cases with decrease in S-Cr in 4-6 and deterioration in 2/6; function stable in 3/9. Further 12-month follow-up: Serum creatinine 1.75 mg/dl (median), no graft losses.

Conclusions: Resolving PVN under ‘low-dose’ immunosuppression shows significant increases in Banff acute inflammation scores and S-Cr. “Bad”inflammation is in part secondary to acute rejection and responds to anti-rejection therapy. “Good” self limiting reconstitution inflammation can be postulated in 1/9 cases (10%) of resolving PVN. PVN results in only mild increases in chronic tissue injury.

SA-PO1066

Effectiveness of Simprevir and Sofosbuvir in the Treatment of Hepatitis C Virus in Genotype 1 Post-Kidney Transplant Recipients
Karolyn S. Horn,1 Michelle T. Martin,2 Ignatius Yun-Sang Tang,3 1Pharmacy Practice, Univ of Illinois at Chicago; 2Medicine, Univ of Illinois at Chicago.

Background: The 2014 American Association for the Study of Liver Diseases (AASLD) guidelines recommended the use of simprevir (SMV) + sofosbuvir (SOF) for the treatment of liver transplant recipients with genotype (GT) 1 hepatitis C virus (HCV). There is a paucity of data on the treatment of other solid organ recipients. We conducted a retrospective, single-center analysis of kidney transplant recipients (KTRs) who received HCV treatment.

Methods: All KTRs who received HCV treatment with 12 weeks of SMV + SOF between January and November 2014 were evaluated. The primary endpoint was the sustained virologic response at 12 weeks after the end of treatment (SVR12). Secondary outcomes included HCV PCR levels, serum creatinine, urine protein/creatinine ratio, trough calcineurin inhibitor (CNI) levels and dose changes, and AST to platelet ratio index (APRI) at week 4, end of treatment (EOT), and 12 weeks post-treatment.

Results: Twelve patients met inclusion criteria: mean age of 60±5.3, 11 males, 8 African American, 6 GT 1a and 6 GT 1b. There were 6 liver-kidney, 4 kidney, and 2 pancreas-kidney transplant recipients. All but 1 patient received tacrolimus as their CNI. Ten of 12 patients (83.3%) achieved SVR12. Mean tacrolimus levels increased significantly by 1.5 ng/mL between week 0 and 4 (p=0.041). Five (41.7%) required a mean tacrolimus dose decrease of 2 mg during treatment. Nine (75%) required a mean dose increase of 2 mg between EOT and SVR12. The APRI scores decreased from 0.64 to 0.17 between baseline and 12 weeks of treatment, but this is not statistically significant (p=0.216). Both serum creatinine and urine protein/creatinine ratio remained stable pre- and post-treatment (p=0.260 and p=0.373, respectively).

Conclusions: SVR12 was achieved in 83.3% of KTRs treated with SMV + SOF. Renal allograft function was stable during and after HCV therapy. Treatment with SMV + SOF increased CNI levels during treatment. CNI dose adjustment is needed to maintain therapeutic levels after SMV + SOF therapy.

SA-PO1067

25-Hydroxivitamin D Insufficiency Is Associated with Higher Risk of BK Virus Re-Activation After Kidney Transplantation

Background: The past decade has seen increased interest in vitD, because new data suggest that it plays a role in the immune system. The purpose of this study was to evaluate the association of 25-hydroxivitamin D level (25[OH]D) after kidney transplant with the risk of BK virus reactivation.

Methods: We identified 498 kidney transplant recipients (2007-2011) who had serum levels of (25[OH]D), and PTH. We evaluated the relationship between the average levels of (25[OH]D and PTH and BK reactivation in blood.

Results: VitD insufficiency (25[OH]D <30 ng/mL, defined by The Endocrine Society Clinical Practice 2011) was observed in 377 (77%) of 498 kidney recipients after transplant. The VitD insufficient and sufficient groups were comparable in terms of gender, age, BMI, race, and immunosuppression. VitD insufficiency was more frequent in recipients of cadaveric allografts (P=0.009, Fisher test). By multivariable Cox regression analysis, vitD deficiency was an independent risk factor for BKV reactivation after kidney transplantation (HR=2.4, 95% CI 1.3-4.7, P=0.002). Moreover, vitD insufficiency was associated with significantly earlier onset of significant BKV reactivation (19 compared to 16 months, P=0.003).

ROC analysis using logistic regression showed that 25[OH]D < 24ng/mL was predictive of BKV reactivation.
SA-PO1068
Different Types of Cytomegalovirus DNAemia and Long-Term Outcomes After Renal Transplantation
Tomas Reischig,1 Martin Kacer,2 Ondrej Hes,2 Daniel Lyisks,3 Mirko Bouda,1 1Internal Medicine I, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic; 2Pathology, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic; 3Hematoooncology, Biomedical Center, Charles Univ Medical School and Teaching Hospital, Pilsen, Czech Republic.

Background: Although occurring very often the role of cytomegalovirus (CMV) DNAemia in patients managed by preemptive therapy or by universal antiviral prophylaxis is not established. The aim of the study was to determine the impact of different types of CMV DNAemia during 4 years after transplantation.

Methods: A total of 180 consecutive renal transplant recipients at risk for CMV (donor and/or recipient CMV seropositive) were included and followed prospectively. Universal prophylaxis for 3 months was given to 132 (high-dose valacyclovir, n=87; valganciclovir n=45), patients were managed by preemptive therapy or by universal antiviral prophylaxis DNAemia in patients managed by preemptive therapy or by universal antiviral prophylaxis is not established. The aim of the study was to determine the impact of different types of CMV DNAemia during 4 years after transplantation.

Results: Early-onset, late-onset, and combined early+late-onset CMV DNAemia occurred in 18%, 25%, and 13% of the patients being asymptomatic in majority (91%) of cases. Graft survival at 4 years was inferior in patients with late-onset CMV DNAemia compared to patients without CMV DNAemia (73% vs. 94%, P=0.002) while no significant differences were observed in patients with early-onset (85%, P=0.139) or combined early+late-onset CMV DNAemia (96%, P=0.682). Patient survival was comparable in all groups. Multivariate analysis revealed that Diabetes (OR 2.45, 95% CI 1.08–5.55, p = 0.03), recipient age (OR 1.02, 95% CI 1.01–1.03, p = 0.01), and recipient BMI (OR 2.18, 95% CI 1.09–4.39, p = 0.029) were independently associated with CMV DNAemia.

Conclusions: Late-onset CMV DNAemia is a risk factor for graft loss after renal transplantation.

SA-PO1069
Assessment of Cytomegalovirus-Specific Cell-Mediated Immunity for the Prediction of Cytomegalovirus Spontaneous Clearance in High-Risk Kidney Transplant Recipients with Cytomegalovirus Viremia
Marine Lochouarn,1 Sylvia Benzaken,2 Laetitia Albano,1 Elisabeth Cassuto,1 Ahmed Jeribi,1 Anne Caramella,1 Valérie Giordanengo,1 Ghislaine Bernard,2 Vincent L.M. Esnault,1 Barbara Seitz-Polaski,1,2 1Nephrology and Kidney Transplantation Dept, Univ Hospital, Nice, France, Metropolitan; 2Laboratory of Immunology, Univ Hospital, Nice, France, Metropolitan.

Background: Cytomegalovirus (CMV) is the most common virus pathogen in kidney transplant recipients (KTR) and CMV disease impacts patient and graft survival. CMV-specific CD8 T cell-mediated immunity (CMI) kinetics may help to assess the risk of CMV disease and to adapt preventive treatment strategies.

Methods: High-risk KTR with CMV seropositive donor/seronegative recipient (D+R−), were longitudinally monitored after CMV prophylaxis discontinuation and during the first year post-transplant for CMV viremia (WHO standardization) and CMI (Quantiferon®-CMV). We analyzed the ability of the CMI-test to predict subsequent spontaneous viral clearance in case of asymptomatic viremia after prophylaxis discontinuation or CMV disease recurrence after curative treatment.

Results: We enrolled 12 consecutive (D+R−) KTR. Eleven patients developed viremia during follow-up. Spontaneous viral clearance occurred in 7 of 11 (63.6%) patients and 4 of 11 (36.4%) developed CMV disease. At viremia onset, 6 of 11 (54.5%) patients had a positive CMI-test. In those patients, the incidence of subsequent spontaneous viral clearance was 6 of 6 (100%) compared with only 1 of 5 (20%) among patients displaying a nonreactive CMI (p = 0.02). This latter patient revealed a positive CMI-test one month later. In the 4 patients who developed CMV disease, persistence of a nonreactive CMI after treatment in one patient was associated with disease recurrence, while patients whose CMI-test became positive under treatment showed no recurrence.

Conclusions: We show for the first time that D+R− KTR with asymptomatic viremia attested by WHO standardized CMV viral load monitoring after prophylaxis discontinuation may benefit from Quantiferon®-CMV to predict spontaneous viral clearance or CMV disease.

Funding: Pharmaceutical Company Support - Cellectis GmbH, a QIAGEN company, Darmstadt, Germany provided equipment entity (Quantiferon®-CMV blood collection tubes)

SA-PO1070
Prevalence of Double Stranded DNA (dsDNA) Viral Infections Among Kidney Transplant Recipients
Essy Mozaffari,1 Jay Lin,2 Melissa Lingoi-Smith,2 1Chimerix Inc., Mendham, NJ; 2Novosys Health, Green Brook, NJ.

Background: Management of immunosuppression following solid organ transplant is a delicate balance between preventing graft rejection and minimizing the risk of infection. Antimicrobial prophylaxis can decrease the risk of infection, while increased immunosuppression can increase these same risks. Our objective was to estimate the occurrence of opportunistic infections, specifically dsDNA viral infections, in kidney transplant recipients.

Methods: Patients who received a kidney transplant between January 2009 and September 2013 were identified from the Premier Hospital database using ICD-9-CM codes. The first transplant procedure was defined as the index event. The frequencies of opportunistic infections, documented by diagnostic codes, were evaluated during the first 12 months after kidney transplant.

Results: Of patients who received kidney transplant (n=5,402; mean age: 50.8 years) 61% were male. Most patients received transplant in urban (98%), large (≥600 beds; 61%), teaching hospitals (84%). During the 12 months post kidney transplant, 33% (1,800 patients) had a diagnostic code for 1 opportunity opportunistic infection, and among these 25% (n=448) had at least one dsDNA viral infection. Among the 448 dsDNA viral infections, 81% (n=365) were cytomegalovirus (CMV), 8% (n=36) BK virus, and 16% (n=70) other dsDNA viral infections (EBV, VZV, HHV, HPV, EVB).

Conclusions: Opportunistic infections frequently result from the immunosuppression required following kidney transplantation. In our study, one-third of the kidney transplant recipients had a discharge diagnosis for at least one opportunistic infection. One of four opportunistic infections were classified as dsDNA viral infections, with the majority caused by human herpesviruses including CMV despite the common use of anti-CMV agents. Our study also highlights the role of BKV-related complications, which represent an unmet need given the absence of therapeutic options for this dsDNA virus and the known association with BK-associated nephropathy.

Funding: Pharmaceutical Company Support - Chimerix Inc.
In 301 transplant recipients, the most common infections (N=255) were UTIs (61%) and pneumonia (9%). 74 kidney transplant recipients received antibiotics during the first month of transplantation (Early Abx Group) and 227 did not (No Early Abx Group). The Early Abx Group had a significantly higher number of infections during post-transplant months 2-12 than the No Early Abx Group (1.2±0.2 vs. 0.3±0.1, P=0.001, Wilcoxon rank-sum test). Within the Early Abx Group, subjects who received anarobic coverage had a significantly higher number of infections during post-transplant months 2-12 than subjects who did not (1.8±0.5 vs. 0.9±0.2, P=0.050).

Conclusions: Early antibiotic usage was associated with increased future bacterial infections in kidney transplant recipients. A decrease in gut microbiol diversity is a biologically plausible pathogenic mechanism.

Funding: Other NIH Support - KL2 Scholars Award from the Weill Cornell Clinical and Transational Science Center (KL2 TR-000458)

SA-PO1072

Successful Treatment of Hepatitis C in Renal Transplant Recipients with Directly Acting Antiviral Agents
Michelle L. Lubetzkzy, Enver Akalin, Paul Gaglio, Graciela De Boccoardo. Transplantation, Montefiore Medical Center, Bronx, NY.

Background: Hepatitis C infection (HCV) in kidney transplant (KTx) recipients has been shown to be an independent risk factor for decreased patient and allograft survival. Historically treatment of HCV has been interferon-alpha based, which is associated with acute rejection in KTx patients. With the development of new, oral, interferon-free directly acting antiviral (DAA) medications, treatment of HCV in renal transplant recipients is possible, but limited data exists on its safety and efficacy.

Methods: We performed a retrospective review of all KTx patients at our center with HCV started on DAA for treatment of HCV. Any patient with at least 30 days of follow up was included in the analysis (n=10). Clinical data including graft function, survival, and response to therapy was collected.

Results: Patient demographics are in Table 1. At a median of 92 days of follow up (range 33, 438), all patients have undetectable viral load. Median time from KTx to treatment was 781 days (range 173,1040). At most recent follow up, mean creatinine was 1.48±0.51 mg/dl and mean proteinuria was 0.47±1.07 g/day with no adverse side effects reported. No patients have lost their grafts or developed acute rejection, but 2 patients had detectable CMV. For the 8 patients on tacrolimus (Tac), there was a drop in 12-hr trough level during therapy (mean 6.3±2.1 ng/ml pre-treatment, and mean of 4.9±2.1 ng/ml after 6 weeks of treatment); during treatment 3 patients had a level <4 ng/ml. All patients with level <4 ng/ml had dose increase and repeat level was in normal range.

Characteristics

<table>
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<tr>
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<td>Mean Creatinine at start of therapy</td>
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<td></td>
<td>1 ledipasvir/sofosbuvir/ribavirin</td>
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</table>

Conclusions: Our data demonstrates that DAA's can be used safely and effectively in patients after KTxs. Tac levels should be monitored closely during therapy. Longer follow up of KTxs treated for HCV is needed to determine the effects treatment has on graft and patient survival.

SA-PO1073

A Systematic Review and Meta-Analysis of Cytomegalovirus Infection in Renal Transplant Recipients Receiving Alemtuzumab versus Anti-Thymocyte Globulin for Induction Therapy
Payvand Milani, Nasrollah Ghafarimani. Medicine, Pennsylvania State Univ College of Medicine, Hershey, PA.

Background: Use of antibody induction for kidney transplant has improved patient outcomes over the past decade. One common induction agent is rabbit anti-thymocyte globulin (ATG), a polyclonal anti-human T-cell antibody. Alemtuzumab, a monoclonal anti-CD52 antibody with stronger lympho-depleting properties, has been used as an induction agent in steroid-sparing or steroid-minimizing protocols. Like all immunosuppressive agents, these agents are associated with opportunistic infections, including cytomegalovirus (CMV). Our aim was to compare the relative risk of CMV infection between the two induction regimens.

Methods: We used five comprehensive search themes (CMV, ATG, alemtuzumab, transplant, and induction) to search electronic databases from 1980 to 2014 using PubMed and The Cochrane Library while also manually reviewing recent abstracts from the American Society of Nephrology and the American Transplant Congress meetings. Studies reporting the number of cases of CMV infection in patients receiving one of the two agents were included. The outcome was the pooled relative risk (RR) of CMV infection in the alemtuzumab group compared to that in the ATG group.

Results: A total of 73 studies were identified and reviewed, 64 of which were excluded upon initial screening. Analysis of the 9 studies (8 complete articles and 1 abstract; 1,735 patients) showed a RR of 0.58 (95% CI: 0.31-1.07) for incidence of CMV infection in patients receiving alemtuzumab versus ATG. Other reported adverse effects in both induction groups (infections, post-transplant lymphoproliferative disorder (PTLD) and/or malignancy, decrease in estimated glomerular filtration rate , and post-transplant diabetes mellitus) were similar in both groups.

Conclusions: This study suggests that for induction therapy in kidney transplant, the incidence of CMV infection associated with alemtuzumab is not significantly different than that associated with ATG.

SA-PO1074

Occurrence and Determinants of Antibiotic Resistance in Bacteriuria After Kidney Transplantation

Background: Asymptomatic bacteriuria is often treated after kidney transplantation, which can result in the development of antibiotic resistance. Our aim was to assess the antibiotic resistance profile of gram-negative bacteria in our kidney transplant population, and to determine the factors associated with antibiotic resistance.

Methods: We performed a single center, retrospective cohort study in patients who received a kidney allograft at our center between January 1st, 2008 and June 1st, 2013. Through chart review, information on all bacteriuric episodes involving gram negative bacilli was collected during follow-up, which ended on June 1st, 2014. Bacteriuria was defined as growth exceeding 10^3 CFU/ml. Multivariable logistic regression using a generalized estimating equation (GEE) procedure was performed to identify the factors associated with resistance to antibiotics.

Results: Amongst the 318 patients studied, 629 bacteriuric episodes involving gram negative bacilli occurred in 143 patients. Resistance to TMP-SMX occurred in 336 episodes (53%), resistance to ciprofloxacin in 142 episodes (23%) and extended beta-lactamase production occurred in 30 episodes (5%). An increased risk of resistance to ciprofloxacin and/or extended spectrum beta lactamase production was statistically associated with the number of previous treatments (odds ratio (OR):2.29, 95%confidence interval (CI ):1.16-4.52), and ≥5 previous treatments (odds ratio (OR):2.99, 95%confidence interval (CI ):1.16-4.52), and ≥5 previous treatments (OR:3.5, 95%CI:1.28-7.26), diabetes (OR:2.57, 95%CI:1.01-6.55), and/or extended spectrum beta lactamase production (OR:0.8, 95%CI:0.16-4.51) and a longer time elapsed between bacteriuria and transplantation (OR:0.32, 95%CI:0.15-0.66, for episodes supervening >1 year post transplant versus ≤ 1 year).

Conclusions: Elevated resistance rates to TMP-SMX and ciprofloxacin were observed in our kidney transplant population, which can reduce the usefulness of prophylaxis with TMP-SMX. Arf against treating asymptomatic bacteriuria, given the association we observed between the number of previous treatment of bacteriuric episodes and resistance to ciprofloxacin/ESBL production.

Funding: Government Support - Non-U.S.

SA-PO1075

Carbenepem-Sparing Antibiotic Regimens for the Treatment of Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae Infections: A Comparative Study
Tiffany Ebony Buss, Gregory Malat, PharmD, Akshay Sharma, Doug Heun Lee, Alden Michael Doyle. Pharmacy, Hahnemann Univ Hospital, Philadelphia, PA; Surgery, Drexel Univ, College of Medicine, Philadelphia, PA; Infectious Diseases and HIV Medicine, Drexel Univ, College of Medicine, Philadelphia, PA.

Background: Extended spectrum beta lactamase producing Enterobacteriaceae (ESBL-PE) has been recognized as a significant cause of mortality in solid organ transplant recipients. Carbapenems are considered the drug of choice for the treatment of ESBL-PE infections. However, antibiotic selective pressure associated with carbapenem use may
contribute to resistance, further stressing hospital epidemiology. Our study sought to compare the effectiveness of carbapenem sparing regimens to carbapenem containing regimens on clinical outcomes in transplant patients with ESBL-PE infections.

Methods: A retrospective, observational cohort study was conducted to evaluate adult patients who underwent a successful kidney transplant (defined as graft survival >30 days) prior to August 2014 with ESBL-PE infection post-transplant. Patients were stratified into 2 cohorts according to antibiotic regimens: carbapenem-containing and carbapenem-sparing. The outcomes of clinical cure, 30-day mortality, and recurrence were assessed.

Results: Fifty-two kidney transplant patients were included in our analysis: 29 in the carbapenem-sparing group and 23 in the carbapenem-containing group. Majority of infections were caused by Escherichia coli (46%) and Klebsiella pneumoniae (44%). The most common infection type was urinary tract infections (46%) followed by bloodstream infections (23%) and nosocomial pneumonias (15%). There was no statistically significant difference in clinical cure rates (91% vs. 76%, p=0.268) and 30-day mortality (24% vs. 9%, p=0.268) in the carbapenem-sparing and carbapenem-containing groups respectively.

Conclusions: ESBL-PE infections pose a serious threat to transplant recipients. Carbapenem sparing regimens may be adequate for the treatment of ESBL-PE infections, while offering advantages against minimizing selective pressure.

SA-PO1076

Clinical Recurrence of Primary Glomerular Disease in Kidney Transplantation

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Background: Recurrence of primary glomerular disease (PGN) in renal transplantation (RT) is a major cause of failure and renal allograft lost which determines the prognosis of the patient.

Methods: We conducted a retrospective analysis of 1513 renal transplants between January 1980 and December 2013, included in our database, medical records and biopsy register, collecting all patients who presented recurrence of PGN. We excluded from the study patients with secondary GN and those without biopsy study. Renal biopsy was indicated according the following criteria: impairment of renal function, proteinuria>1g/day and/or microhematuria. The analysis statistic was SPSS version 18.

Results: 414 of 1513 RT (27%) had chronic GN as underlying disease. 317 patients (260 man;57 woman) were primary GN (21%). The most frequent primary GN was IgA nephropathy (IgAGN) n=122,(38,4%), Membranoproiferative GN (MPGN), n=90(28,6%); Focal segmental GN(FSGS), n=58(15,1%); membranous GN(MGN), n= 33(10,4 %) and rapidly progressive GN (RPGN), n=14(4,4%). Forty(12,6%) patients with primary GN recurred. IgA GN (5%), FSGS (20%), MPGN (17%), MNGN (12%) and GRNP (12%). Three MPGN patients recurred in the second RT. The mean time of recurrence was: 48.18, 33.2, 18 and 33.2 months respectively Patients with graft loss due to GN recurrence were: IgAGN (n=10,75%), MPGN (n=14,93%), FSGS(n=10,75%), MNGN(n=3,70%). No significant difference was observed between GN types(p=0.15) and graft survival. In the Kaplan Meier analysis and COX test, recurrence primary GN had low survival at 10 years (p: 0.002).

Conclusions: Clinical Recurrence of primary GN is an important cause of graft loss. GN with most recurrent was GSF and graft lost was MPGN. We didn’t observe differences in graft survival between type of primary glomerular disease. Graft survival was higher in the group without recurrence at 10 years and no differences at 20 years.

SA-PO1077

Glomerular Diseases following Predisnilone Free Transplant with Low Dose Rituximab and ATG Induction and Protocol Biopsies

Vivek Pathak, Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil-Nadu, India.

Background: The purpose of this study is to document the incidence of post transplant glomerulonephritis in a steroid free protocol and other recurrent renal diseases leading to graft loss.

Methods: 883 patients, who underwent renal transplantation at our institute in nine years and eight months since July 2005 till March 2015 were studied. Thymoglobin was used for induction at a dose of 1.5mg/kg. 3 doses rituximab 200 mg was given before transplant to those patients who were considered to be at high risk for rejection. Maintenance immunosuppression was Tacrolimus and Mycophenolate mofetil. Prednisolone was rapidly discontinued by fifth post operative day. All patients underwent protocol biopsies at 3 months ,1 year and 5 years and indicated biopsies whenever required. The total number of biopsies was 2928. Discussion Our results show only 1% graft loss due to cumulative recurrent Glomerulonephritis at nearly 10 years. Our figures could be low due to Thymoglobin induction therapy. We could prevent graft loss due to recurrent FSGS by achieving complete or partial remission by using Rituximab in 15/19(79%) patients.

SA-PO1078

Post-Transplant Focal Segmental Glomerulosclerosis Recurrence Among Patients with Native Kidney Collapsing Variant: A Single-Center Retrospective Cohort Study

Panupong Hansrivijit,1,2 Katherine D. Westreich,1 Jonathan Alexander Miles,1 Evan Zeitlet,1 Maria E. Ferris,1 Randall K. Detwiler.1 
1University of North Carolina, Chapel Hill, NC; 2Chulalongkorn Univ, Bangkok, Thailand.

Background: Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of end-stage kidney disease (ESKD), and is known to recur in renal transplant grafts. The collapsing variant of FSGS(CvFSGS) is clinically distinct from other variants: it has a stronger association with African-American race, more severe proteinuria, and rapid progression to ESKD. The impact of native FSGS subtype on post-transplant FSGS recurrence rate and subtype is not known.

Methods: Clinical and pathological records were reviewed for renal transplant recipients at UNC between 2000 and 2014 with FSGS as the cause of ESKD. Native FSGS subtype was dichotomized into CvFSGS and FSGS-Other. Baseline demographics (sex, age, race), and rates and subtypes of post-transplant FSGS recurrence were compared between the two groups.

Results: Of 879 patients reviewed, FSGS was the cause of ESKD in 101. Among this subgroup, mean age at time of transplant was 45±17 years; 62% male; 50% non-Hispanic black, 45% non-Hispanic white, and 5% Hispanic. Ten patients (10%) had CvFSGS as the native lesion. Over a mean follow-up time of 2.4 years, the overall rate of recurrent FSGS was 34%. Compared to those with native FSGS-Other, patients with native CvFSGS had a higher rate of post-transplant FSGS of any type (30% vs 31%, RR 1.6), and were also more likely to have collapsing variant as the recurrent lesion (60% vs 11%, RR 5.5).

Conclusions: In a population of predominantly black and Hispanic patients in the Southeastern US, native CvFSGS predicts a 60% higher post-transplant FSGS recurrence rate, and the recurrent lesion is likely to be CvFSGS. However, 11% of patients with native FSGS-Other developed de novo CvFSGS post-transplant. Further study of this cohort will determine the predictive power of native and recurrent CvFSGS with regard to clinical outcomes.

SA-PO1079

Pre-Transplant Rituximab in Recurrent Focal Segmental Glomerulosclerosis

John Manolo,1 Dany Matar,1 Sami Alasfar,1 Jochen Reiser,2 Nada Alachkar.1 
1Johns Hopkins Univ; 2Rush Univ.

Background: Focal segmental glomerulosclerosis (FSGS) recurs in 30-40% of patients after kidney transplant (Tx). Rituximab was suggested to have cross-reactivity with podocyte sphingomyelin-phosphodiesterase-acid-like-3b (SMPLD-3b), which was found to have cross-reactivity with podocyte sphingomyelin-phosphodiesterase-acid-like-3b (SMPLD-3b), which was found to have cross-reactivity with podocyte sphingomyelin-phosphodiesterase-acid-like-3b (SMPLD-3b).
to be reduced in post perfusion biopsies of kidney Tx recipients who later on developed recurrent (rFSGS). However, the use of rituximab to prevent rFSGS remains controversial.

Methods: We enrolled 56 adult patients, 50 with biopsy proven FSGS and 6 with a pre-Tx course highly suggestive of FSGS. Patients underwent kidney transplant between 2008-2014. We compared FSGS recurrence and allograft survival between recipients who received rituximab and those who did not.

Results: Mean time of follow-up was 28.6 months. 24 patients received rituximab (mean 9.4 ± 9.1 yrs) after a diagnosis of FSGS. 22 patients did not receive rituximab (mean 9.1 ± 9.4 yrs). The mean and standard deviation (SD) of eGFR at the most recent follow-up in the patients who received rituximab was 42.2 ±88 versus 39.2 ±1 L/min/1.73m² in those who did not receive it, respectively (p=0.047). A higher percentage of patients who received rituximab had a renal function maintenance that could be removed or diminished by plasmapheresis (PP). In this study, we assessed the efficacy of PP in prevention and treatment of post-Tx rFSGS.

Methods: We prospectively enrolled 56 Tx-patients with biopsy proven FSGS (50) or other causes of TMA (6). Patients were transplanted between 2008-2014. We compared between the preventive and non-preventive PP groups.

Results: Mean time of follow-up was 28 months. Differences between the 2 groups are as following:

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<td>Time from FSGS diagnosis to renal replacement initiation,y(±SD)</td>
<td>6.1(8.6)</td>
<td>10.9(1.9)</td>
</tr>
<tr>
<td>Prior Tx(n)</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Living donor(n)</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Induction with aTGF(α)</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>rFSGS (n)</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Time to rFSGS(month±SD)</td>
<td>7.7(3.7)</td>
<td>10.6(3.5)</td>
</tr>
<tr>
<td>Mean of most recent UPC, g/L(±SD)</td>
<td>2.7(0.5)</td>
<td>0.2(0.1)</td>
</tr>
</tbody>
</table>

rFSGS developed in 35 patients (62%); of whom preventive PP was performed in 19. Out of the 21 cases that did not develop FSGS, 7 received PP (P=0.1). Patients who received preventive PP had a shorter time from FSGS diagnosis to ESRD compared to those who did not (6.1±8.6 yr vs 10.1±9.1 yr (p 0.047)). 33 out of the 35 patients (95%) with rFSGS received therapeutic PP, and 24 also received anti-CD20 therapy. Only 5(15%) did not respond; 2 lost their grafts. Of the 28 who responded, 14 (50%) subsequently relapsed. 71% of the relapses responded to a second course of PP; only 4 lost their grafts. Kaplan-Meier allograft survival in both groups is shown in figure 1.

SA-PO1080

Role of Plasmapheresis in Post-Transplant Focal Segmental Glomerulosclerosis

Samii Alasfar,1 Dany Matar,2 John Manollo,3 Jochen Reiser,4 Nadia Alachkar,5 1Johns Hopkins Univ, Baltimore, MD; 2McKinsey & Company, Washington, DC; 3Rush Univ, Chicago, IL.

Background: Focal segmental glomerulosclerosis (FSGS) commonly recurs after kidney transplant (Tx). This is attributed to the presence of a circulating permeability factor that may be removed or diminished by plasmapheresis (PP). In this study, we assessed the efficacy of PP in prevention and treatment of post-Tx rFSGS.

Methods: We prospectively enrolled 56 Tx-patients with biopsy proven FSGS (50) or other causes of TMA (6). Patients were transplanted between 2008-2014. We compared between the preventive and non-preventive PP groups.

Results: Mean time of follow-up was 28 months. Differences between the 2 groups are as following:

<table>
<thead>
<tr>
<th>Preventive PP(n=26)</th>
<th>No PP(n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Diagnosis, yr</td>
<td>28.5(±18)</td>
<td>33.2(±15)</td>
</tr>
<tr>
<td>Mean Time from Dx to RRT, yr</td>
<td>4.8(±5.6)</td>
<td>10.1(±11.5)</td>
</tr>
<tr>
<td>Mean of cumulative dialysis duration, yr</td>
<td>4.8(±3.8)</td>
<td>2.9±(3.7)</td>
</tr>
<tr>
<td>Mean Age at current Tx, yr</td>
<td>43(±13)</td>
<td>48.8(±13)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (50%)</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Prior tx, n (%)</td>
<td>13 (54%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>ABO Incompatible Tx, n (%)</td>
<td>5 (20%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Allograft failure, n (%)</td>
<td>3 (12%)</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

Conclusions: Preventive PP does not reduce the incidence or delay the development of rFSGS. However, PP remains an effective therapy for post-transplant FSGS.

SA-PO1081

Post-Transplant Thrombotic Microangiopathy: A Single Center Experience

Cinzia Montenegro Teixeira,1 Igor Goulart-Pistrobon,2 Andre Caires Alvim,1 Gianna Mastroianni-kirsztajn,2 Laila Almeida Viana,1 J. Medina-Pestana,1,2 Helio Tedesco Silva,1,2 1Hospital do Rim- Fundação Oswaldo Ramos, Sao Paulo, Brazil; 2Univ Federal de Sao Paulo, Sao Paulo, Brazil.

Background: Thrombotic microangiopathy (TMA) occurs in 1-15% of kidney transplant allografts and predicts poor outcomes.

Methods: We reviewed 35 cases of TMA in the kidney allograft diagnosed at our institution between 2011-2015.

Results: The mean age was 39±14 years with 18 (51%) women. Three (9%) patients were recipients of simultaneous pancreas-kidney transplant. Among the recipients of kidney transplant alone, 21 (66%) received deceased donor grafts. The cause of end stage renal disease was unknown (37%), chronic glomerulonephritis (31%), obstructive uropathy (11%), diabetes (9%), hemolytic uremic syndrome (3%) or others (9%). Induction with thymoglobulin or basiliximab was performed in 24 (63%) patients. Maintenance immunosuppression was prednisone (PRED), tacrolimus (TAC), and azathioprine in 15 (43%), PRED, TAC and mycophenolate sodium in 12 (37%) and PRED, TAC and everolimus in 3 (9%) patients. Patients were diagnosed with TMA at a median of 71 days (range: 1-1645) from transplant, wherein 37% patients developed TMA within 1 month of transplantation and 31% after 1 year. Mean serum creatinine was 4.5±3.3 mg/dL and 13 (41%) patients needed renal replacement therapy after TMA diagnosis. TMA was renal-limited in 23 (66%) patients. Concomitant acute rejection was present in 12 (34%) patients and cellular rejection was the most common (92%) type of rejection related to TMA. Cytomegalovirus infection occurred in 5 (14%) and other infections were present in 19 (54%) patients. Following diagnosis of TMA, calcineurin inhibitor (CNI) withdrawal was performed in 22 (66%) patients. Withdrawal of CNI and treatment of concomitant rejections and infections contribute to renal function maintenance.

Funding: Private Foundation Support

SA-PO1082

Outcome After Eculizumab Therapy to Prevent Recurrence of Atypical Hemolytic Uremic Syndrome: Experience in Eleven Renal Transplant Recipients

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease with a high recurrence rate after kidney transplantation. aHUS is associated with histological lesions of thrombotic microangiopathy (TMA) that mainly leads to graft loss. The successful use of Eculizumab (Ecu) to prevent or to treat post-transplantation aHUS recurrence has been scarcely reported. In this study, we describe 11 patients who received a renal transplantation for aHUS and who were treated by Ecu after renal transplantation.

Methods: Eleven renal transplants recipients, with aHUS on their native kidney, received Ecu at our center between 2010 and 2015. Nine patients received prophylactic
of IgAN. Further analysis is needed to determine risk factors for rIgAN and to establish
urinary protein (0.57 ± 1.29, 0.07 ± 1.14 ng/mL in the control groups (p=0.75) and 8.95 ± 2.03 ng/mL in the
cancer and 8.96 ± 1.04 ng/mL in the control groups (p=0.97). By multiple logistic regression, only smoking status was associated with cancer. The time-averaged tacrolimus level at time of cancer diagnosis was not significantly associated with cancer after adjustment for this variable (Hazard ratio=1.08 per ng/mL, 95% confidence interval 0.97 to 1.5, p=0.65).

Conclusions: The development of de novo nonskin cancer after kidney transplantation was not associated with the level of tacrolimus exposure over time. Transplantation: Clinical and Translational - V

Renal Cell Carcinoma Post Renal Transplant: The Case for Post-Transplant Ultrasonad Surveillance

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Background: Following successful renal transplantation, there is an increased relative risk of renal cell carcinoma in retained native kidneys. Stimulated by a case of widespread metastatic cancer nine months after transplant with a normal pre-transplant ultrasonad, we began routine 6-12 month post-transplant surveillance on all recipients except those with known or dominant non-malignant renal disease.

Methods: 128 consecutive patients were entered into the study. At 6-12 months post-transplant.
Results: 16 suspicious masses were detected (12.5%). Of these only 9 had evidence of an oncologic disease (ACD) (four or more cysts) pre-transplant. The remainder had normal pre-transplant scans showing only small contracted kidneys or less than the required number of cysts to make a diagnosis of acquired cystic disease. We are following 14 of these patients with scans every 6-12 months to detect growth in newly discovered, less than 1 cm solid lesions. We have found 2 patients in which frank renal cell cancers were discovered. We have now adopted an annual screening process for all post-transplant patients at their one-year post-transplant visit.

Conclusions: Routine screening of native kidneys post-transplant appears critical to detect renal cell carcinoma at a stage early enough to achieve a cure by nephrectomy.

SA-PO1088
Non-Melanoma Skin Cancer Mortality in Kidney Transplant Recipients
Michael Thomas Burks,1 Annie-Claire Nadeau-Fredette,1 Carmel M. Hawley,1 Elaine M. Pascoe,1 Stephen P. McDonald,1 Sunil V. Badve,1 David W. Johnson,1 Andrew Green,2 Robert Peter Carroll,1 Nicole Isbel,1 1Dept of Renal Medicine, The Univ of Queensland, Princess Alexandra Hospital, Brisbane; 2Central Northern Adelaide Renal Transplantation & Renal Services, Adelaide; 1Cancer and Population Studies Group, Queensland Inst of Medical Research, Brisbane; 2School of Medicine, The Univ of Queensland, Brisbane.

Background: Non-melanoma skin cancer (NMSC) frequently occurs in kidney transplant recipients (KTRs). However, the frequency of, and risk factors for NMSC mortality in KTRs are poorly characterised.

Methods: Aims: To determine the proportion and predictors of fatal NMSC in KTRs. This cohort study included all KTRs transplanted in Australia and New Zealand between 1980 and 2013, using Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) Registry data. A multivariable competing-risk survival analysis was used to calculate risk factors for fatal NMSC in KTRs.

Results: During the study, 21875 transplant episodes occurred in 19344 patients. Of the 6780 patients who subsequently died, 231 (3.4%) died from NMSC. Of these, 172 (74%) were male, 226 (98%) were Caucasian, 219 (95%) were first graft recipients and 213 (92%) were male, 226 (98%) were Caucasian, 219 (95%) were first graft recipients and 213 (92%) were male, 226 (98%) were Caucasian, 219 (95%) were first graft recipients and 213 (92%).

Conclusions: Screening for NMSC likely leads to survival benefit, but more research is needed to identify risk factors and to optimise screening protocols.

SA-PO1089
NFAT-Regulated Gene Expression in Patients Developing Non-Melanoma Skin Cancer
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Background: After transplantation the risk of non-melanoma skin cancer (NMSC) is significantly increased. Immunosuppression with calcineurin-inhibitors (CNIs) is associated with the development of NMSC. Association to the individual immunosuppressive loads of CNIs assessed by residual NFAT-regulated gene expression was investigated in renal allograft recipients.

Methods: Renal allograft recipients from the Department of Nephrology, University Hospital Heidelberg, Germany, were included. All patients had a regular annual skin examination. Residual expression of NFAT-regulated genes (IL-2, IFNγ, GM-CSF) in PMA/ionomycin-stimulated peripheral blood was measured by quantitative real-time PCR at predose and 2h after Ciclosporin A (CsA) intake.

Results: 258 renal allograft recipients were enrolled (160 male, age 51±14y). Of these patients 75 allograft recipients developed NMSCs after renal transplantation (29.1%). The following NMSCs were histologically confirmed: 36 basal cell carcinoma, 34 squamous cell carcinoma, 33 actinic keratosis, 27 Bowen disease, 8 kerato-acanthoma. As risk factors to develop NMSC were identified: age 60 years, skin type ( Fitzpatrick 1 and 2), and load of immunosuppression. NFAT-regulated gene expression was significantly lower in patients who developed NMSCs compared to patients without NMSCs (8.3±6.5 vs. 12.7±12.8, p=0.001). Squamous cell carcinoma and actinic keratosis were significantly associated with a high inhibition of IL-2 and IFNγ. Patients with basal cell carcinoma and Bowen disease showed a general low expression of NFAT-regulated gene expression. However, in patients with kerato-acanthoma no significant inhibition of NFAT-regulated gene expression could be detected.

Conclusions: The immunosuppressive load contributed to the risk of NMSC. NFAT-regulated gene expression was significantly inhibited in patients developing NMSCs. Monitoring of NFAT-regulated gene expression in CNI treated transplant recipients provides an individual profile of response to CNIs and is a useful tool for an individual immunosuppression with respect to safety and toxicity.
PUB001 Role of Toll-Like Receptors in Aristolochic Acid Nephrotoxicity

Gem Batuman,1 Altaf-M Khan,1 Madlin Alzoubi,2 Vecchi Batuman.1,2 1 Department of Medicine, Section of Nephrology & Hypertension, Tulane Univ School of Medicine, New Orleans, LA; 2 Department of Veterans Affairs, SLVHCS, New Orleans, LA.

Background: Studies demonstrated that aristolochic acid (AA) is toxic to renal tubular epithelium and carcinogenic to urethral epithelium. Although the exact extent of AA nephropathy (AAN) is unknown, case series have been reported in throughout the world and it has been implicated in the etiology of Balkan endemic nephritis (BEN) suggesting that this is a global health problem. The precise mechanisms of AA nephrotoxicity are not known. We investigated the role of Toll-like receptors (TLRs) in the pathophysiology of AAN using human renal proximal tubule epithelial cells (RPTEC’s).

Methods: Confluent RPTECs were exposed to AA (50 µM – 480 µM) for 24 – 48 hr and cytotoxicity was measured using lactate dehydrogenase (LDH) assay. RNA and protein were isolated from AA-exposed and unexposed RPTECs. Real time RT-PCR was performed for various gene primers to evaluate the role of innate immunity in AAN development.

Results: At 240 µM after 48 hr exposure, AA induced significant cytotoxicity in RPTECs as measured by LDH release in the culture medium and significant cell injury was observed morphologically. AA significantly increased mRNA expression of acute kidney injury (AKI) biomarker neutrophil gelatinase-associated lipocalin (NGAL), but at the same time significantly decreased the expression of another AKI biomarker kidney injury molecule 1 (KIM-1). AA also significantly upregulated the expression of prominent AKI-related TLRs (TLR2, TLR4 and TLR6) and their adaptor molecules (MyD88 and TICAM-1) followed by the activation of pro-inflammatory cytokines (IL-6 and TNF-α) and the tumor suppressor protein and a biomarker for apoptosis, p53, in the down-stream signaling pathways of TLRs. AA also significantly upregulated expression of multi drug resistant family gene MDR1 in RPTECs.

Conclusions: AA is toxic to RPTECs and restricts cell growth. NGAL but not KIM-1 could be a diagnostic biomarker for AAN. AKI prominent TLR2 and TLR4 could be potential candidates for therapeutic target in developing new strategies for AAN and BEN treatment.

PUB002 A Case of Severe Symptomatic Iatrogenic Hypermagnesemia

Rohan V Mehta,1 Vandana Niyyar,1 Rahul Mehta.2 1 Renal Medicine, Emory, Atlanta, GA; 2 Hospital Medicine, UVA, Charlottesville, VA.

Background: Hypermagnesemia is an uncommon but a potentially life threatening condition. Symptoms may develop in patients with acute kidney injury (AKI) or chronic kidney disease with the administration of pharmacologic dose of magnesium (Mg), and with use of oral laxatives or magnesium containing enemas.

Methods: A 30-year-old African American man with baseline Cr of 1, admitted for management of multiple fractures, sub adrenal hemorrhage and traumatic brain injury sustained in a motor vehicle accident, suddenly became hypotensive and developed AKI. UOP declined from 2-3 ml/day on admission to 700 ml over the next 24 hours. He became areflexic and developed ARDS, with increasing FiO2 requirements. Repeat laboratory data showed Cr 3.9, hemoglobin 6.9 and Mg 9.5 mg/dl. Review of his chart revealed he had received a total of 8.75g of magnesium citrate through enemas on the previous day. Aggressive resuscitation was started, including IV calcium, but he continued to require multiple pressors. Hypermagnesemia was presumed to be the cause of his ongoing hemodynamic instability. Intermittent hemodialysis was initiated for 2 hours to rapidly remove magnesium and he was then switched to CVVHD for continuous magnesium removal. Within 12 hours of RRT, pressor requirements decreased, UOP improved to 50-60 ml/hr and Mg levels ranged between 2-3 mg/dl. CVVHD was discontinued after 72 hrs and the patient had complete renal recovery to his baseline Cr of 1.

Results: Severe symptomatic hypermagnesemia can develop even with small doses of Mg containing laxatives. It prevents presynaptic acetylcholine release resulting in blockade of neuromuscular transmission. Clinical features of Mg toxicity range from delayed deep tendon reflexes, flaccid paralysis, respiratory failure, to hypotension, bradycardia, complete heart block and cardiac arrest. Management includes rapid supportive measures, fluids, IV calcium, loop diuretics. Urgent hemodialysis can rapidly reverse shock and respiratory failure preventing significant morbidity and mortality.

Conclusions: In summary, we report a case of severe hypermagnesemia, in the setting of AKI, presenting with shock and respiratory failure, requiring RRT.

PUB003 Ischemic and Non-Ischemic Acute Kidney Injury Cause Gut Damage

Tao Jiang Li, Chen Yu. Nephrology Dept, Shanghai Tongji Univ, Tongji Hospital, Shanghai, China; Nephrology Dept, Shanghai Tongji Univ, Tongji Hospital, Shanghai, China.

Background: Chronic uremia induced gut injury has been well documented in a number of studies. However, remote effects of acute kidney injury(AKI) on the intestine are far less investigated. Here we studied whether the gut also suffers damage during inducing of renal ischemia–reperfusion in rats and compared this to bilateral nephrectomy.

Methods: To test our hypothesis, six groups of SD rats (n=6 in each group) were studied: 1) sham operation for 6h; 2) ischemic AKI for 6h (60 min of renal pedicle clamping and then reperfusion for 6h); 3) bilateral nephrectomy for 6h; 4) sham operation for 24h; 5) ischemic AKI for 24h/60 min of renal pedicle clamping and then reperfusion for 24h; 6) bilateral nephrectomy for 24h. Ilium and blood were collected. The damage of gut mucosa was assessed by histological staining. Malondialdehyde(MDA) and apoptosis of the ileum were measured to determine the underlying mechanism of the AKI-induced gut injury.

Results: We found histological evidence of ileum injury following both ischemia and bilateral nephrectomy. MDA, an index of lipid peroxidation, increased in both the renal ischemia and nephrectomy groups, suggesting activation of oxidative stress. Ileum apoptosis, which was quantified by histone-associated DNA fragmentation enzyme-linked immunosorbent assay, were increased after 6 and 24 h of renal ischemia or nephrectomy.

Conclusions: Our study shows that acute kidney ischemia or renal failure activates oxidative stress and promotes apoptosis, and tissue damage in gut. Whether the AKI induced-gut injury by itself is sufficient to provoke systemic inflammatory response need further investigation.

Funding: Government Support - Non-U.S.

PUB004 Serum from Rats with Acute Kidney Injury Contains Reactive Oxygen Species Generating Activity That Causes Oxidative Stress In Vitro

Jon D Ahlstrom,1 Zhuma Hu,1 Nicole Molin,1 Christof Westenfelder.2 1 Medicine, Univ of Utah and VA Medical Centers, Salt Lake City, UT; 2 Physiology, Univ of Utah and VA Medical Centers, Salt Lake City, UT.

Background: The uremic state that is induced by Acute Kidney Injury (AKI) adversely affects multiple organ systems by mechanisms that are still poorly characterized, including those reactive oxygen species (ROS).

Methods: Serum was obtained from rats 24 hrs post ischemia/reperfusion-AKI (50 min bilateral pedicle clamp, AKI serum), and control sera was obtained from rats 24 hrs following SHAM surgery (SHAM serum), or from rats 24 hrs post bilateral nephrectomy (NPHX serum). Serum samples were evaluated for ROS activity with the sensitive Amplex Red H2O2 assay. For in vitro assay, NRK cells (normal rat kidney cells, proximal tubular) or rat mesenchymal stem cells (MSC) were cultured in rat serum for 48 hrs, and then assessed for gene expression, GSH levels, and oxidative stress markers.

Results: Compared to SHAM or NPHX serum, serum from rats with AKI had increased amplex red activity compared to SHAM and NPHX serum controls. Adding catalase to rat serum reduced—but did not eliminate—the ROS activity of AKI serum in a dose-dependent manner. The ROS generating properties of AKI serum were completely destroyed by strong (90 °C for 1 hr) but not mild (45°C for 30 min) heat inactivation. Culturing normal rat kidney cells (NRK, proximal tubular) or rat mesenchymal stem cells (MSC) in 10% AKI serum (compared to SHAM or NPHX serum) resulted in increased oxidative stress, including increased anti-oxidant gene expression (HO-1, catalase), increased GSH levels, and increased cellular ROS (as measured by DCFDA and Amplex Red) and induced apoptosis of the injured kidney releasing heat-sensitive factors into the blood stream (like cytokines and mediators that affect renal tissue and distant organs). The Amplex Red H2O2 assay provides a useful tool for the determination and mechanistic dissection of the ROS activity found in AKI serum.

Funding: Veterans Administration Support

PUB005 Properdin Deficiency Enhances Renal Ischemia Reperfusion Injury in Mice

Zinah Dhevaia Zwaan,1,3 Nigel J. Brunskill,1 Hans-Wilhelm Schwaebel,1 Cordula M. Stover,1 Bin Yang,1,2,5 Infection, Immunity and Inflammation, Univ of Leicester; 2 Renal Group, Univ Hospitals of Leicester; 3 College of Medicine, Univ of Kafur, Iraq; 4 Basic Medical Research Centre, Medical school of Nantong Univ, China; 5 Nephrology, Affiliated Hospital of Nantong Univ, China.

Background: Properdin is the only positive regulator of the alternative pathway of complement activation via stabilizing C3bBb convertase. Properdin has been detected on proximal tubular epithelial cells associating with proteinemic renal damage. Previous studies showed that mice with combined deficiencies of properdin (P−/−), DAF and CD59, the negative regulators of complement activation, had less renal ischemia reperfusion injury (IRI), in 24 hours.

Methods: P−/− mice (n=9) and their wildtype (WT) littermates (n=7) were used to assess the role of properdin in renal IRI. Ischaemia was induced by bilateral clamping of the renal pedicle for 30 minutes followed by 72-hour reperfusion using normal (n=2) and sham operated mice (n=4 or 5) as controls.

Results: Renal IRI was successfully induced in the WT and P−/− mice with more prominent injury in P−/− mice as evidenced in renal function. Serum creatinine was significantly increased after IRI compared with the sham groups, which was further increased

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

Underline represents presenting author.

886A
in P4 in relation to WT mice (1.78±0.29 vs 1.19±0.18, P=0.046) post IRI. Similarly, blood urea nitrogen in IRI mice was higher than the sham animals, with significant increase in P4 in comparison with WT mice.

This difference was supported by histological examination, in which P4 mice showed a worse score of tubulointerstitial damage than WT (2.67±0.26 vs 1.94±0.22, P=0.025) post IRI.

Conclusions: This study shows, for the first time, that properdin deficiency alone enhances IRI shown by worsened renal function and histology. The underlying mechanisms for these unexpected phenotype are under present investigation.

Funding: Government Support - Non-U.S. 

PUB006

Neurogenic Function of Neurons with Renal Afferents Is Altered by Lipopolysaccharides -LPS Kristina Rodionova,1 Martin Ziemer,2 Tilman Ditting,1 Stefan Karl,1 Sonja Heinlein,1 Peter Linz,1 Peter Reeh,1 Kerstin U. Amann,2 Roland Veelken.1 1Dept of Medicine 4 - Nephrology and Hypertension, Universitaetsklinikum Erlangen-Nuernberg, Erlangen, Bavaria, Germany; 2Dept of Nephropathology, Universitaetsklinikum Erlangen-Nuernberg, Erlangen, Bavaria, Germany; 3Dept of Physiology and Pathophysiology, FU Erlangen-Nuernberg, Erlangen, Bavaria, Germany.

Background: Renal afferent nerves (RNs) exert complex neurogenic sympathomodulatory and paracrine effects. Recently, we could demonstrate that lipopolysaccharide (LPS) sensitized TRPV1 receptors and increased the release of CGRP from afferent axons in kidney. Hence, we wanted to test the hypothesis that LPS alters firing patterns and acid induced inward currents in cultured neuron sample.

Methods: Dorsal root ganglion neurons (Th11-L2) of rats were incubated with LPS (E.coli O127:B8, 20ng/ml) 12h before patch clamp recordings. Inward currents were assessed during stimulation of TRPV1 and ASICs with protons (pH6.9 and 5.0). Current clamp mode was performed at physiological conditions and after 12h of LPS-incubation. Neurons were defined as tonic, i.e. sustained AP firing or phasic, i.e.<5 APs in response to current injections.

Results: Firing patterns and currents induced by acidic superfusion were studied in 246 neurons. Renal neurons (RNs) exhibited in 59% tonic firing pattern under control conditions. The number of neurons with tonic response was significantly reduced by exposure to LPS (59% vs.42%, p<0.05). Under control conditions 70.8% of RNs exhibited both sustained and transient inward current, whereas 29.2% showed sustained current. LPS exposure significantly increased sustained,i.e. TRPV1 induced current (79.13±1.46pA vs. 122±4.29± 200pA, p<0.05) and transient, i.e. ASICs induced inward current even under subthreshold proton stimulation (pH6.9) and could not be enhanced further by pH5.0.

Conclusions: LPS altered the properties of neurons with renal axons in a complex way, while the ease of AP production was significantly decreased, the responsiveness to acidic proton stimulation (pH6.9) and could not be enhanced further by pH5.0.

Funding: Other NIH Support - Germany, Bavaria, Erlangen

PUB007

Protective Effect of Nitric Oxide in Aristolochic Acid-Induced Toxic Acute Kidney Injury Ines Jado,1 Anne-Emilie Declives,2 Vanessa Colombo,1 Blanche Martin,1 Isabelle Habsch,1 Eric De Prez,1 Joel L. Nordt,1 Nathalie Caron.1 1Molecular Physiology Research Unit - URPHYM, Faculty of Medicine, Univ of Namur, Namur, Belgium; 2Laboratory of Experimental Nephrology, Faculty of Medicine, Univ Libre de Bruxelles, Brussels, Belgium.

Background: Aristolochic Acid (AA) nephropathy is a pertinent example of tubulo-interstitial (TI) nephritis characterized by an early phase of acute kidney injury (AKI) leading to progressive fibrosis and chronic kidney disease (CKD). Nitric oxide (NO) has been shown to play a critical role in the AKI-to-CKD transition. Here, the AAN model was used to determine the role of NO in this process, focusing on the acute phase.

Methods: C57Bl/6j male mice were randomly assigned to daily i.p. injection of control solution or AA (3.5mg/kg) for 4 days and L-Arginine (L-Arg; substrate for NO synthesis) was supplemented in drinking water (5%) until mice were euthanized, 5 days after the beginning of AA injections.

Results: At day 5, AA-treated mice displayed polyuria, increased plasma creatinine level and proteinuria. In addition, histochemical analyses revealed severe proximal tubular cell necrosis, renal inflammation and increased oxidative stress in AA-treated mice. These changes were associated with a significant reduction of NO bioavailability, as attested by urinary NOx and eGMP levels. L-Arg supplementation in AA-treated mice significantly improved kidney function, as reported by a significant reduction in urine volume, plasma creatinine level and proteinuria. Moreover, L-Arg treatment resulted in a significant reduction of tubular cell necrosis, renal inflammation and oxidative stress. These were concomitant to normalized NO levels.

Conclusions: Our findings demonstrated that sustaining NO bioavailability due to L-Arg supplementation improve the renal outcome of AA-induced AKI phase. Further investigations are ongoing to determine whether increasing NO bioavailability can also prevent chronic injuries in the AAN model.

Funding: Veterans Administration Support, Private Foundation Support

PUB008

The Study of Curcumin-Loaded Nanoparticles against Renal Ischemia-Reperfusion Injury Function and Mechanism Yong Xu,1 Lili Zhong.2 Dept of Nephrology, Huaian Second Hospital, Huaian, Jiang Su, China.

Background: To study the effects of curcumin-loaded nanoparticles against ischemia-reperfusion renal injury, and to investigate its mechanism.

Methods: Synthesize controlled releasing curcumin-loaded nanoparticles by amphilic mPEG-PCL block copolymers and cultivated renal tubular epithelial cell (cell line HK-2) in vitro. HK-2 cells were divided into four groups: Control group; Ischemia reperfusion injury group (IRI group); Curcumin group (Cur group); Curcumin nanoparticle group (CurNP group). In each group, HK-2 cells viability was assessed by dimethyl-thiazol-diphenyltetrazoliumbromide (MTT) test. Apoptotic Cells were measured by Flow Cytometry. H2DCF-DA was used to detect intracellular generation of ROS. BCA were used to detect SOD activity and the Concentration of MDA. Protein levels of procaspase-3 were analyzed by Western Blot.

Results: Successfully constructed curcumin-loaded nanoparticles by amphilic mPEG-PCL block copolymers. Drug loading content(DLS) and encapsulation efficiency(EE) were more than other reports. Data indicated that incorporated Cur could be slow released from the core-shellstructureof polymermicroparticles. 2. CurNP can ameliorate ischemia-reperfusionrenal injury in vitro. 3. The protective effects of Cur-NP against ischemia-reperfusion renal injuries involved in the suppression of oxidative stress reaction.

Funding: Government Support - Non-U.S.

PUB009

Disruption of Polyamine Catabolism Reduces the Severity of Cisplatin Nephrotoxicity Kamyar A. Zahedi,1,2 Sharon L. Barone,1,2 Marybeth Brooks,1 Jie Xu,1 Manoocher Soleimani.1,2 1Dept of Internal Medicine, Univ of Cincinnati, Cincinnati, OH; 2Research Services, Veterans Affairs Medical Center, Cincinnati, OH.

Background: Platinum-based drugs (e.g. cisplatin) are used for treatment of many types of solid organ tumors. Cisplatin crosslinks the DNA, interferes with mitosis, activates the primary anti-tumor mechanism of cisplatin. Platinum-based drugs also cause oxidative cell injury, which may mediate their general toxic effects. Acute kidney injury (AKI), due to oxidative damage, is a major side effect of cisplatin that necessitates dose reduction or withdrawal from treatment thereby reducing the effectiveness of cancer therapy. We hypothesized that treatments that reduce the oxidative tissue damage caused by cisplatin lessen the severity of AKI without interfering with its anti-proliferative DNA damaging effects and obviate the need for dose reduction or drug withdrawal.

Methods: Cisplatin-AKI was compared in wild type and SSAT-KO mice using functional and molecular parameters. Mechanism of polyamine catabolism mediated-cell injury was assessed in cultured cells.

Results: The expression of polyamine catabolic enzymes, spermidine spermine-N1-acetyltransferase (SSAT) and spermine oxidase (SMO) increase in the kidney of cisplatin-treated mice. SSAT-KO mice are protected against tissue damage and renal dysfunction caused by cisplatin. Using cultured cells capable of inducible expression of SSAT, the effect of SSAT on the induction of endoplasmic reticulum stress and unfolded protein response (ERS/UPR). Our results indicate that up-regulation of polyamine catabolism in general, and enhanced production of SSAT in particular, activated the ERS/UPR.

Conclusions: These studies suggest that polyamine catabolism is involved in the mediation of cisplatin-AKI. These and our previous results indicate that the activation of polyamine catabolism causes cell injury through both genotoxic response and ERS/UPR pathways. Our studies suggest that short-circuiting or neutralization of toxic products of polyamine catabolism can be novel therapies that reduce the severity of cisplatin nephrotoxicity.

Funding: Veterans Administration Support, Private Foundation Support

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

Underline represents presenting author.
PB010

Protective Effect of NADPH Oxidase 4 Inhibition in Contrast Induced Nephropathy. Se-Hee Youn,1 Won Min Hwang,1 Sung-Ro Yun,1 Suyukyong Lee,2 Hee-Yeon Jung,2 Ji-Young Choi,2 Sun-Hee Park,2 Chan-Duck Kim,2 Yong-Lim Kim.2 1 Internal Medicine, Konyang Univ; Deajeon, Korea; 2 Internal Medicine, Kyungpook National Univ School of Medicine, Daegu, Korea.

Background: The objective of this study was to investigate the renoprotective effect of NADPH oxidase 4 (Nox4) inhibition in contrast induced nephropathy.

Methods: HK-2 cells were incubated with iohexol (nonionic low-osmolar radiographic contrast agent) at a concentration of 5mg/mL, 150mg/L for 2h. Cells were pre-exposed to GKT137831, a selective Nox1&4 inhibitor (Genkyotex, Switzerland), for 30 min before exposure to iohexol. Cell viability was measured at 0, 3 and 22h after removal of iohexol by ATP/luc assay. Apoptosis was investigated by caspase 3/7 activity assay. For ROS (reactive oxygen species) production was assessed by DHE assay, NADPH oxidase activity using the lucigenin-enhanced chemiluminescence method, and Nox3 expression by western blot and real time PCR.

Results: Nox3 protein expression significantly increased at 30 min after iohexol exposure. GKT137831 pre-exposure showed significantly less cytotoxicity at 3h after removal of iohexol. Caspase 3/7 activity was significantly lower in GKT137831 pre-exposed cells than only iohexol exposed cells at 22h after removal of iohexol. ROS generation was higher with only iohexol exposed cells compared to GKT137831 pre-exposed cells.

Conclusions: A selective Nox4 inhibition induced fewer cytotoxic effects on cultured HK-2 cells than iohexol along with a lower induction of Nox4-dependent ROS generation. This enzyme may represent a potential therapeutic target to prevent iodinated radiographic contrast media related oxidative stress.

PB011

Autophagy Increased in the Early Stage of Rat Acute Kidney Injury Model Junyi Liu,1 Xing Mao,1 Yiwen Shen,2 Huijuan Wu,1 Aimin Xue.1 1 Department of Forensic Medicine, Shanghai Medical College, Fudan University, Shanghai, China; 2 Department of Pathology, Shanghai Medical College, Fudan University, Shanghai, China.

Background: Acute kidney injury (AKI) is a major kidney disease without effective therapies, and thus associated with a high mortality. The pathogenesis of AKI is very complex and still unclear. Recently, researches have shown the induction of autophagy in proximal tubular cells and kidneys during AKI. In this present study, we investigated the role of autophagy in the pathogenesis of rat renal ischemia-reperfusion (IR) model which causes AKI.

Methods: All male Sprague-Dawley rats were subjected to clamping of bilateral renal artery only for 25 min except sham group, and then they were randomly divided into four groups based on different reperfusion time point, including 3h, 6h, 12h and 24h. The Sham group underwent surgical procedures without ischemia as the control. Results: The level of blood urea nitrogen (BUN) and serum creatinine were increased from 3h after IR. By H&E staining, protein casts were found at 3h after IR, which kept increasing at 6h and 12h after IR. At 24h after IR, we found some necrotic proximal tubules. Immunohistochemistry showed the protein level of Beclin-1 and Vps34 and the ratio of LC3 II/I was increased from 3h after IR, which was confirmed by electron microscopy showing the formation of autophagic vacuoles in proximal tubule cells. Moreover, immunohistochemical staining clearly showed an increasing positive staining of Vps34 and LC3 at 3h after IR compared to the control.

Conclusions: Taken together, our results demonstrate the occurrence of autophagy in the very early stage of rats AKI model. Funding: Government Support - Non-U.S.

PB012

The Previous Cardio Exercise (Exe) Normalizes Renal Function of Wistar Rats Subjected to Acute Kidney Injury by Ischemia, and Reperfusion Welsey Vicente Ling, Waldemar S. Almeida, Nestor Schor. Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.

Background: The acute kidney injury (AKI) is characterized by acute reduction of renal function and has a high mortality rate in hospitalized patients and in severe cases may progress to chronic kidney disease (CKD). The AKI by ischemia and reperfusion (IR) causes tubular damage mainly in the proximal convoluted tubule, reducing mitochondrial activity in renal cell and increasing the reactive oxygen species (ROS). It is known that aerobic Exe lower blood pressure (BP), slows the heart rate (HR), improves muscle aerobic capacity, increases both the number and size of muscle mitochondria, however little is known about the effects of the previous Exe in AKI. We suspect that aerobic Exe may be a non-pharmacological resource in the prevention of AKI. Thus, we investigated the effect of previous aerobic Exe on renal injury resulting from IR. To evaluate the effects of the previous aerobic Exe on renal function in Wistar rats subjected to IR.

Methods: We used male Wistar rats with 10 weeks of life and they were separated into two groups Sham clamp (SC) and trained control clamp (TC), moreover the TC were subjected to a prior physical training protocol for four weeks. After completed 14 weeks each group, was subjected to ischemia injury by I/R, the rats were sacrificed in 24 hours after that they were placed in metabolic cages for 24 hours. We evaluate renal function (serum creatinina and proteinuria). Then they will be realized: renal morphological study by light microscopy and mitochondrial (number and size) by electron microscopy. Finally, we will evaluate apoptosis through caspases 3 activity.

Results: The SC group increased weight compared to the TC group (399±536±5g, P<0.05). Proteinuria was significantly different in SC vs. TC group (25.62±4.9±14.5±1.65 mg/24h, P<0.05). Now the creatinina serum showed significant difference in SC vs TC group (0.3±0.8 vs 0.6±0.6 mg/dl; P<0.05). We evidenced that SC group had a damage renal function after 48 hours recovery.

Conclusions: The results of this study are preliminary in nature, but suggest that the previous aerobic Exe can be renoprotective in the model I/R.

PB013

Angiogenin Mediates a Non-Cell Autonomous Response to Endoplasmic Reticulum Stress in the Kidney. Nicolas Palles,1 Danny Anglichean,2 Eric Thertev,1 Iadh Mami.1 1 INSERM U1147, Paris, France; 2 Nephrology, Georges Pompidou European Hospital, Paris, France; 3 Nephrology, Necker Hospital, Paris, France.

Background: Endoplasmic Reticulum (ER) stress is involved in the pathophysiology of kidney diseases, but the molecular basis of its biological outputs remain to be established. Angiogenin (ANG), a secreted ribonuclease, is a previously unappreciated component of the mammalian stress response that acts both in cell-autonomous and non-cell autonomous fashions to promote tissue adaptation to injury. Whether ANG signaling is a genuine component of the ER stress response is currently unknown.

Methods: In the present study, we explored the molecular mechanisms by which ANG is secreted under ER stress, and determined how it contributes to the modulation of the inflammatory microenvironment.

Results: Our results indicate that i) ANG secretion is specifically induced during ER stress and ii) this mechanism is under the selective control of IRE1a signaling. We demonstrate that ANG canonical secretion is induced upon ER stress, similar to the pro-inflammatory cytokine IL-6, and as such might play an immunomodulatory role in macrophage activation. These data are relevant to human disease since we identified ANG as a urinary marker of immune-mediated acute kidney injury.

Conclusions: Collectively, our data identify ANG as a key mediator of ER stress-dependent inflammatory response in kidney diseases, and is a potential non-invasive biomarker of acute kidney injury.

PB014

Sustained Infiltration of Th17 Cells Is Associated with Pulmonary Fibrosis in Rats with Salt Induced CKD Secondary to Renal Ischemia Purvi Mehrotra, Jason Andrieu Collett, David P. Basile, Dept of Cellular and Integrative Physiology, Indiana Univ of Medicine, Indianapolis, IN.

Background: Acute kidney injury (AKI) is associated with high mortality rates and is a leading cause of prolonged hospitalizations. The high risk of death is due in part to distant organ damage (e.g., lungs, heart, brain). It is well established that experimental AKI induced by renal ischemia and reperfusion (IR) induces an increase in pulmonary inflammation. Despite various immune cells like T cells as early as 24 hours post surgery, which may alter endothelial barrier function in the lung. However, the long-term effect of injury induced pulmonary inflammation on lung function and structure and function is not known. We hypothesize that T cells infiltrate into the lung post kidney injury with potential effects on pulmonary structure.

Methods: SD rats were subjected to a model of AKI-to-CKD in which rats are allowed to recover from unilateral I/R (40 min ischemia) for 5 weeks on normal salt diet (0.4% NaCl) and then subjected to contralateral UNX and 4% NaCl diet for 4 additional weeks. Consistent with prior reports, infiltration of CD4+ T cells were detected as early as 24 hours post surgery in the BAL fluid, and these were shown to be predominantly of Th17 phenotype (63±10.1, p<0.05). Interestingly, Th17 cells persisted in the lungs even after 5 weeks of post surgery after resolution of kidney injury (2.3X10³±0.1, p<0.05), when compared to sham (0.5X10³±0.3). Exposure of rats to high salt diet to hasten CKD further increased the number of Th17 cells in the lungs (4.1X10³±0.23, p<0.05). There was a corresponding increase in pulmonary fibrosis in post-AKI rats on high salt relative to sham-controls.

Conclusions: Taken together, these data suggest that AKI leading to CKD is associated with pulmonary fibrosis, an activity that may be due in part to the infiltration of Th17 cells into the lung and influenced by dietary salt.

Funding: NIDDK Support

PB015

Endothelial-to-Mesenchymal Transition and Endothelial Cilia in EPC-Mediated Postischemic Kidney Protection. Daniel Patschan, Susann Patschan, Gerhard A. Mueller. Clinic of Nephrology and Rheumatology, Dept of Internal Medicine, Göttingen, Niedersachsen, Germany.

Background: AKI increases the risk for CKD. Ischemia induces peritubular capillary rarefication and interstitial fibrosis with the latter partly resulting from mesenchymal transitions of renal cells (EndoMT). Endothelial cilia are mechanosensory organelles responsible for transmitting forces of the blood flow into the cell. Early Endothelial Progenitor Cells (eEPCs) have reproducibly been shown to protect mice from AKI in the short-term. Aim of the study was to analyze mid-term consequences of eEPC treatment of murine AKI. Our special interest focused on dynamics of endothelial cilia and EndoMT.

Methods: Male, 8-12 weeks old C57/Bl6N mice were subjected to unilateral renal ischemia (40 post-uniphenectomy). Syngeneic murine eEPCs (0.5X10⁶) were injected once at the time of reperfusion. Animals were investigated 1, 4, and 6 weeks later (renal function,
fibrosis, EndoMT, endothelial alpha-Tubulin). Cultured mature endothelial cells (ECs) were exposed to cisplatin, and the expression decreased, and the transfection groups decreased more obviously. After incubated with cisplatin, h-2 expression of HKC cells decreased obviously and the expression increased when ADSCs were cultured, and co-transfection group was more obviously. After incubated with cisplatin, IL-6 and RANTES were significantly increased in the cisplatin group. The inflammatory factors were determined when ADSCs were cultured, and decreased more obviously in gene transfection group.

Conclusions: EPO has the protective effects on the damaged cells and CXCR4 could promote the migration of stem cells to damage sites. Double genes transected to ADSCs may enhance the protective effect on HKC cells injury.

Funding: Government Support - Non-U.S.

PUB018

The Role of Endosialin in Renal Ischemia-Reperfusion Injury Chin-Hee Liu, Fangming Liu, Shuang-Yang Zheng, Yunchao Long, Yu Zhang, Yonggang Liu, National Taiwan Univ College of Medicine, Taipei, Taiwan; 2)Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.

Background: Many studies reported that Endosialin deficiency can attenuate the inflammation, fibrosis or growth, invasion and metastasis of tumors. It is highly expressed during embryonic development, but largely absent in adult tissue except kidney and uterus. We are intrigued by the role of endosialin in the acute kidney injury.

Methods: We performed unilateral nephrectomy and then ischemia-reperfusion injury to induce acute kidney injury in the endosialin-deficiency (lacZ knock-in) and littermate wild type mice. Plasma levels of blood urea nitrogen and creatinine were analyzed at day 2.5 and 10 after injury. We analyzed the cells expressing endosialin, tubulointerstitial injury, and specific cells by X-Gal staining. Periodic acid-Schiff staining and immunohistochemistry respectively.

Results: Positive X-Gal staining was shown in the glomeruli, small arteries and interstitial cells of the kidney. The capillary density determined by CD31 staining did not show significant difference between endosialin-deficiency and wild type mice. Nephrectomy and ischemia-reperfusion injuries led to marked elevation of plasma blood urea nitrogen and creatinine in wild type mice, however, the elevation of plasma blood urea nitrogen and creatinine was less in endosialin-deficiency mice at day 2 after injury. Interestingly the protective property of endosialin deficiency was lost since day 5 after injury. Conclusions: Endosialin-deficiency can attenuate acute kidney injury induced by ischemia-reperfusion injury, but the protective property is lost during the repair/regenerative phase after acute injury. The protective property of endosialin deficiency is not related to capillary density which has been shown increased in previous study. Further study needs to elucidate the mechanism underlying the protective property and why the protective property is lost during repair/regenerative phase.

Funding: Government Support - Non-U.S.

PUB019

The Mechanism of β2-Adrenergic Receptor/Protein Kinase A Signal Transduction Pathway in Restoration of Acute Kidney Injury by Endothelial Progenitor Cells Ying Zhou, Chen Yu. Dept of Nephrology, Tongji Hospital, Tongji Univ, Shanghai, China.

Background: Endothelial progenitor cells (EPCs) could improve renal microenvironment, stimulate endothelial repair and angiogenesis, and promote AKI restoration. However, the molecular mechanism has not been elucidated. In this study we investigated the role of β2-adrenergic receptor (β2-AR) and its downstream factors (protein kinase A, protein kinase B, protein kinase C) in restoration of acute kidney injury by EPCs.

Methods: The model of ischemia-reperfusion acute kidney injury (I-R AKI) was used in vivo, while sham operation was performed in control group. Renal tissue was collected at day 7. Renal histology was measured by HE staining. The expression of β2-AR was examined using Q-PCR and immunofluorescence staining. The specific antigens on surface of EPCs(CD34 and VEGFR-2) were examined using Q-PCR and immunofluorescence staining in I-R AKI group; while neither appeared in control group. Results: I-R AKI caused significant positive-correlations between VEGFR-2 and CD34(p=0.005), VEGFR-2 and α-SMA(p=0.04) at week 1, and the correlation increased at week 4. PKA levels were not significantly different between groups, and PKA was significantly higher expressed in I-R AKI group than in control group(p<0.05). The protein levels of PKB and PKC were not detected. According to Pearson's correlation analysis, there were positive correlations between VEGFR-2 and PKA(p=0.005), VEGFR-2 and PKB(p=0.005), CD34 and β2-AR(p=0.05), β2-AR and PKA(p=0.05).

Conclusions: When I-R AKI occurred, the mRNA levels of specific antigens on surface of EPCs(CD34 and VEGFR-2) were significantly up-regulated, which suggested that I-R AKI might induce EPCs homing to kidney. At the same time, the mRNA levels of β2-AR and PKA were significantly up-regulated, and most of them were positive-correlated, which suggested that β2-AR/PKA pathway may play a role in the restoration of AKI by EPCs.

Funding: Government Support - Non-U.S.

PUB007

Effect of Double Genes Transfected Adipose-Derived Stem Cells on Cisplatin-induced Renal Tubular Epithelial Cells Injury Nannan Li, Jinmin Hospital of Shanghai.

Background: To observe the effects of adipose-derived stem cells (ADSCs) transfected with CCRX4 and EPO genes on renal tubular epithelial cells (HKC) injury.

Methods: To construct lentivirus expression system consisting of CCRX4 and EPO genes and transfected the system to adipose-derived stem cells (ADSCs), which co-culture with the cisplatin-induced HKC for 48 and 72 hrs. CCK8 detected cell proliferation of HKC. HKC were co-cultured with adipose stromal cells, and cell migration was assayed. Western blot detected the expression of apoptosis proteins in HKC. ELISA detected the expression of inflammatory cytokines in culture medium.

Results: No significant changes were observed in the morphology of ADSCs after gene transfection, and the optical differentiation ability were not affected. Adipose co-cultured the inhibitory effect of cisplatin on HKC cell proliferation was alleviated. Compared with the control group, the migration index of ADSCs was increased after co-culturing with cisplatin-induced HKC, and the gene transfection group were increased significantly as the extension of the culture time, indicating that the target gene transfection can promote the ADSCs migration to the damaged parts. Incubation with cisplatin, HKC cells EPO-R protein expression decreased. After co-culturing with ADSCs, the EPO-R expression increased. After incubated with cisplatin, the expression of Caspase-3, Bax expression in HKC cells increased significantly, which mediates the apoptosis. After co-cultured with ADSCs, the cisplatin-induced HKC cell proliferation decreased, and the transfection groups decreased more obviously. After incubated with cisplatin, h-2 expression of HKC cells decreased obviously and the expression increased when ADSCs were cultured, and co-transfection group was more obviously. After incubated with cisplatin, IL-6 and RANTES were significantly increased in the cisplatin group. The inflammatory factors were determined when ADSCs were cultured, and decreased more obviously in gene transfection group.

Conclusions: EPO has the protective effects on the damaged cells and CXCR4 could promote the migration of stem cells to damage sites. Double genes transected to ADSCs may enhance the protective effect on HKC cells injury.

Funding: Government Support - Non-U.S.
Alpha Lipoic Acid and Dexamethasone Counteract Contrast Media-Induced Proximal Tubule Cell Dysfunction Hayriye Savariloglu,1 Ali Okuyucu,2 Abdulkerim Bedir,3 Osman Salis,4 Eser Yenen,2 1Dept of Nephrology, Ondokuz Mayis Univ Medical Faculty, Samsun, Turkey; 2Dept of Medical Biochemistry, Ondokuz Mayis Univ Medical Faculty, Samsun, Turkey. Background: Contrast medium induced nephropathy (CIN) is one of the most common cause of hospital-acquired acute renal failure. But its pathogenesis is unclear. In this study, we observed the effect of iopromide, low osmolar contrast medium, on tubular cells in HK-2 cell line.

Methods: We observed the effect of iopromide, low osmolar contrast medium, on tubular cells in HK-2 cell line. First, we examined the effects of different doses of iopromide (10, 20, 40 and 80 mg/ml iodine) on proliferation of HK-2 cells by the real time cell analyzer (RTCA). According to the results of RTCA we examined whether the non-toxic doses of iopromide (10 and 20 mg/ml iodine) is causing of the EMT by scratch assay for 20 h. We also observed whether alpha lipoic acid (0.5 mM) and dexamethasone (5 μg/ml) is preventing to EMT in this assay.

Results: We observed whether alpha lipoic acid (0,5 mM) and dexamethasone (5 μg/ml) is preventing to EMT in this assay. Although cytotoxic effect was observed for iopromide with concentration of 80 mg/ml iodine, the iopromide with lower doses did not show any effects for HK-2 cells. In scratch assay, we observed that the non-toxic doses of iopromide (10 and 20 mg/ml iodine) is causing of the cell migration which an indicator of EMT and lipoic acid and dexamethasone prevent the cell migration.

Conclusions: In conclusions, the EMT caused by contrast medium is prevented or reduced by dexamethasone and lipoic acid in HK-2 cells. This result suggest that dexamethasone and lipoic acid may be a potential treatment to prevent the development of CIN in individuals with high-risk.

Contribution of Proliferating Endothelial Cells for Endothelial Repair After Site Specific Endothelial Injury of the Mouse Kidney Jan Sradnick, Anika Luedemann, Vladimir T. Todorov, Christian Hugo, Bernd Hohenstein. Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CCG, Dresden, Germany. Background: Our previous studies have shown that renal endothelial cell regeneration occurs exclusively via local mechanism. To further dissect the relevance of local mechanisms for endothelial repair, we now investigated the contribution of local endothelial cell proliferation in the kidney in our model of site selective endothelial injury (ECI).

Methods: Selective ECI was induced in 9 out of 15 mice by renal arterial perfusion with Concanavalin-A (ConA)-anti-ConA, while 6 mice served as sham operated controls. Edu (15μg/g), a marker of proliferation, was injected starting 24hours after ECI every 12hours intraperitoneally. Kidneys were harvested on day 7 and Edu+ cells were analyzed using flow cytometry and histology. Endothelial cells were stained using CD31, CD105, CD34 and CD36 and hematopoietic cells were detected as CD45+. Inflammatory cells (macrophages, dendritic cells and neutrophils) were analyzed via GR1, CD11c, CD11b and F4/80 positivity. By histology, proliferating EC were detected as anti-EC/EDU double positive cells.

Results: Significantly more Edu+ cells could be detected after ECI on day 7 (sh: 1.2%±0.7; ECI: 7.6%±4.8). Most of those Edu+ cells were positive for CD45 (65%±58) and 3% (sh) up to 7% (ECI) were positive for EC surface markers. In diseased kidneys more endothelial cells were found (sh: 5.5%±0.7; ECI: 7.3%±0.5; p<0.01). A larger amount of Edu+ EC was found in injured kidney (sh: 1.5±0.8 0160 cells; d7: 5%±1.5 0630 cells p<0.01). Histological analysis supported these findings. Glomeruli of ECI kidneys had more ERG/EdU+ cells (0: 0.23±0.16; d1: 1.22±0.06; p<0.01). Inflammatory cells in injured kidneys were slightly increased. Many macrophages (21%±13), neutrophils (38%±17) and dendritic cells (19%±13) were Edu+.

Conclusions: Enhanced endothelial proliferation was detected following ECI. Therefore EC proliferation reflects an relevant repair mechanism following site selective ECI. The further investigation of EC repair will have to dissect the contribution of the proliferative response by adult local EC from other contributors such as local progenitor cells.

Injury of Proximal Tubular Cells in Neonate Rats with Hypoxic-Ischemia Brain Damage Dong Li1,2 Mei Han1,2 1Dept of Medical Dept, Dalian Children’s Hospital, Dalian, Liaoning Province, China; 2Pediatric Internal Medicine Dept, Dalian Children’s Hospital, Dalian, Liaoning Province, China. Background: Proximal tubular cells play a critical role in renal injury. To investigate the consequence of mitochondria in renal proximal tubular cells after hypoxic-ischemia brain damage (HIBD) in rats and the apoptosis in it.

Methods: Neonatal (7 days old) Sprague Dawley rats were randomly divided into 2groups: sham group and operation group (n=5 per group). The Rice method was used for establishment of HIBD model, proximal tubular cells Mitochondria pathology and histology were examined under electron microscope at 1 day, 7days, 14days and 21days after the hypoxic-ischemic treatment, and apoptosis was analyzed by TUNEL.

Results: After the HIBD, the mitochondria of proximal tubular cells were showed damage under EM, some membrane and ridges were broken, the mitochondria bodies were swelling, and partial cristal fragmentation were observed from the 1day till 21days after. And the 21days was the most worst for mitochondria under EM. For the TUNEL, after HIBD, it showed significant increased for 1day, 7days, 14days and 21days groups comparing with sham group. (p<0.05).

Conclusions: After the hypoxic and ischemic brain injury of neonate rats, the mitochondria were damaged in proximal tubular cells, even in 21days after HIBD. And the apoptosis maybe one of the causes of this damage.

Funding: Government Support - Non-U.S.
Primary outcome. Patients who had used red blood cells had 3 times more risk of acute kidney injury as Predictor of Acute Kidney Injury in Patients Undergoing Cardiac Surgery

**Abstract Withdrawn**

**PUB025**

**Transfusion of Red Blood Cell as Predictor of Acute Kidney Injury in Patients Undergoing Cardiac Surgery**

Eudeseley Santana-Santos, Luiz Aparecido Bortolotto, Ludhmila Abramão Hajjar.

**ICU-Cardiac Surgery Postoperative Care, Heart Inst (InCor) Inst do Coração do Hospital das Clínicas da Faculdade de Medicina da Univ de São Paulo, São Paulo, Brazil.**

**Background:** The red blood cell transfusion in the perioperative period of cardiac surgery have been associated with acute kidney injury. Our purpose was to analyze the influence of transfusion of red blood cell in the incidence of acute kidney injury after cardiac surgery.

**Methods:** We performed a prospective cohort study carried out in a tertiary hospital specialized in Cardiology. Adult patients who had undergone elective myocardial revascularization surgery, valvular and aortic surgery and who had agreed to participate in the study were included. The primary endpoint was acute kidney injury defined by KDIGO criterion. Secondary outcomes was serious clinical complications defined according to the guidelines of the Society of Thoracic Surgeons.

**Results:** According to KDIGO criterion, the incidence of AKI was 46.5%. The mean age was 60±12 years old in the AKI group and 58±13 in the no AKI group (p=0.145) and mostly male (56%). The surgical risk assessed by EuroSCORE was greater in the AKI Group 5 (1-25) when compared to the no AKI group 4 (2-10), (p=0.047). There were no differences between the groups for the secondary outcomes. The use of red blood cells in the perioperative period (OR=3.166, p=0.001) and the presence of prior chronic kidney disease (CKD) (OR=2.027, p=0.036) was associated with AKI postoperatively.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p (value)</th>
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<tbody>
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<td>Cardiac Heart Failure</td>
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<td>Male gender</td>
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<td>0.395–1.469</td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>2.027</td>
<td>1.406–3.052</td>
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<tr>
<td>Red Blood Cell Transfusion</td>
<td>3.166</td>
<td>1.572–6.380</td>
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<tr>
<td>Use of Cardiopulmonary Bypass</td>
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</table>

During the period of hospitalization the mortality rate was 6.9%. When we compare the mortality rate between the groups it was 4.3% in the no AKI Group and 10% in the AKI Group (p=0.229).

**Conclusions:** In our study the use of perioperative red blood cells influenced the primary outcome. Patients who had used red blood cells had 3 times more risk of AKI.

Funding: Government Support - Non-U.S.

**PUB026**

A Picture Is Worth a Thousand Words: Simultaneous ATN, AIN, and Post Infectious GN

Ankur Shah, Rachel Criner, Jean Lee.

**Internal Medicine, Temple Univ Hospital, Philadelphia, PA; Nephrology, Temple Univ Hospital, Philadelphia, PA.**

**Background:** The differential diagnosis of hospital acquired acute kidney injury in its most general terms often is described as pre-renal, intrinsic, or post-obstructive. Further differentiating the intrinsic causes of AKI, we are given the differential of Acute Tubular Necrosis, Acute Interstitial Nephritis, Postinfectious Nephritis, and Glomerulonephritis. We present a case of a patient who presented with sepsis and developed acute kidney injury whose biopsy revealed a plethora of pathology.

**Methods:** We present a case of a 54 y/o male with a pmhx of only HTN and DJD who presented with leg pain and weakness for 2 weeks and hematuria found to be bacteremic with MSSA with L spine epidural abscess and bilateral psosas muscle abscesses. He developed acute kidney injury thought clinically and based on microscopy to be secondary to hypotensive acute tubular necrosis and was started on hemodialysis on HD6. He was being treated with cefadroxil and over weeks had minimal return of renal function. The differential diagnosis was revisited and concern for AKIN from the penicillin agent was raised, the patient was switched to Daptomycin, but remained RRT dependent. After 25 days on hemodialysis, a biopsy was obtained which revealed diffuse interstitial inflammation with eosinophils, focal mild-moderate tubular injury with vacuolization, as well as by electron microscopy, subepithelial deposits but not subendothelial deposits, most of which are largely absorbed, including in “notch” areas. These findings are consistent with an acute post-infectious glomerulonephritis, resolving stage; drug induced acute interstitial inflammation, as well as mild-moderate focal tubular injury.

**Conclusions:** This case demonstrates a variety of the potential causes of AKI. The patients course was long and provided multiple opportunities for re-evaluation and a return to the differential diagnosis process. This is an excellent case for the teaching of the fundamentals of medicine, as the differential diagnosis is truly the instrument of the master clinician. This patients aberrance from the expected course prompted reevaluation and his pathology was staggering.

**PUB027**

Monitoring and Follow-Up of Acute Kidney Injury Post-Discharge: Retrospective Case Review Series

Kosmas Papailiadis, Judith H. Veis.

1Medicine, Washington Hospital Center, Washington, DC; 2Nephrology, Washington Hospital Center, Washington, DC.

**Background:** AKI during hospitalization increases risk of progression to CKD and death upon discharge. Recent KDIGO guidelines suggest patients should be evaluated 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. We determined factors associated with whether patients with AKI had kidney function assessed 3 months post-discharge.

**Methods:** Retrospective chart review of hospitalizations in 2013 complicated by AKI, who had follow-up in Ambulatory Medical Clinic to assess discharge communication; serum Cr, urine protein/Cr at 3 and 4-9 months, 1 year outcomes including progression to CKD, death and referral to nephrology.

**Results:** 77 inpatients with AKI (48(66%) stage 1, 9(12%) stage 2, 20(26%) stage 3; and 8(8%) requiring RRT) had a post-discharge visit. Of these, 51(66%) had serum Cr and 1(1%) had urine protein/Cr checked by 3 months. For 4-9 months, 13(17%) had serum Cr and 5(6%) had urine protein/Cr checked; 3(4%) were deceased by 1 year. 26(34%) had normal kidney function pre-AKI and of this group, 10(38%) had CKD by 1 year. Of these 26, only 5(19%) were referred to nephrology. For documentation, 54(77%) had AKI as a problem in the inpatient hospital summary, 42(54%) had AKI documented in the brief outpatient hospital summary and 29(41%) had AKI addressed in the follow-up visit. There was no significant association between AKI severity, need for RRT, or documentation with checking kidney function by 3 months nor between AKI inpatient documentation and addressing AKI at follow-up (p<0.05). There were significant associations between addressing AKI at follow-up and checking kidney function: p=0.043 and between AKI stage and addressing AKI at follow-up: p=0.022 and between AKI outpatient summary and addressing AKI at follow-up: p=0.004.

**Conclusions:** Outpatient follow-up of inpatient AKI is inconsistent despite evidence of poorer outcomes and recent guidelines which suggest the need for closer monitoring. Improving transitions of care through more effective documentation and streamlined EMRs, as well as increasing primary care physician awareness could reduce the risk of progression to CKD and death.

**PUB028**

Late Recovery of Renal Function in Atypical Hemolytic Uremic Syndrome (aHUS) After Eculizumab Therapy

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2Internal Medicine, Temple University Hospital, Philadelphia, PA.

**Background:** A 33-year-old woman with hypertension and left renal agenesis presented with fever and acute kidney injury with serum creatinine of 2.1 mg/dL. Initially, hemoglobin was 11.3 mg/dL and platelets 193,000/ul. Over the next three days, platelets dropped to 55,000/ul and LDH rose to 770 U/L; renal function worsened. Thrombotic microangiopathy was suspected. Stool culture was negative. Urine protein was 6.8 g per 24 hours. Serologic assessment, including C3, C4, ANA, ANCA, HIV, cryoglobulins, dsDNA, lupus anticoagulant, anticardiolipin antibodies, and β-2-glycoprotein I antibodies, was unremarkable. The patient was being treated with cryo-poor plasma exchange and steroids. Hemodialysis was started for uremia. ADAMTS13 was 67% of normal. Renal biopsy included in “notch” areas. These findings are consistent with an acute post-infectious glomerulonephritis, resolving stage; drug induced acute interstitial inflammation, as well as mild-moderate focal tubular injury.

**Conclusions:** This case demonstrates a variety of the potential causes of AKI. The patients course was long and provided multiple opportunities for re-evaluation and a return to the differential diagnosis process. This is an excellent case for the teaching of the fundamentals of medicine, as the differential diagnosis is truly the instrument of the master clinician. This patients aberrance from the expected course prompted reevaluation and his pathology was staggering.

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

Underline represents presenting author.

891A
showed acute thrombotic microangiopathy, acute tubular injury, and moderate interstitial fibrosis. The presentation suggested the diagnosis of aHUS. Eculizumab, an anti-C5 antibody, was initiated at 900 mg weekly for four weeks followed by 1200 mg every two weeks. Eculizumab therapy resulted in resolution of hemolysis. Dialysis was continued thrice weekly. Eculizumab was continued every two weeks, and LDL and platelet counts remained stable. Twenty weeks after initial presentation, urine output increased, proteinuria decreased, and interdialytic weight gains were negligible. Pre-dialysis serum creatinine was 3.9 mg/dL, and a urine collection showed creatinine clearance of 30 ml/minute. She has remained off dialysis for twenty weeks, and latest serum creatinine is 3.4 mg/dL. Screening for complement genetic defects has been negative.

**Conclusions:** Experience with eculizumab is ongoing. Most patients with aHUS has a rapid hematologic response. If they need dialysis, then recovery of renal function is usually prompt; late recovery is rare. We hypothesize that sustained control of complement activation has ameliorated proteinuria and allowed renal remodeling and regeneration, even months later. Patients are at risk for relapse if they stop treatment. This case points out that the presumed genetic defect may require lifelong treatment, and that late recovery of renal function is possible with complement inhibition and supportive care.

**PUB029**

The Effectiveness of Thalidomide in Preventing Cisplatin Related Nephrotoxicity in Patients with Cancer

**Background:** Sixty patients who were planned administration of cisplatin for the first time were included in the study. Patients were divided into two groups as group 1 (n=30) (standard treatment arm) and group II (n=30) (thalidomine arm). Glomerular filtration rate (GFR), NGAL, cystatin C were measured at 3rd day in all of the patients. Also, these parameters were repeated measured at the adminstration of cisplatin, at 24th hour, 48th hour and 72nd day.

**Results:** In both groups after the administration of cisplatin, glomerular filtration rate (GFR) showed a significant decrease within time (p<0.001). Creatinine, in spite of the time, no significant difference was observed between groups and within time. After 2 hours of cisplatin administration, in spite of the difference in GFR, a significant decline was detected in serum creatinine (p<0.001). Urine NGAL was significantly high after 2 hours of cisplatin administration (p<0.001). No significant difference was observed between groups. However, when the time*group effects were considered together, higher NGAL was detected in the group not receiving thalidomide (p<0.025). After 5 days of cisplatin administration, urine protein levels were significantly higher in both groups (p<0.001).

**Conclusions:** Results showed that urine NGAL level is a superior biomarker compared to creatinine and cystatin C in the detection of early acute kidney injury. Thalidomide was found not to bring a complete protection for the kidneys, but less nephrotoxicity was developed when compared to the group not receiving thalidomide.
PUB033
Serum Neutrophil Gelatinase-Associated Lipocalin: A Novel Biomarker for Prediction of AKI Development in Critically Ill Patients
Maggdy M. Elsharkawy, Abdel Rahman Khedr, Amr Mohab, Haitham Ezzat.
Nephrology, Ain Shams Univ, Cairo, Egypt.

Background: Acute kidney injury (AKI) is a frequent complication in critically ill patients and is associated with high morbidity and mortality; therefore, its prophylaxis, diagnosis and intervention positively impact patient evolution. Neutrophil gelatinase-associated lipocalin (NGAL) is thought to be a novel biomarker of AKI of several etiologies and is increased in both serum and urine before the increase of serum creatinine.

Methods: A prospective cohort study was conducted on 100 critically ill patients in ICU. Patients were stratified into 2 groups based on AKI development. Group I which included 50 patients who did not develop AKI, and group II which included 50 patients who developed AKI. AKI was defined based on acute kidney injury network (AKIN) classification. The Sequential Organ Failure Assessment (SOFA) scores were also calculated for all patients. Detailed medical history, demographic data and routine laboratory investigations were done. Serum NGAL was measured upon admission to ICU and upon AKI development.

Results: 60 males and 40 females were included in the study with mean age 37.52 years. As regards risks of AKI development, 9% of patients had sepsis, 15% were dehydrated, 11% had contrast exposure, 12% had rhabdomyolysis, 29% had shock and 24% had history of NSAID intake recently. On admission, there were no significant differences between the patients as regards s.creatinine, hemoglobin level and other laboratory parameters (p > 0.05). Serum levels of NGAL were significantly higher in group II, before AKI development, with mean value 958.5 ng/ml, when compared with group I, mean value (p > 0.05). Serum NGAL was measured upon admission to ICU and upon AKI development. Sequential Organ Failure Assessment (SOFA) scores were also calculated for all patients. The finding that KDIGO Stage 2 means worst medium term survival for the AKI group needs further study.

PUB035
The Effect of Nebivolol on Contrast-Induced Acute Kidney Injury: A Meta-Analysis
Nasirizadeh, Charat Thongprayoon, Yisit Chemungpasitpon.

Background: Nebivolol provides protective effect on contrast-induced acute kidney injury (CI-AKI) in animal models. However, the reports on the efficacy of nebivolol for the prevention of CI-AKI in human remain unclear. The objective of this meta-analysis was to assess the effect of nebivolol for the prevention of CI-AKI.

Methods: Comprehensive literature searches were performed using MEDLINE, EMBASE, and Cochrane Database from inception through February 2015. Studies that reported relative risks, odds ratios or hazard ratios comparing the risk of CI-AKI in patients who received nebivolol versus those who did not were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Four studies (2 RCT and 2 cohort studies) with 543 patients were included in our analysis to assess the risk of CI-AKI and the use of nebivolol. Of 543 patients with contrast exposures, 30 patients (5.32%) had CI-AKI. Patients in the nebivolol group had an overall lower incidence of CI-AKI (14.3%) compared to the control group (17.43%). The pooled RR of CI-AKI in patients receiving nebivolol was 0.66 (95% CI, 0.38-1.15, I² = 0).

When meta-analysis was limited only to RCTs, the pooled RR of CI-AKI in patients receiving nebivolol was 0.70 (95% CI, 0.35-1.79, I² = 0). This finding suggests the need for further studies on the use of nebivolol in addition to standard IV crystalloid hydration in the prevention of CI-AKI.

PUB036
Patients with Cardiovascular Diseases Are Susceptible to Acute Kidney Injury After Non-Cardiac Surgery Under Preoperative Use of Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

Background: It is unknown in which subgroups of patients the preoperative use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) is a predictor for acute kidney injury (AKI) after non-cardiac surgery.

Methods: This is a retrospective cohort study on patients who underwent non-cardiac surgery from 2007 to 2009. After exclusion of urological surgery, missing creatinine values, and preoperative dialysis, the data for 2,725 patients were available. The exposure of interest was preoperative use of ACE-I/ARB. Primary outcome was postoperative AKI (AKIN criteria). The odds ratio (OR) of postoperative AKI among ACE-I/ARB users compared to non-users was analyzed using multivariable logistic regression models, adjusted for the logit of propensity score for ACE-I/ARB use. P < 0.01 was considered statistically significant for interaction.

Results: Mean(SD) age was 61(16) and estimated glomerular filtration rate was 81(24) ml/min/1.73m². There were 40(6.7%) cases of postoperative AKI in ACE-I/ARB users and 97(2.65) (4.3%) in non-users. The adjusted OR of AKI was shown.
History of cardiovascular diseases (CVD) (either coronary artery disease, stroke, peripheral arterial disease, atrial fibrillation, or left ventricular ejection fraction < 40%) was a significant effect modifier for the association of ACE-I/ARB use and AKI (p for interaction = 0.07). The OR (95% CI) of AKI among ACE-I/ARB users was 1.70 (0.73-3.93) and 0.72 (0.42-1.24) in patients with CVD and without CVD, respectively.

Conclusions: ACE-I/ARB use was associated with higher OR of AKI in patients with CVD compared to patients without, suggesting that patients with CVD are more prone to AKI with the use of ACE-I/ARB.

PUB037

Whole Ischemia–Reperfusion Injury: The Effect of Whole-Body Cooling on Renal Function
Silvia De Rosa,1 Zaccaria Ricci,2 Salvador Roberto Lopez,3 Jose Luis Salas,1 Stefano Marcante,1 Sara Samoni,1 Massimo de Cal,1 Silvia Maria Pulitano,2 Massimo Antonelli,2 Raffaele Bonato,1 Claudio Ronco.1
1IRRIF; 2Intensive Care Unit, UCSC, Rome; 3Paediatric Cardiac Intensive Care Unit, OBG, Rome.

Background: Hyperthermia is able to reduce the risk of renal failure after renal ischemia–reperfusion injury in animals. In humans, Cardiac Arrest (CA), a whole-body ischemia–reperfusion syndrome causes warm renal ischemia–reperfusion injury, similar to animal models of ischemic acute kidney injury (AKI). Induced hypothermia (IH) has a treatment potentially efficacious for post-ischemic injury. It is unclear what effect cooling could have on renal function. The aim of the study was to investigate the development of AKI during the IH.

Methods: Between Jan 2013 and Mar 2015, we performed a prospective observational study of 36 comatose pts resuscitated from CA and treated with IH performed with 2 different surface cooling devices: 1) Arctic Sun Temperature Management System (Medivance, Los Angeles, CA); 2) Blanket. Temperature rate and trend, and the development of AKI during the IH (0–6 hrs), maintenance (24 hrs), rewarming (48 hrs), and normothermia (72 hrs) was assessed with RIFE and KDIGO criteria.

Results: Pts were enrolled and followed for the development of AKI during intensive care unit stay. In the induction and maintenance phases, the rate and the target temperature were similar; conversely, the rewarming phase was shorter with a target temperature higher in Blanket than in Arctic Sun group (45.8 min vs 61 min; 37.2°C vs 36.3°C). The trend and rate of temperature, but also the development of AKI is showed in figure 1.

Conclusions: IH could be associated with development of AKI in the rewarming phase (rate 0.25 to 0.5°C). The optimal rewarming rate is unknown. Randomized controlled trials are needed to determine the real effect of temperature on kidney, the optimal rewarming strategy and applications of this treatment for kidney in other settings.

Funding: NIDDK Support

PUB038

Decongestion-Associated Worsening Renal Function Does Not Increase Mortality of Patients with Acute Heart Failure

Background: A significant subset of patients admitted for acute decompensated heart failure (ADHF) develop worsening renal function (WRF). While there is consistent data regarding the negative impact of baseline renal dysfunction on the outcomes of these patients, the evidence on the prognostic implication of WRF during admission for decongestion is less well-understood. The aim of this study is to provide a reappraisal of the effect of decongestion on the prognostic value of WRF in patients admitted for ADHF.

Methods: Articles cited in PubMed database from 1995 to 2015 using key words “congestion”, “heart failure”, “worsening renal function”, and “hemoconcentration” were searched. Those studies evaluating the relationship between decongestion, renal function, and ADHF in patients treated with diuretic-based conventional therapies were selected. Ultrafiltration trials were excluded. Relevant data including change in renal function, diuretic dose, change in weight, and mortality were extracted and compared.

Results: A total of 12,843 patients from 19 clinical trials (9 retrospective and 4 prospective) with data pertaining to decongestion in ADHF patients were included in this study. The mean age of the patients was 67.1 years with follow up periods ranging from 60 days to 5.3 years. Eleven studies reported development of WRF following decongestion. The incidence of WRF was reported to be 10 to 50.1% with weight reduction ranging from 2 to 5.4 kg. Twelve studies did not observe any negative impact for WRF on the mortality of patients with ADHF unless associated with markers of persistent congestion such as lack of hemoconcentration.

Conclusions: Decongestion is associated with markers of fluid removal and WRF in the setting of ADHF. Currently available data suggest that decongestion-associated WRF does not result in increased mortality whereas persistent congestion is likely to be the driving factor for adverse outcomes in these patients. Randomized controlled trials are needed to confirm these findings as they could portend significant therapeutic implications in cardiac syndrome.

PUB039

A 13-Year Mayo Clinic Retrospective Study of the Syndrome of Rapid Onset End Stage Renal Disease (SORO-ESRD) in an Incident Hemodialysis Cohort
Macaulay A. Onuigbo,1 Nnemia Agbasi,1 LaTonya J. Hickson,2 Medicine, Mayo Clinic College of Medicine, Rochester, MN; Nephrology, Mayo Clinic Health System, Eau Claire, WI; Psychiatry Nursing, North East London NHS Foundation Trust, London, United Kingdom.

Background: We first described the syndrome of rapid onset end stage renal disease (SORO-ESRD) in 2010 - acute yet irreversible ESRD after AKI. However, its overall impact on ESRD outcomes in the general US ESRD population remains speculative.

Methods: A retrospective examination of SORO-ESRD among the incident Mayo Clinic ESRD population, 2001-2013 was completed in November 2014.

Results: 149 of 1461 (10%) incident ESRD patients had SORO-ESRD – M:F = 76:73, mean age 62 years (19-95), 139 (93%) native kidneys, 10 (7%) kidney transplant recipients (RTRs). Ninety-nine percent of SORO-ESRD patients’ initial vascular access was a dialysis catheter. Kidney biopsy - the commonest pathologic diagnoses were acute tubular necrosis (ATN) in 3 (25%) KTRs and in 7 (21%) native kidneys. Cardiac arrest was the leading cause of death in SORO-ESRD.

Conclusions: Decongestion is associated with markers of fluid removal and WRF in the setting of ADHF. Currently available data suggest that decongestion-associated WRF does not result in increased mortality whereas persistent congestion is likely to be the driving factor for adverse outcomes in these patients. Randomized controlled trials are needed to confirm these findings as they could portend significant therapeutic implications in cardiac syndrome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: Among 1461 incident ESRD patients seen at Mayo Clinic Dialysis Services, Rochester, 2001–2013, 149 (10%) had SORO-ESRD. There was no gender age disparity between SORO-ESRD patients and the general ESRD cohort. Ninety-nine percent (99%) SORO-ESRD patients’ initial vascular access was a dialysis catheter. ATN was the leading pathologic diagnoses for AKI among KTRs and in native kidneys. Cardiac arrest was the leading cause of death in SORO-ESRD, similar to the general ESRD population. We conclude that SORO-ESRD contributes significantly to incident ESRD here in the USA both among KTRs and in native kidneys. Furthermore, it negatively impacts on the success of AVF-First Programs. Efforts to mitigate AKI in CKD patients must be given more attention and priority by practicing nephrologists in particular, and by physicians in general.

PUB040
Saline-Induced, Diuretics-Responsive Acute Renal Failure (ARF): Evidence that Anasarca Is Nephrotoxic and Diuresis Is Therapeutic
Grant Meltzer, Kai Lu, Helene Ammann, Josefiina Martin, Alicia Mendiluce, Nephrology, Hospital Clinico Univ, Valladolid, Spain.

Background: Recent studies showed the association of fluid overload in ARDS & surgical patients and increased ventilator dependency, ICU & hospital stays, short-term mortalities, & incidence of ARF. But a cause-and-effect relationship was unproven in cross-sectional observations. In grossly edematous in-patients with unexplained ARF, we tested the hypothesis that anasarca caused the renal failure & diuresis induced recovery.

Methods: Entry criteria were fully evaluable patients, ≥3 kg weight or ≥3 L fluid gain, ≥40% acute loss of estimated creatinine clearance (CrCl) or ≥2 x rise in serum creatinine (Scre) without identifiable causes. All data were reviewed, recorded, tabulated & statistically analyzed, notably vital signs, weight, intake, output & lab. 36 qualified patients were diuresed by IV furosemide at rates keeping normotension off anti hypertensives. Serial volume markers & renal responses were noted. Palliative care & hepatorenal syndrome were excluded.

Results: Fluid overload was due to heart failure (40%), liver failure (22%), CKD (16%), proteinuria (9%) & iatrogenic factors (10%). During 42 ARF episodes, mean weight was up 12.5 kg in 13.7d. Scre rose (4.41 vs. 1.27mg/dL) & CrCl fell (25 vs. 76 ml/min). Decrements in CrCl correlated with edema weight gain (p<0.02). Over 11.9 d, 15.2 kg of fluid were diuresed. Renal function greatly improved in 33 patients & unchanged in 3 despite >4 kg diuresis. As an entire group, Scre fell to 1.45 mg% & CrCl rose to 67 ml/min. Increments of CrCl also correlated with diuresis volume (p<0.04). At a diuretic rate of 1.5 kg/d, no adverse events occurred.

Conclusions: 1. Our data support the hypothesis for the entity of Saline-Induced, Diuretics-Responsive Acute Renal Failure. 2. Likely mediated by reduced cardiac output, 3 despite >4 kg diuresis. As an entire group, Scre fell to 1.45 mg% & CrCl rose to 67 ml/min. Increments of CrCl also correlated with diuresis volume (p<0.04). At a diuretic rate of 1.5 kg/d, no adverse events occurred.

PUB041
Is RIFLE Classification a Good Shot for Staging Acute on Chronic Kidney Disease? Maria Isabel Acosta-Ochoa, Josefina Martin, Alicia Mendiluce, Nephrology, Hospital Clinico Univ, Valladolid, Spain.

Background: 8-16% of worlds population may have CKD, which is a risk factor and promoter of AKI. We tested the performance of RIFLE and KDIGO classifications in staging severity and predicting outcomes in Acute on CKD (AcOKD) individuals. KDIGO with a 0.3mg/dL Scre increase includes patients in stage 1 category, and includes automatically in stage 3 patients with peak Scr ≥4.0 mg/dL.

Methods: Retrospective cohorts study. Patients were divided in 2 groups: AKI and AcOKD. We collected clinical data, and classified AKI severity contrasting distribution strata between groups by RIFLE and KDIGO criteria. And tested the ability of both classifications for predicting need for HD and in hospital mortality with a AUC ROC analysis.

Results: 270 patients were included, AKI=125, AcOKD=145. Clinical features and RIFLE and KDIGO stages are listed in table 1.

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>AKI (N=125)</th>
<th>AcOKD (N=145)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>77 (62)</td>
<td>98 (68)</td>
<td>0.3</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>66.9 ± 15</td>
<td>75.4 ± 11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT (%)</td>
<td>96 (77)</td>
<td>131 (99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>44 (35)</td>
<td>70 (48)</td>
<td>0.003</td>
</tr>
<tr>
<td>Chl (SD)</td>
<td>3.8 ± 2.5</td>
<td>4.4 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RIFLE</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No AKI (%)</td>
<td>21 (17)</td>
<td>23 (16)</td>
<td>0.83</td>
</tr>
<tr>
<td>Risk (%)</td>
<td>22 (17)</td>
<td>35 (24)</td>
<td>0.18</td>
</tr>
<tr>
<td>Injury (%)</td>
<td>17 (14)</td>
<td>44 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Failure (%)</td>
<td>65 (52)</td>
<td>43 (30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KDIGO</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage1 (%)</td>
<td>43 (34)</td>
<td>47 (32)</td>
<td>0.19</td>
</tr>
<tr>
<td>Stage2 (%)</td>
<td>17 (14)</td>
<td>16 (11)</td>
<td>0.52</td>
</tr>
<tr>
<td>Stage3 (%)</td>
<td>65 (52)</td>
<td>82 (57)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

65% males, AcOKD individuals were older 66.9y, and had worst Charlson Index (Chal) 4.4. In figure 1 are shown AUC ROC curves for adverse outcomes.

Conclusions: With the KDIGO staging criteria we obtain more homogeneous distribution strata. With the ROC analysis neither classification performs better in predicting adverse outcomes. We found no practical advantage when using neither classification. In the noAKI (by RIFLE) stratum no adverse event was present, so by including a 0,3mg/dL Scre increase augments sensitivity, but may be not specifically.

PUB042
Francois Paquette,1 Amelie Bernier-Jean,1 Veronique Brunette,1 Vincent Pichetto,2 Helene Ammann,3 Stephan Troyanov,3 Josee Bouchard.1 Hôpital du Sacre-Coeur de Montreal, Canada; 2 Hôpital Maisonneuve-Rosemont, Canada.

Background: The KDIGO guidelines recommended to avoid aminoglycosides (AG) in patients at risk or with acute kidney injury (AKI). We determined the frequency of administration, incidence of AKI, and risk factors for AKI and absence of renal recovery in patients receiving AG over the last decade.

Methods: We performed a retrospective cohort study on AG administration in two university-affiliated centers, and then performed a nested case-control study, pairing AG-AKI cases to 2 controls for age and gender. AKI was defined by a 50% increase in creatinine after ≥5 days of AG up until 7 days after cessation of AG, and renal recovery, by a decrease in creatinine to within 50% of baseline creatinine over 3 weeks after cessation of AG.

Results: Between 2001 and 2015, the frequency of AG administration and drug dosing progressively declined. Out of 562 patients, sixty-five developed AKI attributed to AG (12%). In the case-control study (n=195), age was 71 (IQR 58-81) and 46% were male. The duration of AG administration was 10.0 (IQR 7.0-15.0) days, excluding days after AKI diagnosis in AKI patients. Maximal AKI stage was 1 for 55.3%, 2 for 29.2% and 3 for 15.4% of patients. Independent risk factors associated with AKI were concomitant vancomycin administration, high trough levels, heart failure, and site of infection (endocarditis and febrile neutropenia vs. other). Only fifty-one percent (50.8%; 33/65) of patients recovered their kidney function. These patients had an AKI duration of 7.0 (IQR 4.0-11.5) days. Heart failure was associated with a lower likelihood of renal recovery, while cancer patients more likely recovered their kidney function.

Conclusions: Over the last decade, the frequency of AG administration and dosing have progressively decreased but the incidence of AKI remained unchanged. In our cohort, vancomycin administration, high trough levels, heart failure, and site of infection were independent risk factors associated with AKI. Almost half of patients did not recover their kidney function, which was more often seen in patients with heart failure.
PUB043

Prairie Continuous Renal Replacement Therapy (CRRT) Study – Outcomes of CRRT in a Single Canadian Tertiary Centre
Bhanu Prasad,1 Michelle Urbanski,2 Erwin Karrenman,3
1 Nephrology, Regina Qu’Appelle Health Region, Regina, SK, Canada; 2 College of Medicine, Univ of Saskatchewan, Regina, SK, Canada; 3 Research and Performance Support, Regina Qu’Appelle Health Region, Regina, SK, Canada.

Background: Patients with stage III Acute Kidney Injury (AKI) requiring Renal Replacement Therapy (RRT) have the highest short-term and long-term mortality of any group with AKI. Our study aimed to prospectively follow patients with stage III AKI on Continuous Renal Replacement Therapy(CRRT) during their hospitalization in our tertiary care centre from April 2013 to September 2014.

Methods: We prospectively gathered the following: date and time of hospital admission, transfer to ICU, and starting CRRT, creatinine at admission and at CRRT initiation, weight on admission and at CRRT initiation, duration of oliguria and anuria, exposures (sepsis, critical illness, circulatory shock, trauma, cardiac surgery, major non cardiac surgery, nephrotoxic medications, and radio contrast agents) and susceptibilities (dehydration, >65 years of age, female, pre-existing chronic CKD), APACHE score II, Inotrop support, FiO2, ECMO. Survival on CRRT, in ICU and hospital survival and renal recovery was documented.

Results: Of the 2634 patients (2201/2634, 83.6% had no AKI, and 269/2634, 10.2% had stage III AKI of whom 106/269 (40%) were started on CRRT. 8/106 died in ICU and hospital survival and renal recovery was documented. 5/106 patients recovered within 24 hours. 5/106 patients had a shorter stay in ICU prior to starting CRRT (6.06 hours vs. 12.26 hours). Stage III AKI patients had stage III AKI of whom 106/269 (40%) were started on CRRT. 8/106 died in ICU and hospital survival and renal recovery was documented.

Conclusions: We found that 34.6% of patients required RRT. Among patients with stage III AKI, 5/106 patients recovered within 24 hours. 5/106 patients had a shorter stay in ICU prior to starting CRRT (6.06 hours vs. 12.26 hours). Stage III AKI patients had stage III AKI of whom 106/269 (40%) were started on CRRT. 8/106 died in ICU and hospital survival and renal recovery was documented.

PUB046

C3 Glomerulopathy: A Pediatric Case
Luis A. Ortiz,1 Daniel Kleven,2 Harika Gorri,1
1 Ped. Nephrology, Georgia Regents Univ, Augusta, GA; 2 Pathology, Georgia Regents Univ, Augusta, GA.

Background: C3 glomerulopathy (C3G) is characterized by C3 deposit in the glomeruli with minimal Ig deposition. C3G is described as an unregulated activation of the alternative complement pathway due to a genetic mutations in Factor H or I, or acquired factors such as C3 nephritic factor, an IgG autoantibody stabilizing C3 convertase. The pattern of the injury varies from mesangio-proliferative, membranoproliferative, to endocapillary proliferative glomerulonephritis. The EM finding is characteristic orange hump shaped subepithelial deposits, characteristic of acute post-infectious glomerulonephritis (PIGN). We present a pediatric case that met the initial criteria for PIGN, but was diagnosed as C3G according the pathology.

Methods: 15 y/o AA M with Thin Basement D, HTN, asthma presented with 1 hx of sore throat, gross hematuria, facial swelling, no distal edema. Initial oliguria and high Cr. PE revealed periorbital edema, no pharyngeal erythema, lung clear, abdomen with no ascites. On admission, Hb 11.6 g, Cr 3.26mg, Albumin 25.2 g, U/A: 50-50 BRC, UOP: 0.37 ml/hr. Despite treatment with methylprednisolone, albumin and furosemide, his Cr. increased to 6.48, ASO 654 UI, adnAscb normal, CRP 12.6. Group A strep was negative for growth. Kidney biopsy: glomeruli w/segmental sclerosis, endocapillary infiltration of neutrophils, IF: extensive C3 staining with scant IgG and small fibrin deposition (focal necrosis). EM: large subepithelial deposits. Worsening kidney function required hemodialysis. After 6 months, he continues on Hemodialysis.

Conclusions: Kidney biopsy with C3 dominant on IF, large subepithelial deposits on EM, hypocoomplementemia and clinical of gross hematuria preceded by URI suggested acute PIGN, but this overlaps with the histological presentation of C3G of C3 dominant staining with scant IgG deposition, subepithelial deposits and low serum C3. No resolution of AKI after 8 weeks of presentation was unusual for PIGN, steering diagnosis towards C3G. Clinicians should note the high overlap between the clinical and histology of PIGN and C3G. It is imperative to conduct further studies to accurately diagnose and treat patient with C3G.

PUB047

Predictors of End Stage Renal Disease in Scleroderma Renal Crisis – A Single Center Experience
Sumeedha Dhar, Cybele Ghossein.
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Background: Scleroderma renal crisis (SRC) is one of the most acute and life-threatening complications of systemic sclerosis (SSc). It is typically characterized by accelerated hypertension and acute kidney injury (AKI). Angiotensin converting enzyme inhibitors (ACEI) are currently the treatment of choice for this disease. Despite use of ACEI, 50% of patients with SRC develop end stage renal disease (ESRD) which is associated with poor long term outcomes. Our aim was to define the clinical characteristics and outcomes of SRC patients admitted to our institution.

Methods: This was a retrospective chart review of all patients admitted with SRC to Northwestern Memorial Hospital (NMH) between the years of 1/1994 to 4/2015. ESRD was defined as the need for chronic dialysis during admission for SRC.

Results: There were 23 patients with a diagnosis of SRC made either clinically or by renal biopsy during this time period. Mean time to SRC was 1.3 years after diagnosis of SSc. 47% of patients developed ESRD during the same admission. Development of ESRD was not associated with age, gender, race, anti-RNA polymerase III test positivity, intensive care unit (ICU) admission, prior ACEI or angiotensin receptor blocker (ARB) use, or creatinine on admission. ESRD was significantly associated with time to control blood pressure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
896A
Conclusions: SRC is a serious kidney and life threatening complication of SSC. Delay in blood pressure control increases risk of ESRD in SRC patients.

PUB048

Acute Kidney Injury Risk Assessment at the Hospital Front Door: What Is the Best Measure of Risk? Aled O. Phillips,1 Dafydd Phillips,1 Mohamed Hassan,2 John Geen,3 Vikas Lodhi,4 Hernaneth Bolusani,4 Gareth Roberts.1 1Dept of Clinical Biochemistry, Univ of South Wales, Wales, United Kingdom; 2Dept of Medicine, Royal Gwent Hospital, Newport, Wales, United Kingdom; 3Dept of Medicine, University Hospital of Wales, Cardiff, Wales, United Kingdom; 4Dept of Medicine, Prince Charles Hospital, Merthyr Tydfil, Wales, United Kingdom; 5Dept of Medicine, Univ Hospital Llandough, Cardiff, United Kingdom.

Background: We examined the prevalence of AKI-risk factors in the emergency medical unit, generated a modified risk assessment tool and tested its ability to predict AKI.

Methods: 1196 patients admitted to medical admissions units were assessed for patient associated AKI-risk factors. Subsequently, 898 patients were assessed for a limited number of fixed risk factors with the addition of hypotension and sepsis. This was correlated to AKI episodes.

Results: In the first cohort the prevalence of AKI risk factors was 2.1±2.0 per patient, with a positive relationship between age and the number of risk factors and a higher number of risk factors in patients ≥65yrs. In the second cohort 12.3% presented with or developed AKI. Patients with AKI were older and had a higher number of AKI risk factors. In the AKI cohort 72% of the patients had ≥2 AKI risk factors compared to 43% of the cohort with no AKI. When age ≥65 yrs was added as an independent risk factor 84% of those with AKI had ≥2 AKI risk factors compared with 55% of those with no AKI. ROC analysis suggest AKI. When age ≥65 yrs was added as an independent risk factor 84% of those with AKI episodes.

Conclusions: Detailed assessment of well established patient associated AKI-risk factors may not facilitate clinicians to apportion risk. This suggests that additional work is required to develop a more sensitive validated AKI predictive tool which would be useful in this clinical setting.

PUB049

Acute Kidney Injury, Requiring Renal Replacement Therapy – Incidence, Causes and Outcomes: One Center Experience Elena Zakhарова, Nephrology, City Clinical Hospital n.a. s.P. Botkin, Moscow, Russian Federation.

Background: Acute Kidney Injury (AKI) is complex condition, associated with high mortality and morbidity. We aimed to evaluate AKI incidence, causes, risk factors and outcomes in patients, managed in nephrology unit of general hospital and urgently requiring Renal Replacement Therapy (RRT).

Methods: Using electronic database for 2010-2014 (4531 admissions, 2257 patients), we searched 604 cases which met KDIGO AKI definition, and selected patients, required RRT.

Results: Study group included 115 patients (19% of all AKI cases), 51 (44%) male, 64 (56%) female, median age 61 [22; 89] years. In 102 (89%) cases AKI was community acquired. Median serum creatinine prior to start of RRT was 981 [242; 2665] μmol/l, 37 (32%) patients had known CKD. Causes and susceptibilities for AKI are shown in table.

Conclusions: In our patients, three renal manifestations of PNH were identified. They 76 (66%) patients partially or completely recovered kidney function, 27 (23%) were still dialysis-dependent after 3 month of follow-up, and 12 (10%) patients died.

PUB050

Renal Manifestations in Paroxysmal Nocturnal Haemoglobinuria Ram R1, Dakshinamurty K1, Krishna Parasad A.2 1Nephrology, Sri Venkateswara Inst of Medical Sciences, Tirupati, AP, India; 2Nephrology, Mahatma Sri Ramchandra Centenary Memorial Hospital, Hyderabad, Telengana, India; General Medicine, NIMS, Hyderabad, India.

Background: Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired chronic disorder characterized by a triad of clinical features: haemolytic anaemia, purpura, thrombosis. Not many reports of renal involvement in PNH are available in literature.

Methods: We present a case series of PNH with renal involvement. We present the data of PNH patients attended to departments of General Medicine and Nephrology at a government run tertiary care institute in South India. The diagnosis of PNH in these patients during initial phase, between 1998 and 2004 was based on sucrose lysis and Ham’s test. After 2004, the diagnosis was based on flow cytometry to detect CD55 (MIRL), a glycoprotein, and CD55 (DAF) in regulation of complement action. The patient data was collected from 1998 to 2014.

Results: There were 13 patients of paroxysmal nocturnal haemoglobinuria in this period. The mean age was 37 years and the range was 16 to 68 years. There were 7 females. Acute renal failure was noted in 5 patients. Dialysis was performed in three of them. The mean serum creatinine and urea at the initiation of dialysis was 5.4 ± 0.6 mg/dL and 64.1 ± 6.1 mg/dL respectively. The median number of haemodialysis sessions done was four. Renal biopsy was done in four patients. The indication for the biopsy was acute renal failure of more than four weeks. The median number of glomeruli was 9. The tubules showed prominent brown granular pigment within the epithelial cells. It was confirmed as hemosiderin with the Perl’s Prussian blue reaction. A few deposits of hemosiderin were also seen within the tubular lumina. The pathological diagnosis in these four patients was acute tubular necrosis secondary to hemosiderin deposition. In three patients the urinalysis and serum chemistry was suggestive of Fanconi syndrome.

Conclusions: In our patients, three renal manifestations of PNH were identified. They were acute renal failure, renal vessel thrombosis and Fanconi syndrome. Chronic renal failure was not identified.
Filling the Gaps in Acute Kidney Injury Epidemiology: A Multicenter Prospective Study in Amazon

Background: In some areas of developing countries, infectious tropical diseases or animal venoms may be important causes of Acute Kidney Injury (AKI). Epidemiological studies of AKI incidence in these areas are scanty and prospective population-based studies are even scarcer.

Methods: Prospective data on all adult patients admitted in all intensive care units (ICUs) throughout the Western Amazon region (600 square kilometers and 100,000 inhabitants) were collected for 6 months in 2014. Patients with chronic kidney disease stage 5, kidney transplant or ICU stay < 48 hours were excluded. AKI was diagnosed by KDIGO and mortality was assessed 30 days after ICU discharge. Data are presented as mean±SD or percentages.

Results: 367 patients aged 57.8±19.2 years and with 39% white were evaluated. Main reasons for ICU admission were postoperative (34%), hemodynamic instability (22%) and respiratory failure (13%), with only 1% with tropical diseases. AKI incidence was 38%, but was lower in postoperative patients (28% vs 45% in non-postoperative; p=0.005). Mortality was higher in AKI patients (53% vs 30% in non-AKI, p <0.001). Postoperative patients who developed AKI had similar mortality to those non-operative (46% vs 56%, p=0.302).

Conclusions: AKI has a high incidence in ICU patients of the Western Amazon area. The causes of ICU admission did not differ from those seen in developed countries. The few number of patients with the typical tropical diseases of Amazon may be due to poor access to health care. The peculiar social geographical region characteristics, with rivers that are not navigable most of the year, long rain period that difficult access to larger cities and the lack of health services in diverse areas, may be associated to the present findings.

Funding: Government Support - Non-U.S.

Uncovering Complement Mediated Thrombotic Microangiopathy: Use of a Real Time Genetic Assay in the Diagnosis of Atypical Hemolytic Uremic Syndrome

Background: Improved diagnostic tests and greater understanding of pathophysiology of thrombotic microangiopathy (TMA) have led to more rapid differentiation of various types of TMA. While ability to rapidly diagnose TMA (ADAMTS13 activity >5%) has improved, atypical HUS (aHUS) remains diagnosis of exclusion due to poor sensitivity, high cost, and long turnaround time (TAT) of aHUS genetic assays. We describe a patient (pt) with hypothyroidism and renal insufficiency diagnosed with aHUS, using appropriate clinical algorithms for TMA, including “real-time” aHUS genetic assay (TAT 2-5 days).

Methods: 59 y.o. female with 1-2 week (wk) history of fatigue, anemia, thrombocytopenia, renal insufficiency, and recent diagnosis of hypothyroidism with changes in CBC and creatinine (Cr) over 3 wks: hemoglobin (hb) 13.9 to 7.1 g/dl, platelet count (plt ct) 241 to 68 X 10^9/L, and Cr 0.71 to 1.41 mg/dl (baseline Cr 0.56, BMI 19.5). Pt’s CNS status normal; no other signs/symptoms of systemic thrombosis noted. Additional labs: haptoglobin <9 mg/dL, LDH 1942 U/L (312-618 U/L), direct coombs negative, PT/ INR normal, albumin 3.6, IgG 1133 mg/dL, 5.6-schistocytes/high power field, ADAMTS13 activity 79% (40-130%) resulting out TMA.

Results: Pt received 11 plasma exchange (PE) treatments (txs) (hospital day [HD] 3-21). By day 4 of PE (HD 7), plt ct 197 X 10^9/L; despite 11 PE ttxs, LDH remained elevated (686-2123) and Cr rose to 2.72 (3.8-4.9X higher than baseline). aHUS genetic panel (sent HD 10, results on HD 17) revealed: positive variant in CFI gene (predicted to be significant, but not previously described) and hyperhomocysteinemia for 3 CFH polymorphisms. Pt clinically diagnosed with aHUS, received meningococcal vaccine (HD 1), induced eczulizumab started and PE stopped (HD 21). After 2 months of eczulizumab, pt’s Cr normalized.

Conclusions: With development of improved genetic testing (ie, increased sensitivity and speed), aHUS genetic assays may represent “real-time” diagnostic tools enabling more rapid assessment of selected TMA cases leading to more targeted treatment.

Oral Hydration: The Way Forward in the Prevention of Contrast-Induced Nephropathy

Background: Contrast induced nephropathy is defined as increased serum creatinine of 0.5 mg/dL (44.2 μmol/L), or a 25% increase of creatinine from baseline levels checked 48 hours after contrast exposure. Studies have suggested the use of intravenous fluids such as sodium chloride 24 hours prior to contrast exposure. However, this step would require the patient to be admitted prior to contrast medium exposure and incur extra cost for this hospital. This audit explores the use of oral hydration in the prevention of contrast-induced nephropathy.

Methods: Using the ICE computer system, all patients who were diagnosed with Type 2 Diabetes Mellitus and taking metformin were identified from the time period of January 2008 until January 2014. They were then advised to stop their metformin prior to contrast exposure. Recommendations were made for contrast prophylaxis which was given when 2 litres of oral fluids before and after the procedure. Patients were also given advice to get their renal function checked, 48 – 72 hours after contrast exposure. Their renal function pre and post contrast exposure were documented. Any patients with either aCr more than 20% or their eGFR more than 20% were then referred to the nephrology department for follow up.

Results: A total of 277 patients were included in this audit. The mean eGFR was 47 ml/min/1.73m^2. 79% of patients had their renal function checked within 48 – 72 hours, 15% patients had their renal function checked after that time and 6% of patients did not have their renal function rechecked at all. Only 0.7% of patients had deterioration of their renal function that met the criteria above. However it was important to note that these patients had also other multiple co-morbidities and the exposure to contrast was not the sole cause for the deterioration of their renal function.

Conclusions: Oral hydration should be considered as part of the protocol for the prevention of contrast-induced nephropathy. This regime has reduced the need for patients to be admitted into hospital admission for intravenous fluids, thus reducing waiting times for imaging and as well as reducing hospital cost.

Gemcitabine-Mediated Thrombotic Microangiopathy – A Rare Cause of Hemolytic Uremic Syndrome

Background: Thrombotic microangiopathy (TMA) is a pathological diagnosis of endothelial cell injury and microvascular thrombosis. TMA has been categorized in the present era as one of three distinct disease processes: 1) classical hemolytic uremic syndrome, 2) atypical hemolytic uremic syndrome (aHUS), and 3) thrombotic thrombocytopenic purpura. Our focus, aHUS, reflects an underlying aberrancy in regulation of the alternative complement cascade. Several genetic defects have been identified leading to an affinity to develop uncontrolled activation of this cascade which may commence after exposure to a trigger. Gemcitabine is one rare trigger described in the literature.

Methods: A 66 year-old female with locally advanced, unresectable pancreatic cancer who had completed 12 cycles of gemcitabine-abraxane therapy with no major oncologic progression on disease was referred with acute kidney injury. Two months prior to admission, she developed hypertension, nausea, and profound cytopenias requiring platelet and red cell transfusion. She endured a progressive decline in renal function with a nadir eGFR 19 mg/mL/1.73 m^2. One month prior to admission, her urinalysis reflected active sediment. Admission labs demonstrated microangiopathic anemia with thrombocytopenia. ADAMTS13 activity was normal (88%), consistent with aHUS. Renal biopsy confirmed subacute changes consistent with TMA. Despite discontinuation of the gemcitabine-abraxane therapy, she continued to demonstrate progressive anemia and thrombocytopenia in addition to persistent proteinuria, hematuria, and impaired eGFR. The patient was subsequently initiated on eczulizumab therapy.

Conclusions: Gemcitabine-mediated aHUS is rare and associated with a 75% mortality rate at four months. Previous attempts at therapy have included apheresis. However, current guidelines discourage apheresis in this patient population. To date, six cases of gemcitabine-mediated aHUS have reported the successful use of eczulizumab, a terminal complement inhibitor.
Dabigatran Induced Acute Kidney Injury and Management with Hemodialysis

**Background:** A 55-year-old man with a history of A Fib, cirrhosis, portal HTN, esophageal varices arrives in the ED, transferred from an outside hospital following initial presentation with multiple episodes of hematemesis and melena. Medication regimen recently changed with a switch from warfarin to dabigatran 8 months prior to admission in order to avoid frequent INR checks.

**Methods:** On admission, initial blood work was obtained and revealed: Hg 6.3 g/dL, INR 6.9, Scr 15.6 mg/dL and BUN 189 mg/dL. Patient was admitted to the intensive care unit for management of acute blood loss and AKI. On physical exam shows a pulse of 95 bpm and BP of 111/75 mmHg and mild hepatosplenomegaly, the physical exam was unclear but acute blood loss leading to prolonged ischemic insult was largely consistent with ATN, chronic tubulointerstitial nephritis, and IgA Nephropathy (HAA5 class I).

**Results:** Serum dabigatran concentration (conc) drawn on admission was 860 ng/mL. Following the initial emergent hemodialysis (HD) procedure, subsequent dabigatran conc. were determined during the second HD procedure. Predialysis and postdialysis dabigatran conc. were 130 ng/mL and 30 ng/mL, respectively. Pharmacokinetic parameters were calculated and shown in the table.

**Conclusions:** Dabigatran induced AKI is rare. The mechanism of the insult in this case was unclear but acute blood loss leading to prolonged ischemic insult was largely contributive. Hemodialysis was successful in removing the offending agent with resolution of bleeding but patient remains dialysis dependent.

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>mean±sd</th>
<th>BNP pg/mL</th>
<th>NGAL ng/mL</th>
<th>CO I/min</th>
<th>COI I/min</th>
<th>LWWI Kg/m2</th>
<th>SVRI dyns/cm-5 m2</th>
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<tbody>
<tr>
<td>1</td>
<td>1086±185.9</td>
<td>252±36</td>
<td>4.3±0.47</td>
<td>0.25±0.23</td>
<td>0.2±0.25</td>
<td>2338±245.3</td>
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<tr>
<td>2</td>
<td>150.6±420</td>
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<td>4.8</td>
<td>2.6</td>
<td>2.6</td>
<td>1942</td>
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<tr>
<td>3</td>
<td>189.4±52.4</td>
<td>704±141</td>
<td>6.2±0.5</td>
<td>0.3±0.2</td>
<td>0.26±0.36</td>
<td>2082±206.83</td>
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<tr>
<td>4</td>
<td>158.49±7.3</td>
<td>177±65.3</td>
<td>3.0±0.2</td>
<td>0.13±0.08</td>
<td>0.17±0.12</td>
<td>4322±394.5</td>
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<td>5</td>
<td>0.01±0.005</td>
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<td>0.008</td>
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**CO:** CARDIAC OUTPUT; COI: CARDIAC OUTPUT INDEX; LWWI: LEFT VENTRICULAR WORK INDEX; SVRI: SYSTEMIC VASCULAR RESISTANCE INDEX.

**Conclusions:** The use of CTBIA is useful to evaluate and classify patients with cardiorenal or cardiorenal syndrome. There are association between vascular resistance and renal tubular necrosis.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Patients with lower vascular resistance and higher cardiac work have worse prognosis, associated with inflammatory state and thoracic hypervolemia, oliguria and higher renal replacement therapy requirements. But patients with higher thoracic volume have higher risk of respiratory failure.

<table>
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<th>Table 1</th>
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<tr>
<td>CO l/min</td>
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<td>ISI r</td>
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<tr>
<td>p</td>
</tr>
<tr>
<td>CRP: p</td>
</tr>
<tr>
<td>Hypo. p</td>
</tr>
<tr>
<td>Vent.Asis.R. p</td>
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<tr>
<td>YES/NO</td>
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<tr>
<td>RRT. p</td>
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</tbody>
</table>

Conclusions: CTHBA can be used to evaluate prognosis and therapy of higher risk AKI, as patients with vasoplegic state (with inflammatory origin and higher multiorgan failure risk) or thoracic hypervolemia (with higher respiratory failure and intubation risk).

PUB060

Abruptio Placenta as a Complement Amplifying Condition for Atypical Hemolytic Uremic Syndrome


Background: Endothelial injury resulting in microvascular thrombosis is the underlying pathology leading to organ injury in aHUS. The syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to multiple organs including the kidney. Complement amplifying conditions often lead to the activation of complement cascade involved in the pathogenesis of atypical HUS. In this report, we present 33-year-old Hispanic women with abruptio placenta at 33 weeks of gestation and fetal death who underwent cesarean section. Post procedure, patient developed microangiopathic hemolytic anemia (6.7 mg/dl), thrombocytopenia (39,000/µL) and renal failure necessitating initiation of hemodialysis. Fibrogen (267 mg/dl), PT, PTT were normal while LDH was markedly elevated at 2670 IU/L. Haptoglobin was severely reduced at 5.8 mg/dl. Market schistocytosis was observed on peripheral smear. ADAMTS 13 was ordered and plasma exchange was initiated. Five sessions failed to show any improvement and ADAMTS 13 activity returned at 56%. Plasma therapy was unsuccessful and Eculizumab (monoclonal antibody directed against complement C5) was initiated for the diagnosis of aHUS. At a follow-up of two weeks patient is off dialysis with a serum creatinine of 3.4 mg/dl, hemoglobin of 8.8 mg/dl and platelet count of 147,000/µL. We believe that abruptio placenta acted as a complement amplifying condition in this case. However, pregnancy, fetal loss and caesarean section can all serve as complement amplifying conditions for aHUS.

Methods: Case Report

Results: Successful outcome with Eculizumab therapy.

Conclusions: aHUS responding to Eculizumab therapy.

PUB061

Foscarnet Crystal-Induced Nephropathy in a Patient with Diminished Native Renal Capacity

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1Pathology, Univ of Kentucky; 2Nephrology, Univ of Kentucky.

Background: Drug-induced crystalline nephropathies are characterized by glomerular, tubular or interstitial injuries with rising creatinine, hematuria and low grade proteinuria. Foscarnet is a pyrophosphate analog that inhibits DNA polymerase in ganciclovir-resistant CMV. Tubular-interstitial damage due to Foscarnet is common but reports of crystalline-induced nephrotoxicity are rare. We report this unique case of Foscarnet crystal-induced nephropathy in a patient with lymphoma and solitary functioning kidney.

Methods: A 56 year old female with history of solitary functioning left kidney with remote history of right kidney atrophy due to obstructive uropathy was diagnosed with stage IV mantle cell lymphoma. Renal function was normal prior to chemotherapy and stem cell transplant. This was complicated by CMV infection requiring IV Foscarnet for 8 weeks. She developed AKI with nephrotic range proteinuria and hematuria. The patient was initiated on hemodialysis. Renal biopsy showed deposition of calcium crystals in the mesangium and interstitium characterized by short sticks with angular edges and birefringence on polarized light microscopy.

Conclusions: Our study highlights the overestimation of renal function by MDRD equation in critically ill patients with acute kidney injury (AKI). KeGFR may be more accurate in tracking renal function changes in AKI. Further studies are needed to confirm these findings.
A Curious Case of Evans Syndrome
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Evans syndrome is a rare autoimmune condition in which antibodies attack their own RBC and platelets resulting in an hemolytic anemia (AIHA) and ITP in the absence of a known etiology. Both of these can occur simultaneously or sequentially. Although many cases are idiopathic in origin, ES has been associated with other conditions in half of the cases, including infections and lymphoproliferative disorders.

Methods: A 45 year old African American male seen in ED with a Hgb of 6.4 and asymptomatic. The patient has a history of autoimmune hemolytic anemia (AIHA), immune thrombocytopenic anemia (ITP), anti-phospholipid syndrome (APS) with a previous DVT/PE and non-compliant with warfarin. Labs On admission Hgb 6.4, Ptts 14, Bil 1.3, D Bil 0.4, LDH 346, Haptoglobin <8. He had AIHA (Cr 0.9), with new onset nephrotic range proteinuria. Renal US showed medical renal disease. ANA 1:160, double stranded DNA was negative. Anti MPO, P-ANCA, C-ANCA, antiproteinase 3, atypical P-ANCA and glomerular basement membrane antibody were negative. CH 50,C3 and C4 were all low. No cryoglobulins were detected in the blood assay. Urine Electrolytes was negative for monoclonal light chains. Renal biopsy was performed and showed findings consistent with lupus nephritis stage 4/5. The patient was treated with PGBs and given pulse dose steroids for 3 days after which his hemoglobin remained stable.

Results: ES is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at onset. Since it is thought to be secondary to immune dysfunction, a high clinical suspicion should be maintained for underlying autoimmune disease. However this patient was unique, he did not meet the standard criteria for SLE but demonstrated lupus nephritis on biopsy. This case reflects that we should have a high suspicion for SLE and lymphoproliferative diseases even in asymptomatic patients with Evans Syndrome.

Anticoagulation-Free Continuous Renal Replacement Therapy: A Single Center Observation
Akshatha Rao, Ziauddin Ahmed.
Div of Nephrology, Drexel Univ.

Background: Renal failure in the ICU setting is associated with 40-60% mortality. Continuous renal replacement therapy (CRRT) is used for volume and electrolyte management in critical care units. To avoid cloting of hemofilters, patients are routinely started on anticoagulation. In literature, anticoagulation has been associated with complications of increased risk of bleeding and metabolic or electrolyte disturbances based on type of anticoagulation used. We aimed to investigate the length of cartridge use and the association of anticoagulation.

Methods: We conducted a retrospective review of 20 ICU patients who were started on CRRT over a course of 6 months for acute renal failure. We looked at the number of cartridges used per day. Prescription for CRRT was dialisate flow rate of 25-35 ml/kg/h and blood flow rate of 250 ml/h. No anticoagulation was ordered initially due to bleeding changes in this cohort. All patients were ordered 100 ml of normal saline flushes every 4 hours. Results: For 70% of the patients, the hemofilter cartridge lasted >24 hours. 30% of the patients required more than 1 filter per day, of which only 1 patient was started on a heparin drip for anticoagulation due to multiple filter changes. We used predilution replacement fluid to reduce the blood viscosity and hemoconcentration for the patients requiring > 2 filter changes per day. Decreased requirement of filter change was noted after these changes were made. Among the patients with increased filter clotting, 33% had femoral non-tunneled dialysis catheters and 50% had internal jugular tunneled dialysis catheters. Longer duration of dialysis was associated with increased cartridge use per pearson correlation 0.188 (p<0.000). No documentation was made in the nursing notes to distinguish between vascular access problems versus filter clotting.

Conclusions: Recurrent filter clotting leads to interruption of RRT. Frequent filter changes is not cost effective. However anticoagulation in critical care settings poses multiple potential problems. There was an association between percutameters and increased cartridge use.

Rosuvastatin Has a Protective Effect against Hypertonicity-Induced Cell Damage
Miku Sato, Masaru Horio.
Division of Cardiology, Osaka Univ Graduate School of Medicine, Suita, Japan.

Background: Contrast-induced nephropathy (CIN) is one of the causes of acute kidney injury. Some studies raised a concern that statins have protective effect against CIN. Hypertonic stress in renal tubular cell is a possible factor inducing cell damage in CIN. Reactive oxygen species (ROS) can induce apoptosis. We studied the effect of rosuvastatin on hypertonicity induced cell damage in MDCK cells.

Methods: Hypertonic medium was made by addition of NaCl. Rosuvastatin was added 24 hours before the hypertonic exposure. Cell damage was assessed by LDH activity in culture medium. Apoptosis was evaluated by caspase-3 activity. Content of cellular glutathione (GSH), an important antioxidant, was measured.

Results: Hypertonicity more than 600 mOsm showed significant cytotoxic effect in MDCK cells. LDH activity in culture medium of 620, 640 and 660mOsm cells increased in a dosimality dependent manner (Figure). Low concentration (0.1 and 1.0 µM) of rosuvastatin had a protective effect against the hypertonicity-induced cell damage. On the other hand, 10 µM rosuvastatin that had no significant cytotoxic effect in 300mOsm condition, stimulated hypertonicity induced cell damage.

Conclusions: Low dose of rosuvastatin has a protective effect on hypertonicity-induced cell damage in MDCK cells.

Funding: Government Support - Non-U.S.
Conclusions: In summary, high expression of SRF associates with increased fibrosis and decreased survival in IgA nephropathy, perhaps by enhancing TGF-β-mediated downregulation of srps and E-cadherin in HKC.

PUB068
Increased ErythrocYTE Reactive Oxygen Species Production Induced by Indoxyl Sulfate Precedes Red Blood Cell Death
Gabriela Ferreira Dias,1 Viktoriya Kuntsevich,2 Lisa S. Nakao,3 Felype C. Barreto,3 Stephan Thijsen,4 Peter Kotanko,5 Roberto Peccei-Filho,1 Andrea Novais Moreno-Amoral,1 Pontifica Univ Catolica do Parana, Brazil; 1Icahn School of Medicine at Mount Sinai, New York; 2Univ Federal do Parana, Brazil; 3Renal Research Inst, New York.

Background: The uricemic toxin indoxyl sulfate (IS) triggers eryptosis, an event characterized by phosphatidylserine (PS) exposure on red blood cell (RBC). The aim of the present study was to evaluate whether increase in RBC reactive oxygen species (ROS) induced by IS precedes PS exposure.

Methods: RBC from healthy controls (HC) were incubated for 4, 12 or 24 h with IS (free concentration 4.5 mg/L) in the presence or absence of free radicals scavenger N-acetylcycteine (NAC 0.5 mM). Flow cytometry was employed to assess eryptosis (annexin-V+ binding) and ROS (DCFH-DA).

Results: Incubation of HC-RBC with IS over 4 h did not trigger significant eryptosis compared to control cells incubated without IS (4.5 ± 1.2% vs 3.4 ± 0.1%). However, 12 h and 24h incubation with IS increased levels of eryptosis in a time-dependent manner (10.4 ± 3.4% and 16.6 ± 6.1%, respectively). This IS-induced PS exposure on HKC-RBC was inhibited in the presence of NAC (6.0 ± 1.3% and 6.5 ± 1.4%, respectively). On the other hand, ROS production by HC-RBC was increased even after only 4 h of incubation with IS in a time-dependent manner (14 ± 4.2%, 22 ± 1.5 ± 3 and 34 ± 8.15 ± 8% for 4, 12h and 24h respectively) when compared to control cells (6.6 ± 2.3%, 4.2 ± 0.5% and 5.2 ± 1.8%, respectively). ROS production was inhibited in the presence of NAC (6.6 ± 3.4%, 6.3 ± 2% and 13.4 ± 10.5%) demonstrating the ability of an antioxidant to reverse the oxidative stress induced by IS.

Conclusions: Taken together our results suggest that IS in a high free concentration, which is in accordance with reported free toxin concentration in patients, induces ROS production in HC-RBC that precedes PS exposure. Thus, imbalance of RBC redox status induced by IS appears to be an important mechanism of elevated eryptosis observed in CKD that consequently may contribute to renal anemia.

PUB069
Impact of Constitutive C-MIP Expression on Mouse T-Cell Proteome
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Background: The protein c-mip is overexpressed in lymphocytes and podocytes of MCNS patients. In order to dissect its role in INS pathogenesis, we generated a transgenic mouse expressing c-mip in peripheral mature T-cells. We aimed to evaluate the impact of c-mip expression on T-cell proteome in basal and stimulating conditions.

Methods: T-cells from transgenic (TG) and control (WT) mice (n=3) were purified by negative immunoextraction, and subjected to anti-c-CD3 and anti-CD28 stimulation, to mimic activation of antigen presenting cells. At 0 to 60 min post-activation, total proteins were extracted, trypsin digested, and peptides analyzed by nano-RSLQC on Exactive Plus MS. Protein quantification was performed by a label-free approach using MaxQuant and Perseus software on three parallel technical replicates per sample.

Results: The expression levels of 2660 proteins were compared in the four conditions. As a result, 46 proteins were found differentially expressed between TG and WT as a function of T-cell activation (two-way ANOVA interaction, p<0.05). Among these, GO annotation showed a significant enrichment in proteins bearing ATPase activity. Hierarchical clustering by K-means algorithm displayed, most remarkably, a cluster of 14 proteins upregulated upon T-cell activation in WT mice but depleted in TG mice in the same conditions - including KEGG annotations for tight junction, Wnt signaling, TLR signaling, RIG-I-like receptor signaling, Notch signaling, spliceosome, riboflavin metabolism, and DNA replication-, and a cluster of 11 proteins depleted in WT and augmented or unchanged in TG after activation – involved in aminoacid and nicotinamide metabolism, proteasome, and regulation of actin cytoskeleton. Studies are underway to explore the mechanisms involved.

Conclusions: c-mip overexpression elicits profound alterations in the protein expression pattern following T-cell activation in mice, involving diverse signaling, metabolic pathways and cellular functions. These results, along with other preliminary data obtained from the same mouse model, point at a defect in T-cell activation associated with c-mip expression.

Funding: Government Support - Non-U.S.

PUB070
An Investigation into the Prognosis of Nephrotic Syndrome and Regulatory T Cells in Elderly People
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Background: Peripheral blood flow cytometry analysis of nephrotic syndrome (NS) in children has been performed, and among T cells, regulatory T cells (Treg) are involved in NS pathogenesis. There are reports about Tregs and ANCA-associated glomerulonephritis, and the nephritic inhibitory effect of Tregs has become clear. As there has been no investigation focusing only on NS in elderly people, we conducted the analysis in this study.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effects of 1,25-Dihydroxy Vitamin D3 on Treg Cells, Interleukin-17, RORγt in Rats with IgA Nephropathy

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Background: To investigate the relationship between Treg cells, RORγt, IL-17 and rats with IgA nephropathy; to explore the intervention effect of 1,25(OH)2D3 on Treg cells, RORγt, IL-17 expression in rats with IgA nephropathy.

Methods: We chooseister 52 rats, with which 8 rats were chosen in control group (group D) in random, while other 44 rats were established the IgA nephropathy model by mucosal immune with bovine serum albumin and were divided into model group (group E) in random, while other 44 rats were established the IgA nephropathy model by mucosal immune with bovine serum albumin and were divided into model group, 1,25(OH)2D3 treated group, prednisone treatment group and prednisone +1,25(OH)2D3 treatment group.

Results: The change of 24 hours of urinary protein, red blood cells in urine, creatinine and blood calcium of rats were detected. Foxp3, RORγt and IL-17 levels were detected by using RT-PCR, Immunohistochemistry and Westernblot.

Conclusions: These data suggests that the novel chronic renal ischemia model by coating renal artery is an appropriate animal model for CKD, which shows a slowly progressive tubulointerstitial injury.

Funding: Government Support - Non-U.S.

PUB076

Dialysis Induces Morphological Changes and Eryptosis in Erythrocytes

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Background: Death of erythrocytes (eryptosis) is characterized by cell shrinkage, membrane blebbing, activation of proteases, and phosphatidylserine (PS) externalization. Exposed PS is recognized by macrophages that engulf and degrade cells. Eryptosis is a physiological mechanism under complex regulation. During their daily life, erythrocytes (RBCs) are exposed to several stressors, such as oxidative stress, osmotic shock, energy depletion. Eryptosis is observed in a wide range of clinical conditions, such as CKD, malignancy, diabetes and sepsis. The aim of this study was analyzed cell volume and PS abundance at the RBC surface in peritoneal dialysis (PD) and hemodialysis (HD).

Methods: 40 PD patients, 30 HD patients and 17 healthy subjects (CTR) were included in the study. All measurements were made in isolated RBCs. RBC volume and morphology were estimated from forward scatter, PS exposure at the cell surface was estimated from FITC-AnnexinV binding using flow cytometric analyses.

Results: We observed that the RBCs of PD and HD patients are either rather dramatically deranged in their morphology. Furthermore, the PS externalization on the RBC surface was significantly higher in these groups than in CTR (PD patients: 2.6%; IQR 1.6-3.7; HD patients: 2.2%; IQR 1.2-4.1 versus CTR: 0.8%; IQR 0.7-1.3; p<0.000001). We did not find significant differences in PS exposure between the PD and HD patients (p<0.047).

Funding: Private Foundation Support

PUB077

Toll Like Receptor 2, 4 and 9 Expression Is Enhanced in Kidneys of Patients with Anti Neutrophil Cytoplasmic Antibody Associated Vasculitis (AAV)

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Background: Toll like receptors (TLRs) may be the possible link between infection and autoimmunity. This study investigates the distribution of TLR2, 4 and 9 in human kidney biopsies from patients with AAV (40), lupus (8) and controls (with non proliferative glomerular lesions, minimal change and thin membrane disease, 10).

Methods: Biopsies were examined by confocal microscopy with immunofluorescent staining in serial sections for the cellular distribution of TLR2, 4 and 9. Mean fluorescent intensity (MFI) was measured by imaging software (Image J) and was correlated with histopathological parameters.

Results: TLR2, 4 and 9 in the AAV group, (for both MPO and PR3 patients) had significantly stronger staining than controls in glomeruli (1.5 vs 13.3AU; 0.25 vs 32.0AU; 0.7 vs 36.2AU, all P<0.05, respectively) and the interstitium (7.4 vs 63.0AU; 0.41 vs 53.8AU; 1.6 vs 59.6 AU, all P<0.05, respectively). The lupus patients also had higher
expression of TL2R (4.8AU), 4 (12.6AU) and 7 (7.3AU, P<0.05) compared with controls, but their staining was significantly less than that of the AA V group for all TLRs (P<0.05).

Cellular infiltrates contained intense staining for TL2R, 4, 9 and 2 on macrophages and neutrophils in both glomeruli and interstitium. TL2R and TL4 staining was prominent on both endothelial cells and podocytes, although TL9 was particularly evident on podocytes. In AA V glomerular TL4 expression correlated with the % of normal glomeruli (r=0.48, P=0.03) suggesting TL4 prominence occurs in early glomerular lesions. Glomerular TL2R and 9 were present concurrently in more severely affected glomeruli (r=0.71, P=0.0001). TL2R, 4 and 9 were prominent in all crescentic glomeruli of AA V and lupus patients.

Conclusions: this study demonstrates that TL4 expression is most prominent in AA V. Significant expression of TL2Rs was evident on leucocytes and immature glomerular cells. TL4R is prominent in early glomerular lesions, while TL2R and 9 correlate with severe glomerular lesions.

Funding: Government Support - Non-U.S.

PUB078
Podocyte CD40 Expression in Patients with Post-Transplant FSGS Recurrence: Rutger J. Maas,1 Brigit Willemsen,2 Henk Jeroen,3 Jeroen Deegens,3,1 Jack F. Wetzel3,1 Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; 2Pathology, Radboud Univ Medical Center, Nijmegen, Netherlands.

Background: antibodies against CD40 were recently reported to predict post-transplant recurrent FSGS (rFSGS) with 78% accuracy (Deville et al. Sci Transl Med 2014). Using immunohistochemistry, the authors reported strong focal podocyte CD40 expression in glomerular lesions of two patients with rFSGS. We sought to validate this novel finding of podocyte CD40 expression as a potential marker of rFSGS.

Methods: we used formalin-fixed, paraffin embedded kidney tissue from five patients with rFSGS. Two samples were obtained from nephrectomy specimens, and three were needle biopsy specimens. All patients had nephrotic range proteinuria at the time of tissue sampling. A human tonsil was used as a positive control. For immunohistochemistry, four mm slices were cut and deparaffinised. After endogenous peroxidase block, antigen retrieval was performed by boiling in a microwave with EDTA buffer (pH 9.0). Slides were incubated with primary antibody mouse anti CD40 (clone 11E9, Abcam ab50849) diluted in PBS with 1% BSA overnight at 4°C. Slides were incubated with primary antibody mouse anti CD40 (clone 11E9, Abcam ab50849) diluted in PBS with 1% BSA overnight at 4°C. Detection was done with Brightvision biotin-free goat anti rabbit/mouse poly HRP (Immunologic) and DAB as substrate.

Results: specificity and adequacy of the staining was confirmed by strong CD40 expression in tonsillar germinal centers (Figure, panel A). In kidney samples from patients with rFSGS, CD40 staining was found in areas of interstitial cellular infiltration, and some tubular epithelial cells (Figure, panel B). However, no glomerular CD40 was detected in any of the rFSGS samples.

Conclusions: we could not confirm glomerular CD40 staining in rFSGS with immunohistochemistry. The role of CD40 antibodies in rFSGS pathogenesis needs further study and validation.

Funding: Private Foundation Support

PUB079
Increased Cellular Microchimerism in Women with Systemic Lupus Erythematosus: Suzanne Wilhelms,1 Malu Zandbergen,1 Emilie Rijnink,1 Juan D. Diaz de Pool,3 Mathilde M.M. Almekinders,1 Hans J. Baede,1 Jan A. Brujin,1 Ingeborg M. Bajema,2 1Pathology, Leiden Univ Medical Center, Leiden, Netherlands; 2Gynaecology, Leiden Univ Medical Center, Leiden, Netherlands.

Background: Microchimerism (Mc) has been suggested to play a role in the development of systemic lupus erythematosus (SLE). We previously showed that Mc occurs twice as often in kidney biopsies of patients with lupus nephritis as in controls. Recently, it was demonstrated that the amount of Mc in lupus nephritis is associated with renal function (Arthritis Research & Therapy, 2015). Because in previous studies the Y chromosome was used to detect Mc, these studies were limited to detecting male Mc and the origin of the chimeric cells remained largely unknown. The aim of the present study was to determine the frequency, amount and origin of chimeric cells in SLE patients and controls, by using insertion-deletion polymorphisms and null alleles for the detection of Mc.

Methods: We included 11 SLE patients and 22 controls, as well as their children and mothers. A quantitative PCR for insertion-deletion polymorphisms and null alleles was used to detect Mc in peripheral blood mononuclear cells and granulocytes. The relationship between the presence of Mc and disease onset, disease activity and accumulated damage since disease onset was investigated.

Results: Mc was detected more often in SLE patients than in controls (54.4% vs 13.6%, P=0.007), and was fetal in origin in almost all cases. The median total number of fetal chimeric cells was significantly higher in patients than in controls (5x10^5 versus 2.5x10^5, P=0.048). In 50% of SLE patients with Mc, Mc originated from multiple relatives whereas in controls Mc was derived from only one relative. We found no relationship between Mc and clinical or laboratory parameters.

Conclusions: SLE patients had Mc in peripheral blood more often than controls, and at higher levels. We showed that Mc was mostly fetal in origin and, in SLE patients, could be derived from multiple relatives. Our findings substantiate the role for Mc in autoimmune diseases such as SLE.

Funding: Private Foundation Support

PUB080
An Oxalate-Induced Mouse Model of CKD That Displays Common CKD Complications: Hans J. Baelde,1 Shrikant R. Raj,1 Jeroen Deegens,2 Hans J. Baelde,1 Julian A. Marschner,2 Simone Romoli,1 Jyaysi Desai,1 Santhosh Kumar Vr,1 Peter S. Aronson,1 Felix Knauf2 1Univ of Erlangen-Nürnberg; 2Yale Univ School of Medicine.

Background: Chronic kidney disease (CKD) research is limited by the lack of a convenient inducible C57BL/6 mouse model mimicking relevant human CKD complications. We have reported a high soluble oxalate diet (50 µmol/g sodium oxalate mixed with virtually calcium free diet) that induces a progressive decline in glomerular filtration rate (GFR) reflected by increasing creatinine as well as blood urea nitrogen levels in C57BL/6 mice.

Methods: All in vivo experiments were approved by the local government authorities. Computed tomography, ultrasound and MRI were used for imaging.IHC, RT-PCR were used for data analysis. GFR was measured using single i.v. bolus injection of FITC sinistrin in conscious mice.

Results: We now demonstrate that mice fed this high soluble oxalate diet develop typical CKD complications such as sustained hypertension, normochromic anemia, metabolic acidosis, hyperphosphatemia, hyperparathyroidism, and hyperkalemia. Renal histology is characterized by calcium-oxalate crystal plugs in the tubular lumen, tubular atrophy, interstitial fibrosis, and atubular glomeruli. This pathophysiology of CKD resembles that of primary hyperoxaluria type I, also in terms of renal ultrasound, computed tomography, and magnetic resonance imaging. The duration of feeding a high soluble oxalate diet determines the amount of nephron loss, interstitial fibrosis, and impaired GFR equivalent to different stages of CKD. This can be used to produce various levels of stable impaired baseline GFR, a useful way to study, for example, AKI on precedent CKD.

Conclusions: We conclude that feeding a high soluble oxalate diet is a convenient way to induce progressive and stable CKD with clinically established complications in C57BL/6 mice. This model should serve to be useful for many areas of CKD research and avoid surgery to induce nephron loss or renal fibrosis.

Funding: Private Foundation Support

PUB081
Cyclosporine A Reduces Renal Injury Through Protecting Glomerular Barrier Function in Post-Transplant FSGS: Jilong Li,1 Juan Wang,2 Lining Wang,2 Dept of Nephrology, First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning, China.

Background: Cyclosporine A (CsA) has been reported to reduce proteinuria in several kinds of kidney diseases. Glomerular barrier function is important in preventing urinary protein loss. The aim of this study was to elucidate the effects of CsA on glomerular barrier function in post-transplant FSGS.

Methods: Wistar rat PHN model was established by injecting antisera against renal tubular epithelial antigens (anti-FxA1) following pre-immunization. The experiment included Group 1: PHN control, Group 2: PHN plus CsA treatment before anti-FxA1 injection, Group 3: PHN plus CsA treatment for the first 7 days after injection, and Group 4: PHN plus CsA treatment from the 8th day after injection. Serum creatinine (sCr) and urinary protein (uPro) were measured at the 7th and/or the 14th day. Kidney tissues were obtained at the 14th day and labeled with a cation tracer polyethyleneimine (PEI) to study the distribution of negative charges on glomerular basement membrane (GBM). Kidney pathological changes were investigated.

Results: PHN model was established showing proteinuria and kidney injury of the renal GBM, a mass deposition of immune complex (IC), and decreased density and disturbed distribution of negative charges along the GBM. sCr was not increased in all of the groups. With CsA treatment, uPro was significantly declined in Group 2 and 3 at 7th and/or the 14th day. Kidney tissues were obtained at the 14th day and labeled with a cation tracer polyethyleneimine (PEI) to study the distribution of negative charges on glomerular basement membrane (GBM). Kidney pathological changes were investigated.

Conclusions: PHN model was established showing proteinuria and kidney injury of the renal GBM, a mass deposition of immune complex (IC), and decreased density and disturbed distribution of negative charges along the GBM. sCr was not increased in all of the groups. With CsA treatment, uPro was significantly declined in Group 2 and 3 at 7th and/or the 14th day. Kidney tissues were obtained at the 14th day and labeled with a cation tracer polyethyleneimine (PEI) to study the distribution of negative charges on glomerular basement membrane (GBM). Kidney pathological changes were investigated.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
overwhelmed and glomeruli may be exposed to high free heme, exceeding 200 µM.

Results: ADR triggered overexpression of caspase-1 and IL-1β in kidney tissue of WT mice, but not in that of KO mice. ADR induced albuminuria and GS, which was accompanied with decreased kidney weight/body weight ratio (Kw/Bw), and increased Cr and TCH levels in both KO and WT mice. Compared with WT animals, KO mice showed significantly lower ACR, reduced GS scores, increased Kw/Bw, and attenuated Cr levels (P<0.05 each). Meanwhile, elevated expression of TNF-α and INF-γ, augmented 12-LO, and decreased PPAR-α, SDHA, and SOD2 levels were observed in ADR-treated kidneys, and all these changes were shown to be significantly ameliorated in KO mice. In addition, positive correlation between Cr and TCH was recognized in both KO and WT ADR-treated mice.

Conclusions: Cytokine-mediated inflammatory cascade, hyperlipidemic injury, and impaired mitochondrial function can be exposed to high free heme, exceeding 200 µM. However, while HO-1 prominently increases in tubules, it is barely detectable in glomeruli. We hypothesized that this is due to presence of a HO-1 expression “threshold” above which HO-1 induction in glomeruli is not sustainable.

Methods: hmdox1-1 rats were generated by Zinc Finger Nuclease (ZFN)-mediated HO-1 gene disruption and rats with GEC targeted HO-1 overexpression (GEC+HO-1) by Sleeping Beauty Transposon mediated transgenesis using a nphrin promoter. Glomeruli from wild type (WT) or hmdox1-1 or GEC+HO-1 rats were incubated for 18 h with 10% HPX replete (HPX+) or HPX-deficient (HPX-) serum obtained from HPX knock-out mice. Exogenous heme was added at concentrations encountered in hemolytic disorders (100-400 µM). HO-1 protein levels were assessed by western blot.

Results: HO-1 protein was reduced by 70% in hmdox1-1 and increased by 2-fold in GEC+HO-1 glomeruli. HO-1 protein levels were different between 10% HPX+ serum vs serum-free media. In incubations with varying dilutions of HPX serum (1.25, 2.5, 5, 10%) HO-1 levels in WT glomeruli progressively increased and were 2.5-fold higher than 10% HPX serum compared to 10% HPX serum. Co-incubation with 10% HPX serum and heme (200, 400 µM) markedly reduced HO-1. This reduction was attenuated in incubations with higher dilutions (2.5%) of HPX serum or with 10% HPX serum. The effect of heme on HO-1 levels in glomeruli incubated with HPX serum was recapitulated in GEC+HO-1 glomeruli. In contrast, heme further increased HO-1 in hmdox1-1 glomeruli.

Conclusions: Heme-mediated HO-1 induction in glomeruli is limited by HO-1 expression levels attained. This may serve to limit level of HO activity thereby preventing excessive heme-derived Fe stress stimuli of extrinsic coagulation pathways and is also related to various biologic effects of heme repletion, such as activating cell metabolism, oxidative stress, de-differentiation & detachment. The purpose of this study was to compare commonly used conditionally immortalized podocytes with primary podocytes, by measuring podocyte markers and responses to injury.

Results: Primary human podocytes were isolated and cultured from a healthy human donor kidney and compared to 1) a subclone (C5) of conditionally immortalized human podocytes (selected based on podocyte specific gene expression) and 2) conditionally immortalized mouse podocytes. Cellular phenotypes and gene expression were measured using high content screening (HCS), qPCR and western blots. For assessment of diabetic protection often use the storimeters pyruvamiminacacid and TGF-β. We demonstrate cytoprotection by multiple reference compounds with these results. We have also increased the disease relevance of stressors by showing that stress isolated from proteinemia db/db mice differentially elicits podocyte injury across multiple parameters.

Conclusions: Our results validate the use of conditionally immortalized C5 podocytes by benchmarking against primary human podocytes. We have also enhanced the pathological relevance of models of podocyte injury by incorporating key disease-relevant stressors and readouts.

Funding: Pharmaceutical Company Support - AbbVie

PB0806

Hypoxia Stimulates the Expression of Tissue Factor in Human Podocytes in Culture


Background: Hypoxia contributes to tubulointerstitial injury, however, the effect on podocytes and its underlying mechanisms are less well understood. Tissue factor (TF) is the initiator of extrinsic coagulation pathways and is also related to various biologic effects of hypoxia such as activating cell metabolism, oxidative stress, de-differentiation & detachment. The purpose of this study was to compare commonly used conditionally immortalized podocytes with primary podocytes, by measuring podocyte markers and responses to injury.

Methods: Conditionally immortalized human podocytes were grown at 33°C and differentiated at 37°C. The cells were treated in normoxic or hypoxic conditions. mRNA expressions of TF and TFPI were analyzed by quantitative RT-PCR, and protein levels of TF and TFPI in cytoplasm and TFPI in supernatant were analyzed by ELISA. The creation of TF and HIF-1α were demonstrated by immunofluorescent staining. We used sRNA for the temporal knockdown of HIF-1α and Egr-1, and pyridoline dithiocarbamate (PDC) for the inhibition of NF-κB.

Results: Hypoxia increased mRNA expression of TF (6h; 2.3±0.05 fold, p<0.001, 24h; 5.6±2.4 fold, p<0.005) and suppressed TFPI (6h: 0.5±0.04 fold, p=0.05, 24h: 0.2±0.06 fold, p<0.001) compared with normoxia. The protein levels of TF in the cell lysate were increased and TFPI in the supernatant were decreased. The TF staining was enhanced in
The cytostasis of podocyte. As expected, HIF-1α was strongly stained in the nuclei of podocytes exposed to hypoxia for 6h. The expression of TF was not affected by HIF-1α siRNA, and neither Egr-1 siRNA. Whereas, PDTC reduced the induction of TF by hypoxia.

Conclusions: Hypoxia upregulated the expression of TF in human podocyte Nf-κB dependently, and HIF-1α and Egr-1 independently. These changes may be related to the podocyte disorders and lead to proteinuria in the hypoxic condition.

**PUB087**

**Integrity of the Mature APOL1 Protein Is Indispensable for Its Toxicity**

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**Background:** Several clinical reports have demonstrated that the development of higher rates of non-diabetic glomerulosclerosis (GS) amongst African Americans can be attributed to two coding sequence variants (G1 and G2) in the APOL1 gene. Recent studies indicate that the gene products of these APOL1 risk variants have augmented toxicity in kidney cells. The APOL1 protein is composed of several functional domains, including signal peptide (SP), pore forming domain (PFD), membrane address domain (MAD), and SRA-interacting domain. However, it is not clear, which domain contributes to APOL1 induced cellular toxicity. In case, specific domain is contributing to APOL1-induced cellular toxicity, it will suggest us to design therapeutic strategy to target the specific domain.

**Methods:** To investigate the relative contribution of each domain to cell injury, we constructed serial of expression vectors to delete each domain, we transfected these vectors into the human embryonic kidney cell line 293T, and then compared the cytotoxicity. In addition, we conducted studies in which APOL1 wild type (G0) was co-transfected in combination with G1 or G2 to see whether G0 could counteract the toxicity of the risk variants.

**Results:** The results showed that deleting the SP did not abolish the toxicity of APOL1, though deletion of 26 amino acid residues at the N-terminal partially decreased the toxicity. Deleting PFD or MAD or SRA-interacting domain abolished toxicity while, overexpressing each domain alone could not cause toxicity to the host cells. Deletion of the G2 sites while retaining G1 sites in the risk state resulted in persistent toxicity. Either deletion or exchanging the BH3 domain in the PFD led to complete loss of the toxicity in this experimental platform. Adding G0 to either G1 or G2 did not attenuate the toxicity of the either moiety.

**Conclusions:** These findings indicate that the integrity of the mature APOL1 protein is critical for its toxicity.

**Funding:** NIDDK Support

**PUB088**

**Human Podocyte Depletion: The Effects of Ageing and Hypertension**

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**Background:** Podocyte depletion plays a major role in the development and progression of glomerulosclerosis. Many kidney diseases are more common in older age, and usually coexist with the presence of hypertension. We hypothesize that podocyte depletion develops with aging and is exacerbated by the presence of hypertension.

**Methods:** Kidneys from 21 adult Caucasian males without overt renal disease were collected at autopsy in Mississippi, USA. Subjects were categorized based only on age as young adults, middle-aged adults and older adults. Subjects were also categorized based on age and hypertension as young normotensives, older normotensives, and older hypertensives. Demographic data were collected from available medical records. Design-based stereology was used to estimate individual glomerular volume (tGv), podocyte number and podocyte density. Data are presented as mean±SD.

**Results:** Glomeruli from young adults (22±0.27 years; n=6) were small (1.72±0.50 x10³/mm²), and contained 457±97 podocytes and 278±66 podocytes per 10³/mm² of glomerular tissue. Glomeruli from older adults (60±8.6; n=7) were larger (2.94±1.41 x10³/mm²; P<0.001), contained fewer podocytes (390±105; P<0.05) and had lower podocyte density (156±65 podocytes per 10³/mm²; P<0.001). Among normotensives, older age was associated with a 15% increase in IGV (P=0.28); a 12% decrease in podocyte number (P<0.001) and a 17% decrease in podocyte density (P=0.001). Glomeruli from hypertensives and normotensives contained similar numbers of podocytes, but hypertensives had larger glomeruli (P<0.0001) and a markedly lower podocyte density (P<0.001).

**Conclusions:** These findings demonstrate that both aging and hypertension are independent and additive contributors to podocyte depletion in this cohort of white American men without overt kidney disease.

**PUB089**

**Alport Nephropathy Progression Involves Altered Glomerular Mechanical Properties and Activation of the Unfolded Protein Response**

Addie Embry,1 Liping Liu,2 Leslie A. Bruggeman,3 Paul A. Janney,4 Tyler Miller.1 1Medicine, UTSW, Dallas, TX; 2Medicine, CWRU, Cleveland, OH.

**Background:** Tissue and cell mechanics are important factors in the development and maintenance of tissues but are not well defined in renal disease. We determined the biophysical properties of glomeruli over the course of disease in the Cnkd4-/- (Alport) mouse.

**Methods:** Glomerular Elastin was measured with microindentation, gene transcript levels with qRT-PCR and immunofluorescence, and kidney structure with histology.

**Results:** Cnkd4-/- kidneys have normal histology, no proteinuria, and a normal glomerular filtration rate (2,200±200) through 2 mo of age. At approximately 4 mo, early interstitial and glomerular fibrosis and proteinuria appear, and the glomerular Fmax decreases (~1,400Pa). Glomerular softening is characterized of injured glomeruli, is associated with injured podocytes, and could lead to capillary injury even with normal hemodynamics. By 6 mo, the glomeruli regain their original Fmax (~ 2,200 Pa) but with increased proteinuria and more severe glomerular and interstitial fibrosis. By 7-8 mo, the glomerular Fmax increases (~ 2,600 Pa) with further increases in proteinuria and glomerular and interstitial fibrosis. At 2 mo, glomerular transcripts for matrix and fibrinotic factors (CTGF, α-SMA, filamin, lysyl oxidase) are increased and remain so, demonstrating early responses of cells to alter their mechanical environment. Transcripts associated with UPR activation (Bip, CHOP, grp94) are elevated, suggesting that loss of the Cnkd4-/- chain leads to activation of the UPR. Tunicamycin-treated glomeruli demonstrated a markedly reduced Fmax (~1,100Pa), suggesting that UPR activation causes glomerular injury.

**Conclusions:** Biophysical abnormalities occur early in the course of this Alport model, suggest that the reduced Fmax of glomeruli (increased deformability) may lead to mechanical injury of capillaries even with normal hemodynamic force, that cells of glomeruli respond by producing proteins that will reduce deformability, and that glomerular or podocyte injury may be attributable to activation of the UPR.

**Funding:** NIDDK Support, Veterans Administration Support, Private Foundation Support

**PUB090**

**A New Assay to Study Podocyte (De)Differentiation**

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**Background:** Podocytes play an essential role in the formation and maintenance of the glomerular filtration barrier. Glomerular disease is associated with podocyte damage, frequently resulting in podocyte dedifferentiation. The loss of podocyte differentiation is poorly understood. Moreover, there are no drugs available that could halt or even reverse podocyte dedifferentiation. Since podocytes of isolated glomeruli have long been known to spontaneously lose their highly differentiated state over time, we established an assay to follow dedifferentiation of living podocyte in isolated glomeruli over time.

**Methods:** Using magnetic separation with dynabeads, glomeruli were isolated from transgenic mice that express cyan fluorescence protein (CFP) under control of a nephrin promoter fragment (Cui et al., ‘‘<em style="font-family: ‘Times New Roman’; font-size: 16px;’’>3<em>,<em> J Am Soc Nephrol</em>’’[latex] 11: 3247-55, 2000). Results: Isolated glomeruli were cultured on a filter under a low flow of nutrient medium. Isolated glomeruli bound to cell culture dishes. As CFP fluorescence, we recorded z-stacks of several glomeruli at 906A to be observed. The aim of this research was to confirm digestion of enzymes to study the role of the e-GLX removal was not directly quantified. The aim of this research was to confirm e-GLX in glomerular permeability. However, several clinical reports have demonstrated that the development of diabetic glomerulosclerosis (GS) amongst African Americans can be attributed to two coding sequence variants (G1 and G2) in the APOL1 gene. Recent studies suggest that the reduced Emax of glomeruli (increased deformability) may lead to mechanical injury of capillaries even with normal hemodynamic force, that cells of glomeruli respond by producing proteins that will reduce deformability, and that glomerular or podocyte injury may be attributable to activation of the UPR.

**Funding:** Government Support - Non-U.S.

**PUB091**

**Methods to Selectively Remove Murine Endothelial Glycocalyx In Vitro Using Glycosaminoglycan Digesting Enzymes without Causing Non-Target Effects**

Karen L. Onions, Anjila Onifade, Chris R. Neal, Monica Gamez, Gavin Iain Welsh, Andy Salmon, Simon C. Satchell, Rebecca R. Foster. Academic Renal Unit, Univ of Bristol, Bristol, United Kingdom.

**Background:** The endothelial glycocalyx (~GLX) is an important component of the glomerular filtration barrier (GFB), damage to which increases vascular permeability and microalbuminuria. Jeunson and Haraldson previously used glycosaminoglycan (GAG) digesting enzymes to study the role of the e-GLX in glomerular permeability. However, e-GLX removal was not directly quantified. The aim of this research was to confirm removal of systemic e-GLX and identify any non-targeted effects in the glomerular or coronary microcirculation.

**Methods:** Mice were injected LV with chondroitinase (Ch) and hyaluronidase (Hy) at a high (Ch: 87 mU/g, Hy: 15U/g) or low (Ch: 0.087 mU/g, Hy: 15 mU/g) dose. Mice

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

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and the serum level of indoxyl sulfate in CKD patients. These results suggest that BPS has reduced by BPS in GN rats. In addition, in humans, the serum concentration of creatinine and by BPS treatment, the reduced concentration of tryptophan recovered to the normal Arginine, Glycine, Cystathionine) also increased in GN and all of them are reduced by BPS treatment. Among the anionic solute that increased in GN rats, the concentration of 2 anionic solutes (Gluconate and Citrate) are ameliorated by BPS treatment. Solutes were further examined. Among the anionic solute that increased in GN rats, the highest density of NG2+ cells was in the outer medulla, and confirmed the presence of 3-10 cells-containing monochromatic (clonal) tracing units along the cortical vasculature, afferent arteriole, and within the glomerulus (including mesangial and parietal epithelial cells, and a very few podocytes) and the proximal tubule. Spherical or stellate-shaped NG2+ cells were observed in the Bowman’s space and in the proximal tubule lumen suggesting cell migration.

Conclusions: In summary, our data are consistent with highly dynamic cellular remodeling of the renal interstitium, vasculature, glomerulus, and the proximal tubule by single progenitor cells. These results also suggest the presence of a complex nephrin repair program which is augmented in response to salt deprivation. 

Funding: NIDDK Support

PUB093

Beraprost Ameliorates Renal Function and Reduce Uremic Toxin in GN

Background: In CKD patients, the accumulation of uremic toxins exacerbates renal damage. Beraprost sodium (BPS) is prostacyclin analogue and is mainly used to treat atherosclerotic obliterans. Recently, Several reports show that BPS reduced progression of renal damages in CKD. To identify the renoprotective effect of BPS, we measured uremic solutes by capillary electrophoresis with mass spectrometry (CE-MS) in anti-GBM Glomerular Nephropathy(GN) rat model as well as 4 CKD patients before and 5 month after BPS administration.

Methods: A comprehensive and quantitative analysis of charged metabolites by CE-MS was performed. We obtained serum from (1) Normal rats, GBM GN rats and 4 CKD patients. Serum from (2) 16 anionic solutes, 16 anionic solutes and 42 cationic solutes were further examined. Among the anionic solute that increased in GN rats, the concentration of 2 anionic solutes (Gluconate and Citrate) are ameliorated by BPS treatment. Among the cationic solute that increased in GN rats, the concentration of 10 cationic solutes (Arginine, Glycine, Cystathionine) also increased in GN and all of them are reduced by BPS treatment. Conversely, the concentration of 8 metabolites were decreased in GN rats, and by BPS treatment, the reduced concentration of tryptophan recovered to the normal level. GLX in glomerular permeability. Increasing understanding in the nitric oxide mechanism and involving of nitric oxide in the progression of CKD is a potential to prevent the progression of CKD. These results suggest that BPS has a potential to prevent the progression of CKD.

Funding: Pharmaceutical Company Support - Reserch grant from Toray

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

Underline represents presenting author.

907A

PUB094

A Novel Method to Measure Glomerular Permeability

Background: Glomerular capillaries are relatively impermeable to proteins, but in certain kidney diseases, such as diabetic nephropathy, the glomerular permeability (GP) is increased and some of the lower molecular weight (LMW) proteins, especially albumin, are filtered through the glomerular barrier into the Bowman’s space. Increased GP is a hallmark for many kidney diseases. Proteinuria is often implicated for impaired GP. However, since LMW proteins can be reabsorbed by proximal tubules, proteinuria is detected only when the GP is significantly increased. Recently, real-time quantification of GP can be visualized by two-photon microscopy, but it can only be applied to superficial nephrons, where laser can penetrate, in Munich-Wistar rats. We developed a novel method to monitor GP in C57/BL6 mice by using flow丞sent lysine-fixable dextran conjugates without these limitations.

Methods: 100μl Tomato Lectin 594 (endothelial cell marker) plus 50μl 40 KD lysine-fixable dextran 488 (fluid phase marker) were injected intravenously. The kidneys were removed 1 min later and put into liquid nitrogen immediately for 10 minutes followed by fixation with 10% Formalin on ice overnight. Then 100μm thick sections were prepared using a vibratome and the flow丞sent images were collected with two-photon microscopy. The ratio of flow丞sent intensity in Bowman’s space over that in glomerular capillary lumen was used as an index of GP.

Results: In WT mice, the GP is extremely low with a ratio of 0.16±0.08%, N=6 (figure1). In contrast, in diabetic mice induced by alloxan for 8 weeks, the GP is significantly increased with a ratio of 5.9±1.3%, N=6.

Conclusions: In summary, we developed a novel and sensitive method to monitor changes in GP using two-photon microscopy, which can be used for rodents and bigger animals.

Funding: Bluebird Bio, Inc.

PUB095

Vasopressin Regulates the Uptake of Extracellular Vesicles by Kidney Collecting Duct Cells

Background: Urine contains extracellular vesicles (ECVs) originating from the circulation and all cells lining the urinary tract. ECVs are a route of inter-cellular communication along the nephron able to transfer protein and RNA. It is not known whether this is a regulated process analogous to other cell-to-cell signalling systems.

Methods: Kidney cortical collecting duct cells (CCDs) were stimulated with desmopressin, a vasopressin analogue, and uptake of fluorescently-loaded or microRNA-loaded ECVs was measured. In mice, fluorescently-loaded ECVs were intravenously injected before and after administration of the V2 antagonist, tolvaptan, and urinary ECV excretion was measured. By combining antibodies to nephron segment-specific proteins with nanoparticle tracking analysis we measured human urinary ECV excretion in current diabetic nephropathy patients (DI) and after radiocontrast exposure. The ratio of flow丞sent intensity in Bowman’s space over that in glomerular capillary lumen was used as an index of GP.

Results: Desmopressin stimulated ECV uptake into CCDs via V2 receptor stimulation.

Conclusions: Tubular ECV uptake is a specific, hormonally regulated process that is reduced with injury. Physiologically, ECVs are a mechanism of inter-cellular communication; therapeutically, ECVs represent a novel vehicle by which RNA therapy could be targeted for the treatment of kidney disease.

Funding: National Inst of Diabetes and Digestive and Kidney Diseases, National Insts

Wang, Lei Wang, Gensheng Zhang, Jie Zhang, Byeong Cha, Kay-Pong D. Yip, Ruisheng Liu. Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL.

Vasopressin Regulates the Uptake of Extracellular Vesicles by Kidney Collecting Duct Cells

Wifa Owsu-Huenzeg, Jessica R. Ivy, Joram Street, Andrea Caporali, David J. Webb, Chris Gregory, Matthew A. Bailey, James W. Dear. Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom;

Background: Urine contains extracellular vesicles (ECVs) originating from the circulation and all cells lining the urinary tract. ECVs are a route of inter-cellular communication along the nephron able to transfer protein and RNA. It is not known whether this is a regulated process analogous to other cell-to-cell signalling systems.

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Systemic Hypertension and Pro-Inflammatory Cytokines
Massimo de Cal,1 Grazia Maria Virzi,1 Alessandra Brocca,1 Salvador Roberto Lopez,2 José Luis Salas,2 Stefano Marcante,2 Silvia De Rosa,1 Claudio Ronco.1 1Nephrology, S.Bortolo Hospital, Vicenza, Italy; 2ICU, S.Bortolo Hospital, Vicenza, Italy.

Background: Cytokines produced by renal tubular epithelial cells are critical factors in inflammatory processes of renal ischemia-reperfusion injury. Increased levels of cytokines have been reported after resectional surgery from cardiac arrest. Pro-inflammatory cytokines, such as IL-1β, IL-6 and IL-18, produced in the kidney during ischemia-reperfusion injury, are able to contribute to the renal damage. The purpose of this investigation was to define the proinflammatory cytokines response after resection and during extended observation following therapeutic hypothermia phases.

Methods: We performed a prospective observational study in 36 post-cardiac arrest patients treated with Induced Hypothermia (IH) with two different cooling device: 1) Arctic Sun; 2) Blanket. On Admission time and at 12, 24, and 72 hours after the start of treatment, blood and urine samples were collected. Plasma cytokines were measured by ELISA.

Results: During IH, we observed a decrease of IL-6, IL-1β and IL-18u levels in both groups, and an increase of inflammatory during rewarthing phase. The results are shown in table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arctic Sun (26 pts)</th>
<th>Blanket (10 pts)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β Adm</td>
<td>18 (12-20)</td>
<td>27 (9-43)</td>
<td>0.227</td>
</tr>
<tr>
<td>12hrs</td>
<td>17 (13-18)</td>
<td>17 (9-18)</td>
<td>0.841</td>
</tr>
<tr>
<td>24hrs</td>
<td>19 (13-21)</td>
<td>28 (10-51)</td>
<td>0.179</td>
</tr>
<tr>
<td>72hrs</td>
<td>20 (12-24)</td>
<td>35 (13-55)</td>
<td>0.089</td>
</tr>
<tr>
<td>IL-6 Adm</td>
<td>102 (40-121)</td>
<td>79 (29-104)</td>
<td>0.136</td>
</tr>
<tr>
<td>12hrs</td>
<td>100 (28-148)</td>
<td>72 (12-158)</td>
<td>0.194</td>
</tr>
<tr>
<td>24hrs</td>
<td>57 (33-77)</td>
<td>63 (20-112)</td>
<td>0.406</td>
</tr>
<tr>
<td>72hrs</td>
<td>59 (34-64)</td>
<td>67 (50-84)</td>
<td>0.713</td>
</tr>
<tr>
<td>IL-18u Adm</td>
<td>412 (363-978)</td>
<td>847 (189-1017)</td>
<td>0.749</td>
</tr>
<tr>
<td>12hrs</td>
<td>327 (326-365)</td>
<td>265 (201-327)</td>
<td>0.028</td>
</tr>
<tr>
<td>24hrs</td>
<td>348 (290-371)</td>
<td>140 (42-295)</td>
<td>0.005</td>
</tr>
<tr>
<td>72hrs</td>
<td>505 (332-538)</td>
<td>264 (44-337)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Conclusions: Optimal rewarthing rate is unknown. Adverse effects from suboptimal rewarthing could diminish a protective effect from hypothermia. These biomarkers may serve as indicator of an individual patient’s place in the injury-repair continuum. Further investigations are needed.

Impact of Different I.V. Iron Preparations on Monocyte Function and Differentiation
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Background: Treatment of iron deficiency with intravenous (i.v.) iron is a first-line strategy to improve anemia and quality of life in patients with chronic kidney disease (CKD). However, in vitro experiments have demonstrated that certain i.v. iron preparations have immunological side-effects. In the present study we now investigated substance-specific effects of different i.v. iron preparations on monocyte function and differentiation.

Methods: We in vitro stimulated monocytes with different concentrations (0.133 mg/ml, 0.266 mg/ml, 0.533 mg/ml) of iron sucrose (IS), sodium ferric gluconate (SFG), ferric carboxymaltose (FCM), and iron isomaltoside 1000 (IIM) and assessed monocytic adhesion, transmigration and immunophenotypical changes. IS and SFG increased monocytic adhesion, while transmigration was not affected by any preparation. The expression of M1 (CD40) and M2 (CD16, CD206) markers as well as the phagocytosis capacity were significantly reduced in IS and SFG stimulated macrophages. IS and SFG down-regulated CD14 and CD68 in DCs and up-regulated CD141 and HLA-DR. FCM affected macrophage and DC phenotype and function to a lesser degree, and IIM had no measurable immunological effects. In miRNA expression analysis we found IS to strongly dysregulate miRNAs which are linked to TLR and MAPK signaling pathways (e.g. mir-146b-5p, mir-155-5p).

Conclusions: Our findings demonstrate that less stable i.v. iron preparations like IS and SFG substance-specifically affect monocyte function and differentiation into macrophages and DCs in vitro. Future clinical trials should delineate in how far these observations will lead to clinically relevant changes in immune responses and thus affect the infection risk in CKD patients.

The Involvement of p38 MAPK in Neutrophil Bacterial Dysfunction of Hemodialysis Patients
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Background: Mortality from infection has been reported to be higher in hemodialysis (HD) patients than that in healthy subjects. However, the precise mechanism causing it remains to be investigated. Neutrophils play crucial roles in host defenses against bacterial infection. Therefore, we investigated the impact of neutrophil inflammatory signal on bacterial function in HD patients.

Methods: Four HD patients and six healthy subjects were recruited for this study. None of HD patients had diabetes, cardiovascular disease and cancer. Neutrophils were isolated from peripheral blood by density gradient centrifugation. The purity was tested by flow cytometry after lactoferrin staining. Microarray analysis was performed to assess global gene expression in leukocytes. Neutrophil bacterial function was evaluated by the growth rate of Staphylococcus aureus (S.aureus) after co-culture of it with neutrophils obtained from HD patients or healthy subjects. Reactive oxygen species (ROS) production and myeloperoxidase (MPO) activity were measured by fluorescence intensity.

Results: Microarray analysis showed the impairment of p38 mitogen activated protein kinase (MAPK) signal in neutrophils from HD patients. The growth rate of S.aureus was higher in HD patients than that in healthy subjects (490.1±147.1%, 144.5±49.4%, respectively; p<0.01) suggesting that neutrophil anti-bacterial killing function was dysregulated in HD patients. The levels of ROS from neutrophils after co-culture with S.aureus were lower in HD patients than those in healthy subjects (14.6±8.3, 32.4±15.4% for healthy, respectively; p<0.01). On the other hand, there was no difference of MPO activity between both groups. To confirm the importance of p38 MAPK, we examined the effect of the selective pharmacological p38 MAPK inhibitor SB202190 on neutrophil bacterial function. The treatment with SB202190 suppressed anti-bacterial killing function as well as MPO production in neutrophils.

Conclusions: Impaired of p38MAPK signaling pathway might contribute to the suppression of neutrophil bacterial function in HD patients through the dysregulation of ROS production.
NR2 and NF-xb mRNA Expression in Chronic Kidney Disease: A Focus on Non-Dialysis Patients

Denise Mafra,1 Viviane Oliveira Leal,2 Juliana Saldanha,1 Milena Barca Stockler-Pinto,3 Ludmila Fmm Cardo,3 Felipe Rizzato Santos,1 Alex Sandro Duarte Albuquerque,4 Maurilo Leite.4  ‘Graduate Program in Medical Sciences, Federal Univ Flamunense, Rio de Janeiro, Brazil;4 Pedro Ernesto Univ Hospital, State Univ of Rio de Janeiro (UERJ), Rio de Janeiro, Brazil;4 Graduate Program in Cardiovascular Sciences, Federal Univ Flamunense, Rio de Janeiro, Brazil;4 Div of Nephrology, Federal Univ of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.

Background: Nuclear factor erythroid 2-related factor 2 (Nr2), a regulator of genes encoding antioxidant and detoxifying enzymes appear to be downregulated in chronic kidney disease patients undergoing hemodialysis (HD). However, data regarding the expression of NR2 in non-dialysis patients are scanty. Thus, the aim of this study was to evaluate NR2 and nuclear factor kappa-B (NF-xb) mRNA expression in non-dialysis patients, comparing with data from HD patients.

Methods: 20 non-dialysis patients, 20 HD patients and 11 healthy subjects were enrolled. The peripheral blood mononuclear cells were isolated and processed for the evaluation of NF-xb and NR2 expression by quantitative real-time polymerase chain reaction.

Results: NR2 mRNA was significantly higher in non-dialysis when compared to HD patients but similar to healthy individuals. Inversely, NF-xb mRNA was lower in non-dialysis when compared to HD patients and also similar to healthy individuals i.e.

Figure 1. NR2 and NF-xb mRNA expression in healthy individuals, non-dialysis and HD patients.

NR2 mRNA was positively correlated with NF-xb mRNA in non-dialysis patients and healthy individuals. By contrast, NR2 mRNA was inversely correlated with NF-xb mRNA in HD patients.

Conclusions: Non-dialysis patients may conserve regular homeostatic balance between NR2 and NF-xb expressions, being comparable to healthy individuals. As renal disease progresses to more advanced stages, an impaired NR2/NF-xb balance can be observed, as in HD patients.

Funding: Government Support - Non-U.S.

ERK 1/2 and ERK 5 Signaling Pathways via Renin Angiotensin System Activation Play Differential Regulatory Roles During the Progression of Glomerulonephritis

Takashi Nagai,1 Maki Urushihiara,2 Shuji Kondo,1 Toshiaki Tamaki,1 Milena Barca Stockler-Pinto,3 Felipe Rizzato Santos,1 Alex Sandro Duarte Albuquerque,4 Maurilo Leite4 ‘Graduate Program in Medical Sciences, Tokushima Univ Graduate School, Tokushima, Japan;2 Dept of Pediatrics, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan;3 Dept of Pharmacology, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.

Background: Although extracellular signal regulated kinase (ERK)1/2 and ERK5 are key kinases of signaling pathway involved in various cellular functions in kidney injury, the mechanism between those kinase and renin-angiotensin system (RAS) activation in glomerulonephritis (GN) have not been fully elucidated. This study was performed to clarify the potential role of ERK1/2 and ERK5 via RAS activation in the pathogenesis of GN.

Methods: We examined the expression of ERK1/2 and ERK5 in rat progressive model of GN induced by anti-glomerular basement membrane antibodies in Wistar Kyoto rats. In addition, the signal transduction pathway in angiotensin II (Ang II) treated primary cultured mesangial cells (MCs) was evaluated.

Results: GN rat developed typical cellular crescent in glomeruli on day 7 and severe fibrocellular crescent and glomerulosclerosis were found on day 28. Immuno-staining of kidneys revealed that strong expression of phospho-ERK1/2 was observed on day 7 and phospho-ERK5 expression was markedly increased on day 28 of GN. Ang II type II receptor blocker (ARB) suppressed those augmentations. Macrophage infiltration and fibrocellular crescent and glomerulosclerosis were found on day 28. Immuno-staining pathologic alterations were investigated in primary cultured mesangial cells (MCs). In addition, the signal transduction pathway in angiotensin II (Ang II) treated primary cultured mesangial cells (MCs).

Conclusions: Macrophage infiltration and fibrocellular crescent and glomerulosclerosis progresses to more advanced stages, an impaired NR2/NF-xb balance can be observed, as in HD patients.

Funding: NIDDK Support, Private Foundation Support.

Chinese Herbal Medicine for IgA Nephropathy, ShenPing Decoction, Blocks Platelet-Derived Growth Factor Signaling Pathway Activated by IgA1-Containing Immune Complexes in Human Mesangial Cells

Xianwen Chen,1 Jianfei Ma.2 Nephrology; The First Affiliated Hospital of China Medical Univ, Shenyang, China.

Background: IgA1 nephropathy (IgA-N) is characterized by mesangial immune complex deposits containing galactose-deficient IgA1 (Gd-IgA1) usually associated with mesangial proliferation and matrix expansion. There is no disease-specific therapy of IgA-N, although a herbal medicinal prescription, ShenPing decoction (SP), has been used in China for decades to effectively treat IgA-N. Mesangial cell proliferation in IgA-N is likely induced by IgA1-Containing immune complexes (CIC) and this process may involve activation of platelet-derived growth factor (PDGF) signaling pathway. We have shown previously that SP blocks the activation of PDGF pathway induced by PDGF. In this study, we investigated the effect of CIC on PDGF signaling pathway in human mesangial cells (HMC) and assessed the effects of SP on this pathway.

Methods: CIC were isolated from sera of IgA-N patients using size-exclusion chromatography. Primary HMCs were incubated with PDGF or CIC for 15 min or 24 h with or without SP. Cellular proliferation was measured by Syto60. PDGF signaling was evaluated by SDS-PAGE and Western blotting.

Results: 24-h incubation with CIC increased MC proliferation and SP inhibited this effect. Stimulation of HMC with CIC increased phosphorylation of PDGFR and ERK1/2 after 15 min and 24 h. PDGF degradation was not observed in CIC-treated group, which is different from PDGF. SP inhibited CIC- and PDGF-induced phosphorylation and degradation of PDGFR.

Conclusions: CIC induced cellular proliferation of HMC and activation of PDGF pathway without degradation of PDGFR, a normal negative feedback observed for PDGF. CIC possibly caused persistent activation of PDGF pathway. SP inhibited those effects.

Funding: NIDDK Support, Private Foundation Support.

Effects of Fluorofenidone on the Expression of Thiorodoxin-Inter-Acting Protein and Thiorodoxin of Human Peritoneal Mesothelial Cell in High Glucose and Lipopolysaccharide

Yichen Chen,1 Jianfei Ma.2 Nephrology; The First Affiliated Hospital of China Medical Univ, Shenyang, China.

Background: Peritoneal dialysis is one of an important alternative therapies for end-stage kidney disease. But the occurrence of peritoneal dialysis correlation peritonitis has brought high resistance for the development of peritoneal dialysis. Significance of oxidative stress in peritoneal dialysis related peritonitis has been paid more and more attention. In cells that did not receive stimulation, Txnip combined with thioredoxin, when the elevated ROS concentration inside the cell, the formation of the compounds are separated. After dissociation Tx play its functions to remove ROS, whereas Txinap participation NRPL3 activation. Objective:To observe the effects of Fluorofenidone on the Expression of Txnip,Txin,Trx of HPMCs in High Glucose and Lipopolysaccharide.

Methods: The expression of Txnip and Trx mRNA was measured by real-time PCR,The levels of SOD,GPx,IL-6, TGF-b1 in the supernatants of HPMCs(10mM5S) were measured by ELISA, Experimental groups:Control group:high glucose and LPS for different concentrations and different times group;Fluorofenidone intervene group.

Results: Compared with the normal control, high glucose and LPS can significantly increase the expression of Txnip,Txin,Trx,IL-6 and TGF-b1 in a concentration and time dependent manner, all have statistically significant(P<0.05).Compared with 2.5% glucose and 10mg/L LPS group, Fluorofenidone can reduce the expression of Txnip,Trx,IL-6 and TGF-b1, increase the expression of Trx, all have statistically significant (P<0.05).

Conclusions: High glucose and LPS up-regulate the expression of Txnip,Txin,Trx in the protein and gene levels,and increase the expression of IL-6 and TGF-b1. Fluorofenidone could reduce the increase of Trx, IL-6 and TGF-b1, and increase the expression of Trx in HPMCs that have been pre-treated with high glucose and LPS. Fluorofenidone have the effect of anti-oxidant and anti-fibrosis.

Effects of Resveratrol on NRFP2 Expression in Raw 264.7 Macrophages Cells and Non-Dialyzed CKD Patients

Bruce A. Julian,1 Jan Novak.2 NIDDK Support, Private Foundation Support.

Results: Neither Modulation of NRFP2 expression via resveratrol was observed in the macrophage cell line, Raw 264.7, nor in the non-dialyzed CKD patients.

Background: Oxidative stress and inflammation are common in CKD. Bioactive compounds as resveratrol may modulate the Nr2 expression, a transcription factor that could up-regulate cellular antioxidant systems. The aim of this study was observe NRFP2 expression in macrophages cells and in non-dialyzed CKD patients treated with resveratrol.
Methods: Mouse RAW 264.7 macrophages were treated with 50μM of resveratrol in DMEM 1% (v/v). Nucleus and cytoplasm were separated. Western Blot (WB) was performed to quantify Nrf2. qRT-PCR was performed to evaluate Nrf2 expression. 7 non-dialyzed CKD patients (5 women; 64±6.5 years; GFR 37.9±10.4 mL/min) received 500mg of resveratrol/day for 4 weeks. qRT-PCR to evaluate Nrf2 expression was performed in PH1 model cells and after supplementation with resveratrol at the molecular level.

Results: Cells treated with resveratrol showed a significant activation of Nrf2 with an increase in the ratio nucleus/cytoplasm compared to control cells i.e. p=0.02. The same was observed in qRT-PCR (p=0.02). In patients, we observed a trend to increase Nrf2 expression with resveratrol supplementation (p=0.06).

Conclusions: We concluded that both cells and patients treated with resveratrol increased Nrf2 expression. So, we suppose that supplementation with resveratrol can lead to an increase in oxidative stress and inflammatory status among CKD patients.

PUB105
Mitochondrial Implications of Glycolate Metabolism in Primary Hyperoxaluria
Sonia Farague, Tanecia Mitchell, John Knight, Ross P. Holmes.
Urology, Univ of Alabama at Birmingham, Birmingham, AL.

Background: The primary hyperoxalurias (PH) are rare but severe inherited diseases characterized by an increased endogenous production of oxalate and calcium oxalate kidney stones in patients. Deficiency in alanine glyoxylate aminotransferase (AGT, deficient in PH1) or glyoxylate reductase (GR, deficient in PH2) have repercussion on the metabolism of the oxalate precursors glyoxylate and glycolate. Excessive amounts of glycolate are characteristic of PH1, through glyoxylate to glycolate cycling in the presence of glycolate oxidase (GO) and GR. Perturbations in glycolate metabolism may affect mitochondrial function in PH patients. The objective of this study is to assess how over-expression of these enzymes regulates glycolate and glyoxylate generation and mitochondrial function.

Methods: An established transformed CHO cells model was used in which cells express GO ± AGT or GR. Cells were incubated with glycolate or glyoxylate and the extracellular concentrations of oxalate and glycolate, and the induction of oxidative stress were analyzed. Cellular bioenergetics were assessed with a Seahorse XF-96 extracellular flux analyzer.

Results: The metabolism of glycolate by GO generated glyoxylate, oxalate and H₂O₂. Intracellular ROS were produced and cell viability was reduced. Mitochondrial respiration and the cellular biocatalytic reserve capacity were decreased following glycolate oxidation. The expression of AGT or GR reduced the unwanted effects of glycolate metabolism to glyoxylate and oxalate.

Conclusions: The disruption of normal glycolate metabolism by GO, AGT and GR in a cells model causes the production of stress-related metabolites and mitochondrial dysfunction. Limiting mitochondrial dysfunction might be a therapeutic approach in treating PH patients.

Funding: Private Foundation Support

PUB106
Effect of Fasudil on Response Oxidative Stress in High Glucose and Lipo polysaccharide Induced Human Peritoneal Mesothelial Cells
Ye Hu, Jianfei Ma.
Nephrology, The First Affiliated Hospital of China Medical Univ, Shenyang, Liaoning Province, China.

Background: Peritoneal fibrosis is a common cause of chronic peritoneal dialysis patients withdrew from peritoneal dialysis. Research shows that, there are oxidative stress exists in peritoneal dialysis patients. Rho/Rho kinase signaling pathway is involved in the regulation of multiple biological process, including inflammation, oxidative stress and fibrosis. The transcription factor Nrf2 related factor is a central regulator of cellular antioxidant responses. Rho kinase inhibitor fasudil is a Rock inhibitor which currently used in clinic and experiment, can regulate cell proliferation, migration, adhesion and movement at the cellular level. It also can regulate a variety of factors in inflammation, thrombogenesis, oxalosis, and fibrosis at the molecular level.

Methods: By using the method of Real Time-PCR to detect the expression of RhoA, ROCK1, Nrf2 and HO-1 mRNA; Western Blot to detect the expression of RhoA, ROCK1, Nrf2 and HO-1 protein; chemistry fluorescence test to detect the expression of ROS protein; chemical colorimetry to detect the expression of GSH-PX protein. ELISA to detect the expression of TGF-β1 protein in the human peritoneal mesothelial cell. Experimental groups: Control group; High glucose and LPS for different concentrations group; Fasudil intervene group.

Results: Compared with the normal control, high glucose and LPS can significantly increase the expression of RhoA, ROCK-1, ROS and TGF-β1, reduce the expression of Nrf2, HO-1 and GSH-PX in a concentration dependent manner, all have statistically significant (P<0.05). Compared with 2.5% glucose and 10mg/L LPS, group, fasudil can reduce the expression of RhoA, Rock-1, ROS and TGF-β1, increase the expression of Nrf2, HO-1 and GSH-PX, all have statistically significant (P<0.05).

Conclusions: High glucose and LPS up-regulate the expression of RhoA and ROCK1 but reduce Nrf2 in the protein and gene levels and increase the expression of ROS and TGF-β1 but reduce the expression of HO-1 and GSH-PX. Fasudil could reverse the increase of RhoA and Rock1 and the reduce of Nrf2 in HPMCs that have been pre-treated with high glucose and LPS play the role of anti-oxidant and anti-fibrosis.

PUB107
Glucose Induces Mitochondrial Reactive Oxygen Species Through Carbonyl Stress and Respiratory Chain In Rat Peritoneal Mesothelial Cells
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Background: Glucose and its degradation products (GPDs) play a major role in the peritonal injury and affect peritoneal dialysis vintage. Peritoneal mesothelial cell dysfunction has been demonstrated to involve in peritoneal injury by glycolysis and GPs. GPDs induced carbonyl stress has been demonstrated to induce mitochondrial dysfunction in several cell types. The present study was designed to determine the role of GPDs and respiratory chain in glucose induced mitochondrial ROS in peritoneal mesothelial cells.

Methods: The primary rat peritoneal mesothelial cell (RPMC) were isolated from Wistar rats. Real-time mitochondrial superoxide was monitored using a specific fluorescent indicator Mito SOX red under fluorescence microscope equipped with temperature controlled chamber. RPMC was stimulated with 90 mmol/L of glucose and compared to those of vehicle. In separate experiments, RPMC was pre-incubated with a mitochondrial specific superoxide dismutase mimetic mite mimotEMP0, respiratory chain inhibitor rotenone or carbonyl stress inhibitor pyridoxamine to determine the mechanism of glucose induced mitochondrial ROS production.

Results: 90 mmol/L glucose significantly increased mitochondrial superoxide production within 200 seconds in primary cultured RPMC (0.21±0.07 AU, n=8, P<0.05 vs vehicle). These responses were abolished when RPMC was pre-incubated with mitoTEMPO (-0.04±0.15 AU, n=5, P<0.14 vs vehicle), rotenone (0.00±0.06 AU, n=6, P<0.54 vs vehicle) and pyridoxamine (-0.34±0.34 AU, n=5, P<0.26 vs vehicle), indicating that mitochondrial superoxide production through respiratory chain and GPD.

Conclusions: The results in the present study indicate that glucose and GDP present in the PD effluent is responsible for oxidative stress in the peritoneal mesothelial cells by stimulation of mitochondrial ROS production, which could play a role in peritoneal function and injury during PD.

PUB108
Renal Cell Carcinoma Models: Effect of Chemopreventative Agents on the Carcinogenic Potential of Potassium Bromate in Human Renal Epithelial Cells
Issam Obaidi, Tara McMorrow.
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Background: Renal Cell Carcinoma (RCC) is a leading cause of renal cancer worldwide. The cause of RCC remains unknown, with many chemicals implicated in its development. We have developed an in vitro model of RCC using the carcinogen, potassium bromate, to investigate potential prevention and possible treatment options of RCC. Chemoprevention is the use of different chemicals, natural or synthetic, to halt, block or reverse the process of carcinogenesis. It is one of the novel approaches that is being used to control cancer and it is a good alternative to the conventional therapies that are associated with a long list of side effects and limitations. These agents have antioxidant, anti-inflammatory, antiangiogenic effects and induce phase II enzymes, apoptosis, cell cycle arrest, and differentiation. They antagonize hormones and growth factor-induced tumor proliferation. The aim of this study was to examine the functional and mechanistic effects of chemopreventative agents on chemically induced RCC using human (RPTEC/ TERT1) renal cells and carcinogen (AChN) renal cell lines.

Methods: Morphological changes, viability and cytotoxicity assays were used to assess the toxicity of both the chemopreventatives and the carcinogen when RPTEC/ TERT1 cells were exposed to them individually and in combinations. Oxidative stress was also...
assessed by measuring the intracellular concentration of H2O2. Oxidative stress-induced DNA damage was estimated quantitatively by measuring 8-OHdG concentrations. Western blot analysis was used to detect the changes in particular oxidative stress-induced proteins.

Results: The carcinogenic effects induced by potassium bromate were reduced by the co-administration with all of the chemopreventive agents used. Oxidative stress markers, H2O2 and DNA adduct formation, were reduced.

Conclusions: These results suggest that chemopreventive agents show significant potential against KBtO3-induced carcinogenicity. Further analysis is being carried out to understand the functional mechanisms of this chemoprevention on the cells, in particular on the genetic and epigenetic mechanisms involved.

Funding: Government Support - Non-U.S.

PUB109

The Podocyte as a Target for the Actions of Levamisole in Nephrotic Syndrome

Jochen Seufert,1 Oliver Witzke,1 Fliser2

Background: Levamisole is an antihelminthic agent that has also been shown to be effective as a second line treatment for steroid-dependent or frequently-relapsing nephrotic syndrome (SD/FRNS) in children. Levamisole is able to decrease steroid dosages and reduce the relapse frequency and severity. We have recently reported the effectiveness of levamisole in a small cohort of adult patients and provided evidence suggests that levamisole’s mode of action in SSNS is attributable to its direct effects on podocytes.

Methods: To further clarify its therapeutic effectiveness and identify the therapeutic targets of this drug, we have employed RNA-sequencing technology to profile transcriptional changes of human podocytes in response to levamisole.

Results: We have identified a number of genes which are differentially expressed in podocytes in response to levamisole. These include genes linked to the cellular interferon response pathways and a number which overlap with those regulated by dexamethasone in podocytes. These have been validated in vitro and are now being studied in animal models of nephrotic syndrome.

Conclusions: Together, our molecular evidence strongly supports the promising use of levamisole in treating nephrotic syndrome.

Funding: NIDDK Support

PUB110

The PRIMAVERA Study: A Prospective, Randomized, Multicenter Trial Assessing the Effect of Continuous Erythropoiesis Receptor Activator (C.E.R.A.) on Renal Function in Non-Anemic Patients with Chronic Kidney Disease (CKD)

Stephanie Leduc,1 Massimo Ruggenenti,2 Davide Loir,3 L. Raphael,4 Linda F. Fried,4,5 Andrew N. Hoofnagle,6 Michael F. Flessner,7 Joanne F. Shumway,8 Desirée De Laat,9 Andrew C. Nieuwenhuijzen,10 Jerome Brun,11 Andrew C. Nieuwenhuijzen,12 Northern Light Hospital, Northpole, Alaska; 2Department of Nephrology, Dialysis, ECHO-CMCM - Pôle Santé Sud, Le Mans, France; 3Gastro-enterologie, Centre Hospitalier du Mans, Le Mans, France; 4Laboratoire de Pharmaco-Toxicologie, Hôpital Bichat-Claude Bernard, Paris, France; 5Biologie, Laboratoire Pôle Santé Sud, Le Mans, France.

Background: Elevated serum phosphate and FGF23 are associated with CVD, CKD progression, and mortality in CKD. Phosphate binders consistently reduce phosphate and FGF23 levels. Nicotinamide (vitamin B3) decreases active phosphate transport by down regulating NaPi2b in the gut. Whether nicotinamide alone or in combination with binders can safely and tolerably lower phosphate and FGF23 levels in CKD is unknown.

Methods: We designed a 4 arm parallel group randomized double blind trial comparing lanthanum carbonate (1000mg tid), nicotinamide (750mg bid), neither, or both. Supported by the NIDDK CKD Pilot Clinical Trials U10, 200 participants with eGFR 20-45 ml/min/1.73m2 were recruited from 7 centers across the US will be randomized 1:1:1:1 and treated for 12 months. Main exclusions include phosphate < 2.8mg/dl, liver dysfunction and thrombocytopenia. The dual primary efficacy endpoints are change in phosphate and FGF23. Secondary endpoints are change in LV mass and renal fibrosis by MRI. Enrollment began in March 2015.

Results: To date, 45 persons were screened, 33 were eligible, 26 entered run-in, and 18 were randomized. Baseline characteristics of randomized participants are shown in the table. Updated data will be available at presentation.

Randomized Patients (n) 18

Age<SD 65±14

Male, n(%) 12 (67%)

Black, n(%) 5 (28%)

Diabetes, n(%) 7 (44%)

eGFR/SD 30±9

Serum Phosphates/SD 3.9±0.6

Serum Calcium/SD 9.5±0.4

Inact PTH, median (IQR) 104 (71, 135)

Conclusions: Simultaneous blockade of NaPi2b and intestinal phosphate binding using nicotinamide and binders provides a new strategy for phosphate and FGF23 lowering in CKD, but efficacy, safety, and tolerability are uncertain. The COMBINE trial will inform us about combined therapy compared to either therapy alone, and to dual placebo in CKD 3b-4.

Funding: NIDDK Support

PUB111

A New Approach to Phosphate and FGF23 Lowering: Design of the COMBINE Trial

Joachim H. H. L.1 Tamara Isakova,2 Stuart M. Sprague,2 Kalani L. Raphael,1 Jennifer J. Gassman,3 Linda F. Fried,4 Dominic S. Raj,4 Alfred K. Cheung,4 Andrew N. Hoofnagle,6 John W. Kusek,7 Michael F. Flessner,7 Geoffrey A. Block,2 Myles S. Wolf,11 The pilot clinical trials in Ckd study group.1

Background: Phosphorus and FGF23 are important factors in the development of cardiovascular disease and bone disease in patients with chronic kidney disease (CKD). Currently, the optimal treatment for these conditions remains uncertain.

Methods: The pilot clinical trials in Ckd study group.

Results: The pilot clinical trials in Ckd study group.

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

Underline represents presenting author.

911A
The Rationale for and Design of TREVI TR02: A Multicenter Randomized, Double-Blind, Placebo-Controlled Trial of Nalbuphine ER for the Treatment of Uremic Pruritus in Hemodialysis Patients

Vandana S. Mathur,1 Michael J. Germain,1 Roberta Duncan,1 Thomas Sciascia,2 Mathur Consulting, Woodside, CA;1 Western New England Renal & Transplant Associates, PC, Hamden, MA;1 Trevi Therapeutics, New Haven, CT.

Background: Uremic pruritus (UP) is common in hemodialysis patients, but there are no FDA-approved treatments or “regulatory roadmap” for the development of new drugs. Nevertheless, the significant quality of life (QOL) burden of chronic itch underscores need for treatments. The striking bilateral, non-dermatomal distribution of itching and perception of non-pruritogenic skin stimuli as itch suggest that UP is centrally mediated, like neuropathic pain. Reduction in endogenous κ/µ opioid ligand ratio is hypothesized to be a mechanism. Our goal was to evaluate nalbuphine ER tablet (NAL), a µ-agonist and κ-antagonist as a treatment for UP.

Methods: The study was powered for an α = 0.05, β = 0.9 for a group difference of 1.5 (SD = 3.5) in worst itching numerical rating scale (NRS, 0-10): N = 120/arm (NAL 120 mg BID, NAL 60 mg BID, and placebo BID). Patients with NRS ≥ 4.5 (moderate to severe pruritus) were enrolled at ~45 US and 6 EU sites.

Results:

Key Scientific Considerations Study Design Solution
1. Itch is subjectively perceived. Itching intensity and QOL were relevant endpoints. Used patient-reported outcomes previously validated in UP patients including NRS and Skindex-10 (1st and 2nd endpoints).
2. Opioid drugs require titration to minimize opioid side effects To perform a blinded opioid titration with a self-administered oral drug, we used blister cards that were labeled for each study day.
3. Long enough duration to demonstrate durability and lack of tolerance but short enough to avoid excessive dropouts due to background comorbidities. Used an 8-week blinded treatment duration.
4. Post-treatment safety Added a 2-week washout period after the blinded treatment period.
5. Day-to-day variability in NRS was expected The mean of 2 weeks of measurements at baseline and on treatment (Wks 7 and 8) were used for the calculation of the 1st endpoint.

Conclusions: The trial design overcame the challenges. Unblinded results will be presented.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

The Rationale and Design of Trevi TR02 Extension: A Multi-Center Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl Extended Release Tablets in Uremic Pruritus Patients on Hemodialysis

Thomas Sciascia,1 Howard Hait,2 Arnaie Hawi,1 Roberta Duncan,1 Vandana S. Mathur,1 Trevi Therapeutics, Inc., New Haven, CT;1 Edenridge Associates LLC, Wilmington, DE;1 Hawi Consulting, Ridgefield, CT;1 Mathur Consulting, Woodside, CA.

Background: Nalbuphine HCl is a µ antagonist/kappa agonist being investigated for the treatment of pruritus in hemodialysis patients (UP). The safety and long-term benefits of Nalbuphine ER in the treatment of urermic pruritus is being investigated in this ongoing open-label extension study.

Methods: TR02ext is a 26-week multicenter open-label extension study of a double-blind placebo controlled study in which UP patients with a baseline NRS >4.5 were treated with Nalbuphine ER or placebo for 8 weeks followed by a 2-week washout period. At the end of study, patients that opt to roll over into the extension study, and have an NRS ≥ 2 enrolled in a 26-week Treatment Period (TP), while patients with an NRS ≤ 2 entered a 13-week Observation Period (OP). If a patient’s itch worsened (NRS > 2) within the OP, they entered the TP for the remainder of the study.

All patients on treatment were titrated between 30 mg QD-120 mg BID over a 3-4 week period based on reported tolerability and efficacy and then maintained their dose until end of study. Patients whose itch intensity failed to improve during the TP were discontinued from treatment.

Conclusion: Approximately 70% of the eligible patients who completed the blinded controlled study, enrolled in the extension study. Final study data will be presented once the study is complete.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

Assessing Treatment Safety and Efficacy of a New Patient-Centered Hemodialysis System

Luis Alvarez1 Geoffrey A. Block,2 May L. You,1 Glenn Matthew Hertog,4 1Palo Alto Medical Foundation, Palo Alto, CA;1 Denver Nephrology, Denver, CO;2 Outset Medical, San Jose, CA;3 Stanford School of Medicine, Stanford, CA.

Background: Many studies designed and conducted for the evaluation of new technologies utilized in hemodialysis have been small, observational studies. These studies may have underestimated the rate of clinical symptoms yielding biased safety results.

Methods: We designed a prospective, multicenter, open-label, non-randomized, cross-over study where patients serve as their own control. The study was designed with novel approaches to ensure accuracy of clinical symptom reporting both in the home and clinic setting. Up to 50 patients will be enrolled in the study for 19 weeks and will use the Table™ Hemodialysis System for treatments 4 times/week.

Conclusion: During each study phase, patients will record intra- and inter-dialytic symptoms for each treatment via questionnaire. Research staff will review all responses weekly to determine if an adverse event (AE) has occurred. In addition, research staff will conduct weekly visits to the dialysis clinic and to home to educate patients on AEs and to collect questionnaires. Patients will also be assessed to determine if a standardized weekly Kt/V of 2.1 has been achieved.

Results: Study enrollment is expected to begin in 2015 with results expected in 2016.

Conclusion: By utilizing patients to collect AE data both in-center and at home, we should more accurately capture AE rates due to the uniformity of the reporting mechanism. In terms of the clinical efficacy endpoint of the study, modelled clearance data suggests the majority of patients will achieve the weekly standard Kt/V target. Actual clearance data will be forthcoming at the completion of the trial.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

Interim Analysis of Comprehensive CKD Education Modality Choice Outcomes

Andrew K. Eason,1 Dumitru Rotaru,2 Fahd Syed,1 Manisha Singh,1 Ashutosh M. Shukla,1 Sudhir V. Shah,1 1Univ of Arkansas for Medical Sciences;2 University of Florida.

Background: Preliminary data from a study comparing telemedicine vs conventional CKD education is presented here. The primary aim is to see if patients are able to make a modality choice by the end of the third visit.

Methods: Patients are enrolled in three groups as shown in the pilot study design.

Study Design

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

Underline represents presenting author.

PUB113

PUB115

PUB116

912A

Publication Only
Each group attends 3 sessions and are given handouts or an 82 page workbook designed specifically for the study. They are asked about their modality choice pre-education and at the end of each session. Results: To date 80 subjects have been enrolled and 32 have completed all sessions. After 3 sessions, 38% chose peritoneal dialysis (PD), 28% chose home hemodialysis (HHD), 28% chose in center hemodialysis (ICHHD). 3% chose no dialysis (ND). 3% could not make a choice (NC) and 84% chose transplant. On enrollment, 47% made a choice with 40% choosing home modalities. At the end of 3 sessions, 97% were able to make a modality choice with 66% choosing home modalities. Of the 6 subjects who have completed 1 visit and started renal replacement therapy (RRT), 5 started PD and 1 had a pre-emptive transplant. Additionally, 4 subjects did not complete all visits: 3 started ICHHD (2 with AVFs) and 1 died. Enrollment in the teledermne program has been slower than expected. Strategies to involve community leaders and local providers were developed and are being implemented. Communities interested in the program have been added as teledermene sites. Conclusions: This preliminary data shows that at the end of 3 education sessions there is a significant increase in subjects being able to make a RRT choice (97% vs. 47%) and most chose home dialysis(66% vs. 40%). Community engagement is key to a successful outreach of this state-wide CKD education program. Further strategies are being developed to improve local involvement.

Funding: Pharmaceutical Company Support - Baxter Renal Discoveries Extramural Grant Program

PUB117

Determination of Oxidative Stress and Inflammation Index in Patients with Different Dialysis Modalities and Analysis of Related Factors


Background: This study through the determination of serum AOPPs, GSH-PX, PTX-3, IL-6 level in ESRD patients with different treatment groups, to explore the changes and influence factors of oxidative stress and inflammation in dialysis patients.

Methods: 70 cases of ESRD patients divided into three groups: 26 cases of PD patients, 26 cases of MHD patients, 18 cases of CKD5 patients. Select 14 normal persons as control group. Age, gender and other data of the four groups were matched. Get Serum of each group of subjects, using ELISA for determination of serum AOPPs, GSH-PX, PTX-3, IL-6 content in each group.

Results: 1. The concentration of AOPPs: PD group (25.04 ± 12.18) ng/mL, MHD group (18.46 ± 10.47) ng/mL, CKD5 group (7.17 ± 6.81) ng/mL, healthy group (15.73 ± 6.68) ng/mL. PD group was statistically significant different with other groups (p < 0.05). 2. The concentration of GSH-PX: PD group (188.54 ± 112.04) U/mL, MHD group (157.12 ± 82.47) U/mL, healthy group (133.59 ± 65.59) U/mL, healthy control group (176.03 ± 98.80) U/mL. There was no significant different between the groups. 3. The concentration of PTX-3: PD group (9.55 ± 5.13) ng/mL, MHD group (7.54 ± 4.07) ng/mL, CKD5 group (6.69 ± 3.12) ng/mL, healthy control group (6.08 ± 2.49) ng/mL. The PD group was statistically significant different with other groups (p < 0.05). 4. The concentration of IL-6: PD group (123.69 ± 84.46) ng/L, MHD group (81.17 ± 72.48) ng/L, CKD5 group (64.92 ± 36.92) ng/L, healthy control group (59.08 ± 19.27) ng/L. The PD group was statistically significant different with other groups (p < 0.05). Through correlation analysis in PD group (p < 0.05): AOPPs was positively correlated with PTX-3 (R = 0.956, P < 0.000), AOPPs was positively correlated with IL-6 (R = 0.934, P < 0.000), PTX-3 and IL-6 levels were positively correlated (R = 0.939, P < 0.000).

Conclusions: Determination of serum AOPPs, GSH-PX, PTX-3, IL-6 content in Experience group is significantly increased compared with the control group. The PD patients compared with patients in other treatment groups have more severe oxidative stress and microinflammation state. Oxidative stress is closely related to the state of inflammation in PD patients.

PUB118

Impact of Type of Referral and Dialysis Start on Clinical Outcomes and Final Renal Replacement Therapy in a Multicenter Integrated Care Setting

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Background: Early referral, choice of RRT modality and planned start increase patient survival, however international reports show disparities between desirable patterns and practice. Objectives: To analyze the effects of Integrated Care and education on dialysis start (planned vs. non-planned) and RRT modality choice.

Methods: Retrospective analysis of 547 incident patients starting dialysis in 23 HD/PD clinics from PL, HU and RO during 2012. Scheduled initiation of dialysis with a permanent vascular or peritoneal access was considered as planned start.

Results: Population: 30% DM, mean age 64 years, 84% with previous medical care of renal disease, 49% late referral, 58% unplaned start, 92% on HD as modality, 37% of those with unplanned start had previous Nephrology follow-up. Patients (n=332) with GFR <30 ml/min were followed up mainly by “general nephrologists” (68%) and 29% in structured predialysis units. Modality information (80% of all these information’s) could lead to develop a personal care. Type D (distressed) personality is defined as a tendency to experience both negative affectivity (NA) and social inhibition (SI). The prevalence of this personality and his effect on HRQoL in dialysis patients are assessed.

Methods: Participants were from outpatient clinic. DS 14 was used. A score of 10 on both NA and SI subscales indicates that the person has a type D personality. HRQoL was measured using the Dutch version of the Kidney Disease Quality of Life. Six components of the KDQOL were the primary end points (general health perceptions, burden of kidney disease, effect on daily life, cognitive function, pain, emotional welfare).

Results: 147 patients with mean age of 71.2 (±11.7). Mean time on dialysis 37 months. The prevalence of type D personality was 30% HRQoL in patients with type D personality was lower compared with non type D. It was statistically significant in all components except for emotional welfare.

Funding: Pharmaceutical Company Support - Regulus Therapeutics Inc., Clinical Revenue Support

PUB119

ATHENA: A Natural History Study to Observe Disease Progression, Standard of Care, and Investigate Biomarkers in Alport Syndrome Patients

Jacqui Blem, Paul C. Grint, Victoria Pratola, James F. Simon. Regulus Therapeutics Inc., San Diego, CA; Cleveland Clinic, Cleveland, OH.

Background: Alport syndrome (AS) is a rare genetic disorder caused by mutations in genes coding for type IV collagen (COL4) α3, α4 and α5 proteins leading to hematuria, renal failure, hearing loss and eye involvement in affected patients. With COL4α5 mutations develop end stage renal disease (ESRD). While there are currently no approved therapies for AS, ACE-inhibitors have been shown to delay the onset of ESRD. A better understanding of the decline of kidney function in AS is necessary to design clinical trials to enable the development of new therapeutics.

Methods: Regulus’ Natural History of Disease Study, ATHENA, is an international multi-center observational study designed to characterize the progression of renal dysfunction in up to 120 subjects that have been clinically or genetically diagnosed with AS with a measured GFR (mGFR) between 30-75cc/min/1.73m². Genetic mutation analysis is performed at enrollment. mGFR (iohexol), 24 hour urine protein excretion and serum creatinine levels are measured every 3-6 months. Serum and urine biomarkers of renal stress (microRNAs, ADMA, TGFβ, CTGF and NGAL) will also be collected.

Results: 48 subjects with clinically or genetically diagnosed Alport syndrome have been enrolled to date. The population has an age range of 20 to 67 years of age and 29% are male. Average baseline mGFR was 54.8 cc/min/1.73m². Ethnicity is reported at 91% Caucasian, 2% Hispanic or Latino, 2% African American and 5% Asian.

Conclusions: Data gathered from the ATHENA study will investigate links between genetic mutations, biomarkers of renal stress and disease progression in AS patients. The correlative data collected from the ATHENA study will provide clinically important basis for the design of the Phase 2 clinical proof of concept study to determine efficacy of RG-012 (an anti-miR targeting microRNA-21) on the decline in renal function and time to end-stage renal disease in Alport syndrome patients.

Funding: Pharmaceutical Company Support - Regulus Therapeutics Inc., Clinical Revenue Support

PUB120

Health-Related Quality of Life in Dialysis Patients: Effect of Type D Personality

Christopher Susanto, Constantijn Konings, Jeroen Kooman. Nephrology, Ekerleie Hospital, Helmond, Netherlands; Nephrology, Catharina Hospital, Eindhoven, Netherlands; Nephrology, Maastricht Univ Medical Centre, Maastricht, Netherlands.

Background: Measurement of HRQoL is a useful tool to describe the burden of illness and impact of treatment. These informations could be essential to develop a personal care. Type D (distressed) personality is defined as a tendency to experience both negative affectivity (NA) and social inhibition (SI). The prevalence of this personality and his effect on HRQoL in dialysis patients are assessed.

Methods: Participants were from outpatient clinic. DS 14 was used. A score of 10 on both NA and SI subscales indicates that the person has a type D personality. HRQoL was measured using the Dutch version of the Kidney Disease Quality of Life. Six components of the KDQOL were the primary end points (general health perceptions, burden of kidney disease, effect on daily life, cognitive function, pain, emotional welfare).

Results: 147 patients with mean age of 71.2 (±11.7). Mean time on dialysis 37 months. The prevalence of type D personality was 30% HRQoL in patients with type D personality was lower compared with non type D. It was statistically significant in all components except for emotional welfare.
PUB121

Sleep Disorder and mRNA Expression Profile of Sleep-Related Gene in Peripheral Blood Cells in Patients with CKD  Shintaro Iwata, Yasuyuki Shinozaki, Norihiko Sakai, Miho Shimizu, Kengo Furuchi, Takashi Wada. Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.

Background: Although uremic substances would be candidates involved in sleep disorder, detailed mechanisms remain unclear so far. we performed polymorphonuclear analysis in CKD patients and used PBCs to examine the expression of genes related to sleep and wakefulness states.

Methods: Polymorphonuclear analysis was performed in 9 CKD patients and 6 healthy controls. Genes related to sleep and wakefulness were evaluated by RNA microarray in 15 subjects, including CKD patients and control subjects.

Results: Polymorphonuclear analysis revealed that the duration of the rapid eye movement (REM)/non-REM phases during total sleep time was different between CKD patients and healthy controls. In mRNA microarray evaluation, hierarchical clustering analysis showed the different pattern of sleep related gene expression in the patients with HD. The mRNA expression levels of GABA receptor, noradrenaline receptor, dopamine receptor and histamine receptor showed an inverse correlation with renal function. Moreover, orexin and its receptor mRNA expression also showed an inverse correlation with renal function.

Conclusions: These data raise the possibility that sleep related gene expression on PBC in CKD/HD patients may be associated with sleep disorder.

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Underline represents presenting author.

914A
PUB124

**Hemodynamic Determinants of Glomerular Filtration Rate in Pulmonary Hypertension: A Prospective Cohort Analysis**

Laurent Birker,1 Cecile Payet,3 Florence Sens,1,4 Turquier Segolene,2 Antoine Duclos,1,4 Vincent Cottin,1,4 Laurent Juillard,1 1Nephrology, Hospices Civils de Lyon, Lyon, France; 2Pneumology, Hospices Civils de Lyon, Lyon, France; 3Medical Research and Statistics Dept, Hospices Civils de Lyon, Lyon, France; 4Univ of Lyon, Lyon, France.

**Background:** Up to date, renal dysfunction incidence and determinants remain unevaluated in pulmonary hypertension (PHT). We aim to assess hemodynamic and demographic factors associated with a decrease in glomerular filtration rate (GFR) in the context of PHT.

**Methods:** The regional competence center for PHT of Lyon (France) prospectively compiles demographic, hemodynamic and biological variables among newly diagnosed patients. We retrospectively analyzed data for patients with pulmonary arterial hypertension (PAH, group 1 of PHT classification) after exclusion of the following causes of PHT: thromboembolic, lung diseases and/or hypoxia and left heart disease. Hemodynamic variables from the right heart catheterization and estimated GFR (eGFR, CKD-EPI formula) were assessed at PAH diagnosis time.

**Results:** 209 patients (mean age 59.1±17.1, 63.2% women) were included from October 1998 to July 2012. 40.2% presented with systemic arterial hypertension (HT) and 12.9% with diabetes. Mean eGFR was 83.9±27.1 ml/min/1.73m² eGFR inferior to 60 ml/min/1.73m² in 18.5% of cases. Mean values of mPAP, right atrial pressure (RAP) and cardiac index (CI) were 41.5±12.6 mmHg, 7.8±5.3 mmHg and 2.6±0.9 L/min/1.73m². In multivariate analysis, age, male gender, HT, anorectic-related PAH and a CI inferior to 2.5 L/min/1.73m² were associated with a significant decrease in eGFR of 1.0 ± 1.73m²/year (95% confidence interval, 0.8 to 1.2), 11.8 ml/min/1.73m² (5.8 to 7.8), 6.6 ml/min/1.73m² (0.1 to 13.2), 13.4 ml/min/1.73m² (2.3 to 24.5) and 10.1 ml/min/1.73m² (4.4 to 15.9). RAP were not statistically related to eGFR levels.

**Conclusions:** Renal dysfunction is frequent from diagnosis among PAH patients. A low CI is associated with a significant decrease in eGFR, whereas RAP seem unrelated.

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PUB125

**Kidney Function and Cause-Specific Mortality in Drug-Treated Older Cardiac Patients: A 10-Year Follow-Up Study**

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**Background:** Chronic kidney disease (CKD) is highly prevalent among older (>60y) cardiac patients. The relation between CKD and cause-specific mortality among older cardiac patients who are treated with state-of-the-art pharmaceuticals is unclear.

**Methods:** From 2002-2006, 60-80 years old Dutch post-myocardial infarction patients were enrolled in the Alpha Omega Trial and followed until death or January 2012. We estimated Glomerular Filtration Rate (eGFR) with serum cystatin C (cysC) and creatinine using the CKD-EPI equations. Kidney function was available in 4,561 (94.3%) participants and analyzed in relation to major causes of death using Cox models and four-knot restricted cubic splines.

**Results:** At baseline mean age was 69y, 79% were men, 21% had diabetes, 90% used antihypertensive drugs, 85% used statins. Patients were divided into four categories of GFR: G1 (<60 ml/min/1.73m²), G2 (60-89 ml/min/1.73m²), G3 (30-59 ml/min/1.73m²), and G4 (≤30 ml/min/1.73m²). Median follow-up time was 6.4y. During follow-up, 973 (19%) patients died, of which 370 (42%) from cardiovascular causes, 309 (35%) from cancer, and 192 (22%) from other causes. The hazard ratios (95%-CI) for any death according to eGFR category, after adjustment for major risk factors, were: 1 (reference), 1.4 (1.1-1.7), 2.9 (2.3-3.6) and 4.4 (3.0-6.4). For cardiovascular mortality the corresponding figures were 1.6, 3.6 and 6.0, for cancer 1.2, 2.1 and 1.6, and for other causes 1.4, 3.1 and 6.7. Similar, but weaker, results were obtained with creatinine-based eGFR.

**Conclusions:** We found a strong inverse graded relation between kidney function and mortality in drug-treated older cardiac patients, in particular due to cardiovascular and non-cardiovascular-non-cancer causes.

**Funding:** Other NIH Support - Dutch Kidney Foundation (PV41)

US National Institute of Health (NIH)

Netherlands Health Foundation

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PUB126

**The Association Between Serum Uric Acid and Incidence of Non-Fatal Stroke in a Community-Based Population: A Longitudinal Survey of a Nationwide Cohort in Japan**

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**Background:** Hyperuricemia is a risk for adverse renal outcomes in chronic kidney disease. This study investigated the effect of uric acid on incidence of non-fatal stroke in a community-based population.

**Methods:** We used a nationwide database of 160,164 subjects (aged 29–74, male 39%), participated in an annual health check, “The Specific Health Check and Guidance in Japan” between 2008–2010, and examined the relationship between the gender-specific quintiles of serum uric acid levels and the incidence of non-fatal stroke (PAH, group 1 of PHT classification) after exclusion of the following causes of PHT: thromboembolic, lung diseases and/or hypoxia and left heart disease. Hemodynamic variables from the right heart catheterization and estimated eGFR (eGFR, CKD-EPI formula) were assessed at PAH diagnosis time.

**Results:** During the follow-up period 2,081 non-fatal stroke occurred (1.3%). The incidence of non-fatal stroke showed a significant J-shaped association with the increase in serum uric acid levels (P for trend<0.001, lowest [1.2%] in the 3rd quintile of uric acid [Q1]: males 5.7–6.2 mg/dL, females 4.4–4.8 mg/dL) and highest [1.6%] in the 5th quintile (Q5: males ≥7.1 mg/dL, females ≥5.5 mg/dL). After adjusting for possible confounders, the odds ratio for stroke incidence was significantly higher in Q5, compared with Q3 (OR 1.21, 95%CI 1.05–1.39, P = 0.007). The odds ratio of hyperuricemia (serum uric acid ≥7 mg/dL) for incident stroke was significantly increased in total subjects (OR 1.22, 95%CI 1.07–1.39), especially in females (OR 1.46, 95%CI 1.04–1.99) and non-hypertensive subjects (OR 1.34, 95%CI 1.04–1.70). In contrast, the association between serum uric acid levels and incident stroke was not significant in subjects with diabetes, proteinuria and renal insufficiency.

**Conclusions:** This study showed that serum uric acid level is significantly associated with incident non-fatal stroke and that hyperuricemia might be an independent risk for non-fatal stroke in the general population.

**Funding:** Government Support - Non-U.S.

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PUB127

**The Association Between Serum Calcium and Mortality in a Community-Based Population: The Takahata Study**

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**Background:** The low intake of calcium is a risk for cardiovascular events. This study investigated the association between serum calcium and mortality in a community-based population.

**Methods:** This study included 1,314 participants (aged 40–87, males 45%) at local health checkup in Takahata, Japan. We divided them into 3 groups according to the tertiles of serum calcium at baseline and compared the mortality during 8-year follow-up period. Serum calcium was corrected for serum albumin.

**Results:** At baseline serum calcium level was 9.8 ± 0.4 mg/dL (mean ± SD). In the multivariate linear regression analysis serum calcium was positively associated with serum sodium, potassium, phosphorus, albumin, uric acid and total cholesterol, and was negatively associated with serum chloride and HDL-cholesterol, and urinary beta2-microglobulin. During the follow-up period 62 deaths, including 14 cardiovascular deaths occurred. In Kaplan-Meier analysis all-cause mortality was significantly increased along with the decrease in serum calcium (Log-rank P = 0.03). In Cox proportional hazard analysis adjusted for confounders including age, gender, smoking and drinking habits, comorbidities and other serum electolytes, the association of serum calcium was of borderline significance with all-cause mortality (HR 2.95, 95%CI 0.94–4.75), P = 0.07, low tertile [≤5.6 mg/dL vs. high tertile [≥10.0 mg/dL]] and was significant with cardiovascular mortality (HR 6.33, 95%CI [1.13–43.7], P = 0.04, low tertile vs. high tertile). In addition, there was a significant interaction between serum calcium and sodium on all-cause mortality (P = 0.03) and the association of serum calcium with the mortality was significant in the subjects with low serum sodium (< 150 mEq/L), but not high sodium.

**Conclusions:** This study showed that serum calcium was significantly associated with various environmental factors and low serum calcium was an independent predictor for the mortality in the general Japanese population.

**Funding:** Government Support - Non-U.S.
Endothelial Dysfunction According to Classification of Serum Phosphorus Level within Normal Range in Chronic Kidney Disease

Background: Hyperphosphatemia is a important problem because of its effect on endothelial function as well as homeostasis of bone. Chronic kidney disease (CKD) patients tend to have higher serum phosphorus values than those in healthy population due to their positive balance of phosphorus in kidney. There are a few studies which reported that serum phosphorus level was correlated with endothelial function. Recently it has been reported the patients with higher serum phosphorus level related to the worse endothelial function in healthy population. Thus, the following study was carried out in an effort to redefine the relationship between serum phosphorus level and endothelial dysfunction to those on chronic kidney disease.

Methods: This is a cross-sectional study and the enrolled 85 CKD patients with exception of CKD stage 5 or receiving renal replacement therapy. They were subjected to their positive balance of phosphorus in kidney. There are a few studies which reported that serum phosphorus level was correlated with endothelial function. Recently it has been reported the patients with higher serum phosphorus level related to the worse endothelial function in healthy population. Thus, the following study was carried out in an effort to redefine the relationship between serum phosphorus level and endothelial dysfunction to those on chronic kidney disease.

Methods: The following studies were identified: The IDNT; The final outcome of diabetes was achieved by 14%. However, no significant difference was found on CV outcome, including death, non-fatal MI, stroke or heart failure. The ONTARGET, in a sub-analysis; looking at renal outcome, including doubling S. Cr., dialysis and death, it revealed that although the ACE Inh. and the ARB combination had successfully reduced proteinuria, it resulted in worse renal outcome. The TRANSCEND; by looking specifically at the renal outcome, including doubling and disabling serum Cr., it was found that GFR had decreased. The AASK trial; the results did not show a positive solid endpoint associated with lowering proteinuria, no statistical difference was encountered. The ROADMAP; the result revealed that decreasing microalbuminuria as well as blood pressure in the Olmisartan subgroup was found in decreased cardiovascular death. The Attitude trial; decreased proteinuria did not show a significant evidence in the primary renal or cardiovascular composite endpoints. Moreover, the study was terminated prematurely because of severe decline in eGFR, hyperkalemia and hypotension. The NEPHRON-D; The final outcome was not statistically different. The study was stopped prematurely because of more acute renal injury and hyperkalemia in the combination arm.

Conclusions: Decreased proteinuria was associated with negative cardiac and renal outcomes. This could be due to the effect of RAAS combination, but we have to admit that these repeated observations carries an evidence, at least to question our standard belief, that proteinuria might not be more than a cardiac risk factor indicator.

Prevalence of Hematuria and Associations with All-Cause and Cardiovascular Mortality in China

Background: Hematuria is one of the indicators of kidney damage. We aimed to estimate the prevalence of hematuria in China and evaluate its association with mortality and cardiovascular adverse outcome.

Methods: A nationally representative sample of 47,204 Chinese adults was obtained during the survey conducted between January 2009, and December 2012. Each participant’s survival status was identified through Dec 31, 2013. Causes of death in ICD code 100-199 were classified as cardiovascular disease. Hematuria was defined as ³3 red cells per high-power field in microscopic examination. Subjects with pyuria and women undergoing menestration were excluded from the analysis. The associations between hematuria and all-cause and cardiovascular mortality were studied by using the Cox regression model.

Results: The mean age of the population at baseline was 49.6±15.2 years, and 42.7% of the participants were male. Altogether, 2,126 (4.5%) of the population was detected with hematuria. The all-cause and cardiovascular mortality for participants with hematuria were 3.8 and 2.6 per 1000 person-years, while those for participants without hematuria were 3.4 and 1.3 per 1000 person-years. Hematuria was found to be significantly associated with increased risk of cardiovascular mortality with the multivariable adjusted hazard ratio of 1.7 (95% confidence interval: 1.1-2.7), compared with those without hematuria. However, no significant associations were found between hematuria and all-cause mortality.
Conclusions: Mortality, especially due to cardiovascular diseases, was greater among the Chinese patients with hematuria. These results suggest the possible effect of hematuria on cardiovascular mortality.

Funding: Government Support - Non-U.S.

PUB133
Glomerular Filtration Rate Is a Predictor of Subclinical Left Ventricular Diastolic Dysfunction in Patients with Rheumatoid Arthritis
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Background: Rheumatoid arthritis (RA) is a systemic disease effecting primarily joints with subclinical kidney involvement. Subclinical cardiovascular disease (CVD) is a leading cause of morbidity & mortality in RA. Chronic kidney disease (CKD) at early stages. Subclinical cardiovascular dysfunction (LVDD) is a principal pathophysiological mechanism & essential diagnostic indexes of HF with preserved ejection fraction (HFPEF).

Results: Renal parameters correlated with echocardiographic findings in patients with RA & eGFR as estimated (MDRD, equation). Doppler echocardiography was performed by pulse wave Doppler with sample volume at tip of mitral valve in apical 4-chamber views. Peak early (E) & late (A) diastolic velocities were measured as indicator of LVED pressure. Assessment of peak early (E′) & late (A′) diastolic mitral annulus velocity was performed by pulsed wave tissue Doppler imaging (TDI) of lateral wall in apical 4-chamber view & to diagnose LVDD (E′/E > 8).

Interim results: Analysis of 29 (3, 26%) with RA diagnosed (ACR1988), aged 46 ± 12 years & GFR < 60 ml/min. Univariate regression showed a negative linear relationship of GFR & age (p < 0.001, CI = 27,73, 1.03, age)/RA onset (p = 0.001, CI = 3.23, 0.63, age). RA diagnosis (p = 0.002, CI = 2.5, 0.66), SBP (p = 0.032, CI = 1.51, 0.07), ESR (p = 0.005, CI = 1.09, 2.21), ferritin level (p = 0.008, CI = 0.45, 0.08), EE (p = 0.005, CI = 20.76, 4.26). Multiple regression maintained a negative relationship between GFR & age of each (p = 0.004, CI = 0.52, 0.07), E′/E (p = 0.014, CI = 0.32), E′/A (p = 0.011). Kt/V = 2.5.

Conclusions: RA patient have subclinical CKD and cardiac dysfunction & eGFR independently & negatively correlated to LVDD with moderate correlation (0.54). eGFR increased with decreasing GFR & higher than in patients GFR < 90. LVDD influenced by increase LV preload due CKD progression & it’s a preclinical predictor of future HF & mortality. However, milder form of LVDD may stabilize or improve subset of patients may, over time, be at risk for functional deterioration. Inflammation as a major pathological key in RA may be underlying cause for increased subclinical kidney & ventricles.

PUB134
The Association Between Creatinine versus Cystatin-C-Based eGFR and Cardiovascular Risk Factors in Children with Chronic Kidney Disease

Background: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular events (e.g. stroke, myocardial infarction) in adults. Children with mild-moderate CKD have a high prevalence of cardiovascular risk factors (CRF). Higher levels of cystatin-C demonstrate a stronger predictive value for cardiovascular events compared with creatinine-based eGFR in adults. However, whether similar associations exist in children in young adults has yet to be determined. We hypothesize that cystatin-C based eGFR will demonstrate a stronger association with CRF compared with creatinine-based eGFR in children and young adults.

Methods: We used cross-sectional data of 93 subjects aged 8-25 years with CKD and 70 healthy controls. eGFR was calculated using age appropriate creatinine and cystatin-C based formulas. The CRF included were anemia (hemoglobin < 9.2 standard deviations below the mean), hypertrophy & hypertension (eGFR < 90.2 ml/min) or urine albumin/creatinine > 30 mg/g). Multivariate analysis assessed the association between creatinine and cystatin based eGFR and each risk factor after adjusting for age, gender, race.

Summary: Cystatin-C based eGFR had a stronger association with decreased ejection fraction, increased left ventricular hypertrophy, arterial hypertension, anemia, uremic symptoms, and inflammatory states, malnutrition, mass of the left ventricle, problems with the contractile function of the left ventricle as well as decreased relaxation of the left ventricle in the group of patients treated with peritoneal dialysis with regard to survival prognosis.

Results: The study was conducted on 105 patients (40 men, 56 women) treated with peritoneal dialysis with the average time of 36.1 ± 27.7 months. The control group consisted of 30 healthy volunteers (20 women, 10 men, mean age 55.0 ± 23.8 years). Based on general known vascular and cardiac risk factors the patients were divided into subgroups: elderly patients (> 65 years of age), male, patients treated on peritoneal dialysis over 3 years, daily diuresis > 500 ml, Kt/V > 1, arterial hypertension, anemia, inflammatory states, malnutrition.

Conclusions: Chronic low-grade inflammation and advanced age seem to be two most common negative prognostic factors decreasing life expectancy. Further research is necessary to verify the intricate relationships between demographic factors and prognosis in the group of patients undergoing peritoneal dialysis.
Conclusions: Low ABI tended to be associated with higher risk of exertional leg pain. A low ABI value may be useful to identify ischemic etiology of leg pain even among dialysis patients with high prevalence of leg symptoms due to various conditions.

Funding: NIDDK Support

PUB138

Predictors of In-Hospital Mortality of CKD4-6 Patients with Takotsubo Cardiomyopathy

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Background: The pathophysiology of Takotsubo cardiomyopathy (TTC) remains poorly understood and little is known about the factors predicting mortality in these patients among those with chronic kidney disease. We aimed to study the epidemiology of TTC and predictors of mortality in these patients.

Methods: All patients with CKD 4 to CKD 6 (ICD9 585.4-585.6) diagnosed with TTC (ICD9 429.83) in the Nationwide Inpatient Sample database between 2007 and 2012, were compared to CKD4 - CKD6 patients without TTC. Capturing only cases undergoing inpatient care for TTC provided valuable information about TTC, its use for patients with CKD is difficult due to the risk of contrast induced nephropathy (CIN). To our knowledge, there have been no studies to explore the association of CAD and advanced CKD. The objectives of this study are to assess the severity of CAD in advanced CKD patients by MDCT and clarify the association between CAD and renal function.

Methods: We retrospectively collected the data from 168 advanced CKD patients, stage 3b to 5, who underwent MDCT angiography at St Luke’s international hospital between 2011 and 2014. We assessed CAD by coronary artery calcification score (CACS), coronary plaque characteristics and number of vessel disease. Risk factors for CAD were sought using univariate and multivariate logistic regression.

Results: Among the 168 patients (56 females, age 60±17.0), 108 patients were CKD stage 3b, 42 patients were stage 4, and 18 patients were stage 5. No patient developed CIN by MDCT. On univariate analysis, patients with CASC100 were older (P=0.003), male sex (P=0.011), diabetes (P=0.045), and more likely to be a smoker (P=0.014). Multivariate logistic regression analysis identified age (hazard ratio = 1.08, P<0.01), male sex (hazard ratio = 2.97, P=0.031), and CKD stage (hazard ratio = 2.58, P=0.041) as independent risk factors for CASC100.

Conclusions: Coronary artery calcification is worsened significantly with decreasing renal function in advanced CKD. Given the high morbidity and mortality of cardiovascular disease in CKD, our study underscores the importance of evaluating CAD in advanced CKD.

PUB140

Cardiovascular Biomarkers and Coronal Calcium in CKD Patients

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Background: Cardiac and vascular calcification and mortality are highly prevalent in patients with CKD. Biomarkers help to an early diagnose, like osteoprotegerin (OPG) a glycoprotein from TNF family that has been associated with cardiovascular (CV) disease. FGF-23, a phosphatonin protein has been linked to vascular calcification, ventricular hypertrophy and mortality. Coronary artery calcification (CACS) measured with Agatston score (AS) by CT is associated to CV disease in CKD patients. We hypothesized that OPG and FGF-23 are abnormally elevated in CKD and are associated CACS measured with AS.

Methods: An observational study including 138 CKD 3-5 patients, and 20 control subjects were included. Serum FGF-23 and OPG levels were measured by ELISA and CAC was determined by multi-detector computed tomography (AS). Biochemical regular labs (Cr, Ca, P and PTH) were measured.

Results: Compared with control subjects, CKD patients exhibited significantly augmented serum FGF-23 (16.2 vs 304.8pg/mL; P<0.001), and increased proportionally to CKD stage. FGF-23 and OPG were correlated to PTH and P (P<0.001) and OPG correlated with renal function (sCr) in non-dialysis patients(P<0.05). CKD 5 patients showed significantly increased CACS compared with control group (CACS:117±117.7pmol/L; r=0.58; P<0.001) and increased proportionally to CKD stage. FGF-23 and OPG were correlated to AS (r=0.24; P<0.05 and r=0.37; P<0.01, respectively). Among KD patients, high CACS (AS>800) compared to low CAC patients (AS≤150) showed higher FGF-23 (374.9 vs 156.1; P<0.05) and OPG levels (2121.2 vs 1305.2; P<0.001).

Conclusions: CKD is related to high coronary artery calcification levels. FGF-23 and OPG are higher in CKD patients and are significantly associated to coronary artery calcification. Further investigations are needed to determine if they could promptly assess increased cardiovascular risk in CKD patients.

PUB141

Rate of Kidney Function Decline and Risk of Hospitalizations

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Background: Risk of hospitalizations is increased in patients with chronic kidney disease (CKD). We sought to examine the association between rate of kidney function decline and risk of hospitalization in a cohort of patients with early CKD.

Methods: We built a cohort of 241,274 United States veterans with an estimated glomerular filtration rate (eGFR) between 60 and 45 mL/min on October 1, 1999 and who had at least 1 additional eGFR measurement between October 2003 and September 2004. Patients were followed longitudinally from October 2004 until September 2013. We built
survival models to examine the association between rate of kidney function decline and risk of hospitalization, and readmission. We built linear regression models to estimate the length of hospital stay.

**Results:** Over a median follow-up of 9 years (IQR 5.42–9.00), compared to patients who experienced mild eGFR decline, patients with moderate and severe eGFR decline exhibited an increased risk of hospitalizations HR=1.10 (CI:1.07-1.12), and HR=1.29 (CI:1.26-1.32); respectively. The number of hospitalizations modified the association between rate of decline and risk of hospitalizations in that the risk was increasingly more pronounced with increased number of hospitalizations (p value for interaction <0.0001). Compared to patients with mild decline in kidney function, patients with moderate and severe kidney function decline had increased risk of future readmission, HR=1.16 (CI:1.10-1.21), and HR=1.47 (CI:1.39-1.55); respectively. Among patients with severe kidney function decline, the risk of readmission was increasingly stronger with increased number of readmissions (p value for interaction < 0.0001). Compared to patients with mild decline in kidney function, patients with moderate and severe decline experienced an additional length of stay of 0.91 (CI: 0.58-1.25) and 2.82 (CI: 2.43-3.20) day/year; respectively.

**Conclusions:** Our findings suggest that rate of kidney function decline is associated with future risk of increased health care utilization.

**Funding:** Veterans Administration Support

**PUB142**

**Racial Influences on the Association of Albumin and Hemoglobin in Chronic Kidney Disease**

**Background:** In CKD, anemia is associated with reduced kidney function, female gender, diabetes, older age, African-American race(AA), iron deficiency, low albumin, renin-angiotensin blockade, and chronic inflammation. There is a paucity of studies evaluating relationship of albumin and hemoglobin(Hb) in CKD among racial groups.

**Methods:** Retrospective cross section design of 196 patients with CKD stages 2-5, in a community clinic over a 7 months period. Averages of hemoglobin, albumin, body mass index (bmi), and glomerular filtration rate(GFR) were obtained for each individual patient. Patients on dialysis and on erythropoesis-stimulating agents were excluded. Multi-linear regression analysis (MLR) was then done between serum albumin and hemoglobin adjusting for age, sex, diabetic status, GFR, bmi, and Ace inhibitors/angiotensin receptors blockers intake (ACEi) among African-Americans(AA) and Caucasians(W).

**Results:** 51% were AA. 49% were diabetics. Mean Hb was 11.7 in AA compared to 12.3 in Caucasians. Mean serum albumin was also lower (3.5 AA versus 3.8 in W). Bmi and GFR were higher in AA (36.4 and 42.8 in AA vs 32.3 and 39.9 in W respectively). Using MLR, there was a statistically significant positive association between GFR(coefficient=0.02,p<0.001), albumin (coefficient=0.77,p=0.002) and hemoglobin. AA race was negatively related to hemoglobin (coefficient= -0.56,p=0.02). When MLR was done separately among racial groups, there was a persistent positive relationship between albumin and hemoglobin among AA (coef=0.95, p=0.001). In Caucasians however there was no association between albumin and hemoglobin (p=0.181).

**Conclusions:** In CKD-2, using multilinear regression analysis, there was a positive association between serum albumin and hemoglobin. This relationship occurs only in AA and disappears among Caucasians. It is of interest that in our sample AA had higher baseline bmi and GFR and lower serum albumin and hemoglobin. More needs to be done to understand the interplay between bmi , albumin and markers of inflammation and nutrition among African Americans with chronic kidney disease and their relationships to hemoglobin levels.

**Funding:** Pharmaceutical Company Support - Extramural grant: Roche Products Limited UK

**PUB143**

**Mirceura Use in Chronic Kidney Disease Patients with Symptomatic Renal Anemia: The Real Life Setting**

**Background:** Randomized controlled trials have confirmed non inferiority of Mirceura in the management of renal anemia when compared to other erythropoiesin stimulating agents (ESAs). Many of these trials had strict exclusion criteria which perhaps confounded any benefit that may be seen in an unselected cohort of patients. This multicenter audit assessed the outcomes of Mirceura use in the real life setting.

**Methods:** A prospective audit was conducted by 6 UK Renal Centers between 2009 and 2011. Demographic data, as well as hematological and biochemical parameters were longitudinally collected from 1000 adult patients requiring ESAs, over a 1 year period. A cohort of 500 patients were switched from previous ESAs to Mirceura and 500 patients remained on their existing ESA therapy. Patients with hemoglobinopathies or malignancies were excluded. Achievement of target hemoglobin (Hb) as per the National Institute of Clinical Excellence (NICE) guidelines was ascertained as the primary objective. Hb variability was reviewed as a secondary objective.

**Results:** Demographic data confirmed both cohorts were comparable. Only 11% of Mirceura treated patients had their Hb maintained within range (10-12g/dl) over the entire 1 year versus 4% in the non-Mirceura group (p<0.05). (If an Hb recording was out of range the patient was classified as ‘not maintained’). Parameters such as B12, folate and iron were similar in both cohorts. Hb was less variable in the Mirceura group compared to the non-Mirceura group. Hb variability was reviewed as a secondary objective. In the Mirceura group, Hb variability was reduced from 28% before to 21% after switching to Mirceura. Hb variability was reduced from 31% before to 25% after switching to Mirceura. Hb variability was reduced from 31% before to 25% after switching to Mirceura. Hb variability was reduced from 31% before to 25% after switching to Mirceura. Hb variability was reduced from 31% before to 25% after switching to Mirceura.

**Conclusions:** The results of this audit confirm that Mirceura use in the correction of anemia associated with CKD is equally efficacious as other ESA therapies in this real life setting. Over a year period, Hb variability was noted to be reduced in the Mirceura treated cohort suggesting a role for its use in patients with fluctuant Hb levels.

**Funding:** Veterans Administration Support

**PUB144**

**Latent Profiles of Patient Reported Outcomes in Nephrotic Syndrome Patients**

**Background:** Nephrotic syndrome (NS) can significantly impair the quality of life in children and adults. The purpose of this study was to demonstrate the feasibility and utility in using a latent profile analysis (LPA), a type of cluster analysis, to identify subgroups of patients based on their patient reported outcomes using the Patient Reported Outcomes Measurement Information System® (PROMIS®) measures as well as identifying significant predictors of those subgroups.

**Methods:** Prospective data were collected on 121 children with NS from the PROMIS-II study. Data from 55 children and 254 adults with biopsy confirmed NS from the NEPTUNE cohort were used as validation. LPA was used to identify distinct patterns and subgroups of patients based on PROMIS domain scores. Classification was assessed using entropy statistics. Generalized multinomial logit models were used to identify predictors of profile membership as well as transitions between profiles over time.

**Results:** We identified three patient reported outcome profiles (figure1) in the PROMIS-II cohort with strong indicators of membership classification (entropy>0.86).

**Conclusions:** LPA may be an effective tool in stratifying NS patients by quality of life. Profile membership changed in response to changes in disease status over time.

**Funding:** NIDDK Support
Sex Hormone Status in Women with Chronic Kidney Disease: A Survey of Nephrologists

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Background: Chronic kidney disease (CKD) in women is often accompanied by menstrual and fertility disorders due to kidney-mediated endocrine disturbances. Whether this issue is recognized by nephrologists and discussed by them with their patients is unknown.

Methods: We electronically surveyed 111 nephrologists in Canada, identified via Canadian Society of Nephrology membership (39% response rate), regarding their impressions of sex hormone status, menstrual cycle, fertility and the role of postmenopausal hormone therapy (HT) in women with CKD. Responses were stratified by kidney transplant nephrologist status.

Results: Fourteen percent of respondents were transplant nephrologists. There were no differences in age or sex between transplant and non-transplant nephrologists. Ninety-three percent of respondents agreed that kidney function has an important impact on regulation of sex hormones. However, only 35% reported discussing fertility, and even fewer (14%) reported discussing menstrual irregularities with their patients. Only 40% of respondents advised their patients to address these concerns with their family physician or an endocrinologist or gynecologist. Most of the of nephrologists responded that they do not know if there is a role for hormone replacement therapy in patients with CKD (48%), 23% of nephrologists disagreed with the statement. Nephrologists did not know whether the potential benefits of postmenopausal hormone therapy outweighed the risks in CKD (51%) or if the formulation (44%), route of administration (46%), and time of HRT initiation (50%) play a role in the actions of postmenopausal hormone therapy.

Conclusions: While nephrologists recognize the impact of CKD on sex hormone status in women, few address fertility and menstrual disorders with their patients. Our survey highlights existing uncertainties of nephrologists about how to manage disturbances of sex hormones in people with CKD.

Funding: Private Foundation Support

Use of Urine Biomarker-derived Clusters to Predict CKD Risk and All-Cause Mortality in HIV + women

Use of urine biomarker-derived clusters to predict CKD risk and all-cause mortality in HIV+ women: Robert Ekart,1,2 Robert waving,3 Robert L. Green,4 Robert H. Loh,5 Steve B. Wilton,6 Sofia B. Ahmed.1,2,3

Background: Urinary N-acetylglucosaminidase (NAG), Neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, are commonly used as urea and citric acid cycles. Urea is then transported through the bloodstream to be excreted into the urine by the kidneys. In patients with chronic kidney disease (CKD) an equilibrium concentration of ammonia and urea becomes imbalanced, concentrations exceeding physiological values and breath ammonia can be used for detecting increased urinary wastes in patients. In our pilot study, the breath ammonia sensor was used to measure and analyze breath ammonia in healthy volunteers and CKD patients.

Methods: Six CKD patients and eight healthy volunteers were enrolled. The mean age of CKD patients was 47.2 years, mean age of healthy volunteers 61.3 years. One controlled breath sample was given from each participant. Immediately after the sample was collected gas analyzer (BA-NH3, Echo, d.o.o.) was used for measuring breath ammonia in our participants. BA-NH3 detects breath ammonia in parts per million (ppm) and measures the electric current in milliamperes (mA). BA-NH3 was validated with reference gas samples prepared with a precise accredited gas mixing device (M4-1 S-220, Echo, d.o.o.) using calibrated mass flow controllers controlled with computer software.

Results: Mean serum creatinine in CKD patients was 455.17±294.12 µmol/L and 62.13±7.5 µmol/L in healthy volunteers. BA-NH3 detected more ppm of ammonia in breath of CKD patients (mean 3.32±2.19; range 1.26-6.33) compared to healthy volunteers (mean ppm 0.49±0.08; range 0.38-0.64 ppm) (p=0.003) and measured higher electric current from breath samples of CKD patients (mean mA 4.33±0.25; range 4.10-4.67 mA) comparing to healthy volunteers (mean mA 4.01±0.01; range 4.00-4.03 mA) (p=0.003).

Conclusions: Results of our pilot study show that breath monitoring of ammonia can be an useful simple, fast and noninvasive tool for detection of kidney impairment.

Association of biomarker-derived cluster* with incident CKD and all-cause mortality in HIV + women

<table>
<thead>
<tr>
<th>Incident CKD</th>
<th>Cluster 1 n=369</th>
<th>Cluster 2 n=435</th>
<th>Cluster 3 n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event rate</td>
<td>13%</td>
<td>21%</td>
<td>50%</td>
</tr>
<tr>
<td>Unadjusted Risk Ratio (95%CI)</td>
<td>1.7 (1.2, 2.4)</td>
<td>3.9 (2.7, 5.6)</td>
<td></td>
</tr>
<tr>
<td>Adjusted Risk Ratio (95%CI)</td>
<td>1.6 (1.1, 2.3)</td>
<td>2.9 (2.0, 4.3)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Cluster 1 n=381</td>
<td>Cluster 2 n=470</td>
<td>Cluster 3 n=131</td>
</tr>
<tr>
<td>Event rate</td>
<td>7%</td>
<td>13%</td>
<td>34%</td>
</tr>
<tr>
<td>Unadjusted Hazard Ratio (95%CI)</td>
<td>1.9 (1.3, 3.0)</td>
<td>5.4 (3.2, 9.0)</td>
<td></td>
</tr>
<tr>
<td>Adjusted Hazard Ratio (95%CI)</td>
<td>1.5 (0.9, 2.5)</td>
<td>2.8 (1.6, 4.8)</td>
<td></td>
</tr>
</tbody>
</table>

* Clusters were derived using NAG, sCr, and KIM-1. Adjusted models control for traditional kidney risk factors and HIV-related risk factors.

Funding: Other NIH Support - The WHIS Kidney Aging Study is funded by grant 1 R01 AG034853-01A2 (PL. Shlipak), which was administered by the Northern California Institute for Research and Education, and with resources of the Veterans Affairs Medical Center, San Francisco, California. Data in this manuscript were collected by the VAMC Medical Research Agency HIV Study (WHIS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). WHIS (Principal Investigators): UAB-MS WHIS (Michael Saag, Mirjam-Colette Kempf, and Deborah Konkle-Parker), U01-AI-103401; Atlanta WHIS (Jgeu (dka): U01-AI-100368; Rush; Albert Einstein; Georgetown.

Background: Individual urine biomarkers are associated with CKD incidence and all-cause mortality in the setting of HIV infection, but their combined utility for prediction remains unknown.

Methods: We measured 8 urine biomarkers in 902 HIV+ women: NAG, KIM-1, alpha 1 microglobulin (a1m), IL-18, NGAL, ACR, L-FABP, and AAG. A novel cluster method classified each participant into 3 groups using the three most distinguishing markers (NAG, KIM-1, and a1m). We evaluated associations of each cluster with incident CKD and all-cause mortality, adjusting for traditional and HIV-related risk factors.

Results: Over 8 years of follow-up, 177 CKD events and 128 deaths occurred. As shown in the Table, incidence of CKD and mortality increased incrementally across the 3 clusters. After multivariable adjustment, cluster 3 remained associated with a nearly 3-fold risk of both outcomes compared with cluster 1. Addition of the clusters to the multivariable model increased discrimination for CKD (c-statistic=0.72 to 0.76, p=0.0029), but only marginally for mortality (c=0.79 to 0.80, p=0.099). Clusters derived with all 8 markers were no better for discrimination than the 3 biomarker clusters.

Conclusions: Among HIV+ women, clusters developed from 3 urine biomarkers moderately improved discrimination for CKD risk, but not for all-cause mortality.
WHIS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH). Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Deafness and other Communication Disorders (NIDCD), and the NIH Office of Research on Women’s Health. WHIS data collection is also supported by UL1TR000004 (UCSF CTSA) and UL1-TR000454 (Atlanta CTSA).

### PUB149

**Minimizing Erythropoietin Stimulating Agents Requirement by Comprehensive Clinical Care**

Rachita Singh Dhull, Rossana Baracco, Melissa J. Gregory, Tej K. Mattoo.

**Pediatric Nephrology, Children’s Hospital of Michigan, Detroit, MI.**

**Background:** Anemia is a common problem in children with chronic kidney disease (CKD). The objective of the study was to evaluate prevalence of anemia, use of iron supplement and erythropoietin stimulating agents (ESA) in children with CKD stage 2-4, and compare the same with previous pediatric studies.

**Methods:** This is a retrospective chart review of children with CKD stage 2-4 (defined per KDOQI), aged between 1-18 years followed at Children’s Hospital of Michigan (CHM) in 2013. Data on transferrin saturation, hemoglobin level, use of iron supplements and ESA was collected.

**Results:** Total number of patients were 62. The mean age was 10.12 ± 5.52 years and 27.4% were female. The main causes of CKD were renal dysplasia (20%), obstructive uropathy (18%), reflux nephropathy (14.5%), cystic dysplasia (13%), glomerular pathology (11.2%) and others (23.3%). In our cohort, 27% patients had anemia compared to 44% in CKd study and 43.5% in study by Wong et al. Also, only 6.5% of CKD patients were on ESA, compared to 18% in CKd study and 19.5% in study by Wong et al. Results are elaborated in the table below.

<table>
<thead>
<tr>
<th>CKD STAGE</th>
<th>Patients(% with anemia)*</th>
<th>Patients(% with anemia)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>21/39</td>
<td>28.57/106</td>
</tr>
<tr>
<td>3</td>
<td>38/217</td>
<td>65.38/38</td>
</tr>
<tr>
<td>4</td>
<td>73/82</td>
<td>93.31/52</td>
</tr>
<tr>
<td>TOTAL</td>
<td>45/338</td>
<td>43.51/59</td>
</tr>
</tbody>
</table>

*Anemia as defined by hemoglobin (Hb) level < 9% percentile for age and sex according to NHANES III data.

**Conclusions:** Our CKD patients had a lower prevalence of anemia and lower use of ESA compared to other pediatric studies. We maintain adequate iron stores by using iron supplements even in children with normal hemoglobins. The administration of supplemental iron prior to the development of anemia in children with CKD decreases the need for ESA.

### PUB150

**Validation of Urinary Biomarkers for the Diagnosis of Urothelial Carcinoma in Patients with Chronic Kidney Disease**

Chin-Ching Huang,1 Che-yi Chou,1 Chao-Jun Chung.2

*Kidney Inst, China Medical Univ and Hospitals, Taichung, Taiwan; 1Proteomics Core Laboratory, Dept of Medical Research, China Medical Univ, Taichung, Taiwan.**

**Background:** Many urine biomarkers for diagnosis of urothelial carcinoma(UC) have been published. CKD patients are prone to have UC. Most of the studies are tested in healthy controls and UC patients. Whether these biomarkers are specific to diagnose UC in CKD patients have not been studied before. **AIMS:** To investigate whether urinary biomarkers are specific to diagnose UC in CKD patients.

**Methods:** This is a multicenter prospective case-control study, carried out at 7 tertiary medical centers in Taiwan (Taiwan UC Consortium). Subjects were healthy adults (healthy controls), patients with CKD but without UC (disease controls) and patients with ongoing UC. Urine was collected from each patient and frozen immediately after collection. We measured 9 urinary UC biomarkers : BLCA-1.HAI-1.HtrA1, NMP22, CYFRA21-1, TSCSTD2, BLCA-4, BTA and Midkine showed significant increase of urinary concentrations in UC patients when compared to healthy controls. Nevertheless, only Midkine and CYFRA 21-1 had significantly increased concentrations in UC patients when compared to CKD controls. The other 4 UC biomarkers did not show significant higher concentrations in UC patients than CKD controls.

**Results:** Among 9 biomarkers tested, only two showed statistically significant higher urinary concentrations in UC patients than matched CKD patients. Our findings would raise caution of interpreting urinary biomarkers for UC diagnosis in CKD patients.

**Funding:** Government Support - Non-U.S.

### PUB151

**Predictors for 30-Day Hospital Readmission in a Nephrology Ward**

Carla S. Moreira,1 Ligia Bessa,2 Vanda Guardado;3 Jorge Malheiro;1 Josefa S. Lascasas,2 António Cabrita.1

*Nephrology, Centro Hospitalar do Porto, Porto, Portugal; 1Nephrology, Hospital Militar de Luanda, Luanda, Angola.

**Background:** Rehospitalization, particularly 30-day hospital readmission is a growing concern in health care services. In this study we searched for predictors of 30-day readmissions (including emergency department visits) and 12-months hospitalization rate in patients admitted to a nephrology ward.

**Methods:** A group of 144 patients admitted to our nephrology ward from 2012 to 2013 were randomly selected. Their medical records regarding demographic and clinical-laboratorial data were collected. The statistical analysis was performed using univariate and multivariate logistic regression, and poisson regression.

**Results:** Median age was 66yos (IQR 56-81), with 63% of male patients. The majority of the patients had an emergent admission (63%) and regular hospital follow-up (55%). The median length of hospital stay was 7 days. The readmission rate was 23% and the median length until readmission was 13 days. The prevalence of chronic kidney disease was 89%, with 30% of these patients undergoing chronic intermittent hemodialysis and 11% peritoneal dialysis. The median Charlson Comorbidity Index (CCI) was 7 points (IQR 4-11). In the univariate analysis we found a significant statistical association between diabetes mellitus (OR =2.45, p=0.04), lower (<3.5g/dL vs. ≥ 3.5g/dL) albumin level (OR=8.73, p=0.006), higher (>8 vs ≥ 8) CCI score (OR=2.94, p=0.02) and 30-day hospital readmission. In the binary logistic regression only albumin level kept its significant association (OR=7.9, p=0.01), with diabetes mellitus maintaining a tendency for significance (OR=2.97, p=0.09). The rate of rehospitalizations at the first year adjusted for gender was 2.6 vs 6.4 rehospitalizations/100 patients-month in the lower and higher CCI score groups, respectively (p=0.01). The rate of emergency department episodes adjusted for gender was 29 versus 75 episodes/100 patient-month in the lower and higher CCI score groups, respectively (p=0.001).

**Conclusions:** The Charlson Comorbidity Index and albumin level may be valuable predictors of hospital readmission risk in patients from a nephrology ward.

### PUB152

**Urine Protein Fragment Excretion in Diabetic Patients with Chronic Kidney Disease**

Michele V. Clarke,1 Elfia Eksini,2 Nicholas J. Radcliffe,1 Richard J. Maclachac,1 George Jerums,1 Wayne Comper.1

*Austin Health, Melbourne; 1Uni of Melbourne, Melbourne; 2St. Vincent’s Hospital, Melbourne; Sal Aqua Diagnostics, New York.

**Background:** Albuminuria is an established marker for the development of diabetic nephropathy. Normal renal handling of albumin involves endocytosis by proximal tubule cells through a lysosomal pathway. This returns small albumin fragments, undetectable by standard clinical assays, to the tubular lumen. Albuminuria has been shown in patients with type 1 diabetes to be associated with an impaired degradation pathway, and urinary peptides have been shown to be reduced in patients with macromucinuria. However, urine peptide excretion studies have not controlled for changes in estimated glomerular filtration rate (eGFR) in patients with diabetes.

**Methods:** Patients with diabetes and eGFR >60ml/min were stratified into normo-(<20mg/min, n=9), micro- (20-200mg/min, n=12) or macroalbuminuric (>200mg/min, n=9) groups. 24 hr urines were passed through a 10kDa protein filter, and the <10kDa and >10kDa fractions were assayed separately using the BCA protein assay to detect peptide bonds.

**Results:** Macroalbuminuric patients had a reduced proportion of peptide fragment excretion (<10kDa) compared to micro- and normoalbuminuric patients (81.1% vs 89.0%, p=0.05 & 86.8%, p=0.001 respectively); however there was no difference between micro- and normoalbuminuric groups (Figure 1). Mean fragment concentrations were lower in micro- and macro- groups compared to normoalbuminuric patients, (338g/µl and 3480g/ 

### Key:

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

**Underlines** represent presenting author.
Conclusions: In patients with diabetes and reduced renal function, we have demonstrated a reduction in peptide fragment proportional excretion in macroalbuminuric (ESKD). Although ESKD is very common, there is little to no data addressing prevalence.

Sonar Bangla Foundation (SBF) in Bangladesh. SBF is a leading non-profit organization, socio-

Pilot Study Sonar Bangla Foundation Dialysis Centers in Bangladesh: A Cross-Sectional site studies

in high-risk populations that would provide insights into the importance of region-specific

environment, genetics, and lifestyle. Thus, to identify the causative factors of CKDu,
exposures that are heterogeneous and vary by region. It remains unknown whether the

in South Asia, family history, agrochemical use, and heavy metal exposures were reported

across all geographical regions. In South Asia, family history, agrochemical use, and heavy metal exposures were reported most frequently while altitude and temperature were reported only in studies from Central America. Across all regions, CKDu was most frequently associated with a family history of CKDu, farming occupation, male gender, middle-age, snake bites and heavy metal exposures. Among high risk populations, CKDu prevalence was reported to be 7.3%-14.9% in South Asia and 13%-25.9% in Central America.

Conclusions: Studies examining etiologies of CKDu have reported many potential exposures that are heterogeneous and vary by region. It remains unknown whether the regional variation in CKDu risk factors reflects inconsistencies in measurement across studies or complexity in the interactions between global exposures and local factors such as environment, genetics, and lifestyle. Thus, to identify the causative factors of CKDu, one important approach could be to design consistent and comparative multi-site studies in high-risk populations which would provide insights into the importance of region-specific versus global risk factors.

PB154

Understanding the Socio-Demographic Status of Patients Receiving Care at Sanor Bangla Foundation Dialysis Centers in Bangladesh: A Cross-Sectional Pilot Study Tamanna M. Novoy,1 Mahmood Hussain,2 Imtiaz M. Islam,3 Akm Monoarul Islam,4 Abu hena M. Kamal,1 ‘Sonar Bangla Foundation, Santa Clara, CA; 2Marketing, San Francisco State Univ, San Francisco, CA; 3Nephrology, Good Samaritan Specialists, Kearney, NE; 4Nephrology, Rajshahi Medical College & Hospital, Rajshahi, Bangladesh.

Background: This study constitutes an exploratory investigation to understand the socio-demographic status of patients receiving care at the nine dialysis centers operated by Sanor Bangla Foundation (SBF) in Bangladesh. SBF is a leading non-profit organization, exclusively dedicated to the care of patients suffering from End-Stage Kidney Disease (ESKD). Although ESKD is very common, there is little to no data addressing prevalence of ESKD in Bangladesh. Without understanding its prevalence and the socio-demographic status of patients, little can be done to increase effectiveness and quantity of dialysis centers throughout Bangladesh. This study was launched in April 2015 and will continue throughout the dialysis centers’ operations.

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

Underline represents presenting author.

922A

Conclusions: There’s no significant difference in the disease staging or immunofluorescences staining. However, the young adult patients had fewer mesangial, interstitial, tubular and arteriolar lesions, and fewer inflammatory cells infiltration as well (P<0.01). For the therapy, the number of ACEI/ARB regimen applied in the three groups were 72/95/75, while cortical associated with immunosuppressive agents regimen was 66/92/140 (P<0.01).

Conclusions: About a quarter of all IMN patients are young adults. They had fewer cardiovascular risk factors, higher serum albumin level and better renal function. Their pathological lesions were milder. ACEI/ARB regime is more widely applied in young adults patients.

PB156

Effect of Glycemic Control on Estimated Glomerular Filtration Rate by Cystatin C Masaru Horio,1 Enyu Imai,2 Yoshinori Yamasaki,2 Tsuyoshi Watanabe,2 Hitoshi Yokoyama,1 Hiroaki Makino,2 Seichi Matsu,2 1 Osaka Univ Graduate School of Medicine, Suita, Japan; 2Nakayamadera Imai Clinic, Takarazuka, Japan; 3Nagoya Univ Graduate School of Medicine, Nagoya, Japan; 4Fukushima Medical Univ, Fukushima, Japan; 5Kanazawa Medical Univ School of Medicine, Kanazawa, Japan; 6Okayama Univ Graduate School of Medicine, Okayama, Japan.

Background: Cystatin C has been proposed as an alternative marker for estimating glomerular filtration rate (GFR). But, some factors other than GFR affect the accuracy of estimated GFR (eGFR). Some studies raised a concern that poor glycemic control may cause inaccuracy of estimation of GFR. We studied the effect of glycemic control on eGFR based on serum cystatin C (eGFRcys).

Methods: eGFR was measured by inulin clearance (Cin). Estimated GFRs were calculated by CKD-EPI equation (CKD-EPI) and Japanese GFR equation (J-Eq) based on standardized cystatin C. Glycemic control was evaluated by serum glycated albumin (GA). Three hundred and forty five Subjects with normal GA (12.4-16.3%), and 126 subjects with high GA (>16.3%) were included. Effects of age, gender, BMI, GA and serum albumin on eGFRcys / Cin, eGFRcys (J-Eq) and eGFRcys (CKD-EPI) in normal GA were 57.9±34.0, 56.1±31.7 and 57.9±33.9 ml/min/1.73m², respectively. Cin, eGFRcys (J-Eq) and eGFRcys (CKD-EPI) in high GA were 36.2±28.9, 36.7±27.5 and 36.7±28.5 ml/min/1.73m², respectively. There was no significant difference among Cin, eGFRcys (J-Eq) and eGFRcys (CKD-EPI) in both subjects. Slopes (95%CI) of the regression lines with zero intercepts in subjects

Methods: A one-time survey is being conducted to obtain clinical and demographic information on all existing and new patients at SBF.

Results: Currently, the study reveals a large gender disparity amongst dialysis recipients, 1 out of 4 patients is female (n=101). The average age of male patients is 44.7 years (SD ±12.7), while the average age of female patients is 45.3 years (SD ±14.2). Furthermore, patients from at least 20 different districts receive dialysis at the center. The study also finds a significant positive correlation between education level and the frequency of dialysis received.

Conclusions: Data collected throughout this study will be incorporated into an expanding database, first of its kind in Bangladesh. ESKD is a devastating disease that forces patients to become dependent on a machine. By understanding the education level, financial status, distance traveled and other factors in relation to the frequency of dialysis received, services provided by SBF centers could be greatly improved. The study aims to change the quality of kidney care in Bangladesh.

PB155

Clinical and Pathological Features of Idiopathic Membranous Nephropathy in Young Adults Chenxi Gao, Jing Xia, Wen Zhang, Xiaoxian Pan, Xiao Li, Nan Chen. Nephrology, Ruijin Hospital, Shanghai Jiaotong Univ, Shanghai, China.

Background: Membranous nephropathy (MN) is a common pathological types in elderly nephrotic syndrome (NS) patients. Few researches focus on the young idiopathic MN population.

Results: 583 patients hospitalized between Jan 2009 and Dec 2014 in our department, with biopsy-proved MN eliminating secondary causes, are enrolled. All patients were divided into 3 groups: 150 patients (25.1%) in young adult group (≤44 yrs), 202 (34.7%) in middle-aged group (45-59 yrs) and 231 (39.6%) in elderly group (≥60 yrs). We and compared and collected their clinical and pathological data as well as therapy strategies.

Results: 310 male and 273 female enrolled. The young adult groups had a lower rate of NS (P<0.02), higher serum albumin (P<0.01), estimated-GFR (P<0.01) and hemoglobin level (P<0.01), and lower fast blood glucose level (P<0.01).

Table 1. Clinical features in three groups

<table>
<thead>
<tr>
<th></th>
<th>young adults group (n=150)</th>
<th>middle-aged group (n=202)</th>
<th>elderly group (n=231)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>proteinuria (mg/d)</td>
<td>4.7±3.8</td>
<td>4.6±3.9</td>
<td>5.1±3.4</td>
<td>0.271</td>
</tr>
<tr>
<td>serum albumin (g/l)</td>
<td>23.8±7.8</td>
<td>23.9±6.9</td>
<td>21.2±6.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>nephrotic syndrome</td>
<td>73</td>
<td>105</td>
<td>143</td>
<td>0.022</td>
</tr>
<tr>
<td>fast blood glucose (mmol/l)</td>
<td>4.5±0.9</td>
<td>4.8±0.9</td>
<td>4.9±1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>serum creatinine (μmol/l)</td>
<td>64.2±175</td>
<td>71.0±243</td>
<td>85.2±40.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>124.6±31.2</td>
<td>102.2±29.3</td>
<td>83.6±25.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>hemoglobin (g/l)</td>
<td>135.4±18.1</td>
<td>132.8±18.1</td>
<td>123.2±17.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
with high GA were 0.989 (0.944-1.035) in J-Eq and 0.965 (0.922-1.009) in CKD-EPI. The slopes were not significantly different from 1.00, suggesting that eGFRcys performed well in subjects with high GA. Multiple regression analysis showed that, age, gender, BMI, GA and serum albumin were not significant factors affecting both eGFRcys(CKD-EPI)/Cr and eGFRcys(3-Eq)/Cr.

- **Conclusions:** Estimated GFR based on cystatin C performed well in subjects with high GA.

**Funding:** Government Support - Non-U.S.

### PUB157

**Renal Hyperfiltration and Outcome in HIV-Infected Subjects**

Gianni Cappelli,1 Elisabetta Ascione,1 Giovanni Guaraldi,2 Andrea Malagoli,2 Elisabetta Rubbettini,1 Antonio Bellasi.1 1Univ Hospital of Modena, Nephrology Dialysis and Renal Transplantation Unit, Modena, Italy; 2Univ Hospital of Modena, Metabolic Clinic, Infectious and Tropical Diseases Unit, Modena, Italy; 3Azienda Ospedaliera S. Anna, Como, Dept of Health Sciences, Univ of Milan, Nephrology and Dialysis Unit, Como, Italy.

**Background:** Although highly active antiretroviral therapy (HAART) improves life expectancy of HIV-infected subjects, it is also associated with numerous comorbidities. Evidence suggests that renal hyperfiltration (RFH) is associated with various lifestyles, clinical conditions and portends poor prognosis in the general population. We sought at determining prevalence of RFH and its associations with traditional and HIV-related risk factors as well as all-cause mortality in a large cohort of HIV-infected subjects.

**Methods:** Retrospective study of 3875 HIV-infected patients attending at the “Modena Metabolic HIV Clinic”. The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) was used to estimate glomerular filtration rate (eGFR). Linear regression was used to model eGFR against age and sex. RFH was defined as eGFR with residuals above the 95th percentile. Anova, Chi-square, logist regression and survival analyses were used to identify factors and the risks associated with RFH.

**Results:** Overall, we investigated middle-age (44.5±7.5 years) men and women (male 65.1%) with preserved renal function (eGFR 94.5±17.1 ml/min/1.73 m²). RFH was inversely associated with age (Odds Ratio 0.93), hemoglobin (OR 0.8), WBCs (OR 0.9) and positively associated with HIV-infection (OR 1.07). Of interest, no association with HAART was noted. Over mean follow-up of 7 years, 75 persons died. RFH was associated with all-cause mortality independently of potential confounders (Hazard ratio: 4.17, 95%CI: 1.81 - 9.6; p<0.001).

**Conclusions:** RFH is influenced by HIV infection duration independently of established factors and related with the risk of all-cause of death. Future efforts are needed to clarify what are the mechanisms that link RFH with poor prognosis if and how RFH modulation improves survival in HIV-infected subjects.

### PUB158

**Bioelectrical Impedance Analysis as a Screening Tool for Chronic Kidney Disease**

Anita Saxena, Amit Gupta. Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.

**Background:** Chronic Kidney Disease (CKD) has a latent period during which the disease is present but asymptomatic. With increasing incidence of hypertension and diabetes, incidence and prevalence of CKD is on increase. Bioelectric impedance analysis (BIA) is a noninvasive method for estimation of body composition in clinical setting but it has not been used for CKD screening. Purpose: To evaluate applicability of BIA as a screening tool for presence of kidney disease in general population with creatinine clearance and glomerular filtration rate (GFR).

**Methods:** A pilot cross-sectional CKD screening study on randomly selected 52 subjects from general population. Maliron BIOSCAN analyzer 915/916 was validated with Hume et al’s equation for estimation of total body water. BIA derived GFR was validated with 99m Tc-DTPA nuclear scan derived GFR, a study done on voluntary healthy kidney donors.

**Results:** There was no significant difference between total body water estimated with BIA and Hume et al’s equation and BIA derived GFR and DTPA nuclear scan GFR. Mean serum creatinine for males was 0.94 ± 0.14mg% and 0.91 ± 0.84mg% for females. BIA derived creatinine clearance was 97.39 ± 28.98 in males and 107.60 ± 34.03 in females. GFR was 74.1±25.98 ml/min/1.73 m² in males and 65.17 ± 21.14 ml/min/1.73 m² in females. Based on GFR subjects were classified into CKD. Out of 52 subjects 8 were in CKD stage 1 (15.5%), 23 (44.2%) were in CKD stage 2, 18 (34.6%) were in CKD stage 3, 1 (1.9%)/ 1.9% each in CKD stage 4 and CKD stage 5 respectively. Incidentally, 13.5% were diabetic.

**Conclusions:** BIA derived creatinine clearance was 97.39 ± 28.98 in males and 107.60 ± 34.03 in females. GFR was 74.1±25.98 ml/min/1.73 m² in males and 65.17 ± 21.14 ml/min/1.73 m² in females. Based on GFR subjects were classified into CKD. Out of 52 subjects 8 were in CKD stage 1 (15.5%), 23 (44.2%) were in CKD stage 2, 18 (34.6%) were in CKD stage 3, 1 (1.9%)/ 1.9% each in CKD stage 4 and CKD stage 5 respectively. Incidentally, 13.5% were diabetic.

**Funding:** Private Foundation Support

### PUB159

**Design and Implementation of a Chronic Kidney Disease Prevalence Study in Rivas, Nicaragua**

Kailey Minninghs,1 Martha Mosco,2 Madeline M. Fiore,3 Eric S. Korns,4 Juan Jose Amador,5 Rulan S. Parekh,6 Louis D. Fiore.7 1Faculty of Medicine, Univ of Toronto, Toronto, ON, Canada; 2Lowering Poverty and Disease, Boston, MA; 3Tulane Univ, New Orleans, LA; 4Warren Alpert Medical School, Brown Univ, Providence, RI; 5School of Public Health, Boston Univ, Boston, MA; 6Hospital for Sick Children, Toronto, ON, Canada.

**Background:** High rates of chronic kidney disease of unknown etiology (CKDu) have been noted in certain populations along the Pacific coast of Central America. CKDu is unlike traditional CKD in that the usual underlying risk factors are not present. CKDu in Nicaragua has been noted to affect mainly sugarcane workers although there is a paucity of data for the general population.

**Methods:** A population based cross sectional study using a random sampling of 32 communities was carried out in the department of Rivas in Nicaragua. Visits were conducted in Spanish in 2012 for screening and in 2014 for repeat evaluations. Participants were consented and completed a baseline questionnaire. Serum creatinine was initially screened using a finger stick creatinine measurement device. Repeat measurements to confirm CKD were performed centrally at the Centro Nacional de Diagnostico y Referencia in Managua using the Cobas Integra Fage Generation 2 assay, which has been standardized to the IDMS method.

**Results:** The study sample consisted of 1240 individuals representing 75% of adults living in the 533 homes visited. The refusal rate was 9.3%. The median age was 36.4 years, 57% were female, 6.6% reported DM, and 27% reported HTN. The study cohort is slightly enriched for women, while young people are slightly underrepresented when compared to census data. Repeat measurement was done in 320 with elevated creatinine to confirm CKD over 2 years. The re-contact rate was 85%.

**Conclusions:** This cross sectional study population is representative of the general population of the department of Rivas in Nicaragua. Establishment of this study population will allow investigators to determine the prevalence of CKD in a random selection of the general population in both urban and rural areas of Nicaragua not previously studied.

**Funding:** Private Foundation Support

### PUB160

**Validation of the Lund Model Combining Simultaneous Cystatin C and Creatinine-Based eGFR**

Emil Den Bakker, Arend Bokenkamp. Pediatric Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.

**Background:** Estimated GFR (eGFR) based on serum creatinine (crea) and/or cystatin C (cys) is used to monitor GFR. Based on known limitations of either marker (muscle wasting for crea, corticosteroids for cys) Grubb et al have proposed the “Lund model” to identify such patients by calculating the difference between crea and cys-based eGFR (Scand J Clin Lab Invest 70 (2010): 65-70). If the difference is below a certain cut-off, the mean of eGFRCrea and eGFRCys is used. Otherwise a choice is made for one or the other as a more accurate estimate based on patient history. The aim of this study was to test the “Lund model” using eGFR equations from the CKiD study (Kidney Int 82 (2012): 445-55).

**Methods:** Retrospective analysis of 489 single injection intravenous clearance (mGFR) studies, in which serum crea, cys and urea had been measured simultaneously. Calculation of eGFR using crea (CKD1), cys (CKD2) or crea+cys/urea (CKD3) as well as the average of CKD1 and CKD2 (avCKD1-2). For the Lund approach, the relative difference (ΔCKD1-2) between CKD1 and CKD2 was calculated as percentage of avCKD1-2 and categorized as <40%, 40%-40%, 20%-30%. If ΔCKD1-2 was >40%, a choice was made for CKD1 (corticosteroid) or CKD2 (neuromuscular disease, wasting, malignancy). The performance of the different approaches was studied using bias (mGFR minus eGFR in ml/ min/1.73m²) and accuracy (% of measurements within ±30% of mGFR).

**Results:** CKD1, CKD2 and CKD3 had a bias of 4.6, 14.2 and 2.8 and an accuracy of 81.7, 80.6 and 90.4, respectively. avCKD1-2 had a bias of 9.4 and an accuracy of 88.9. ΔCKD1-2 was >40% in 11.4%, 30%-40% in 18.9% and 20%-30% in 33.9% of the studies. The Lund model was applied in 51 studies with ΔCKD1-2<40%. In 42/51 studies, a choice could be made based on history (CKD1 n=16, CKD2 n=26). This resulted in a bias of 10.5 and an accuracy of 86.4.

**Conclusions:** The various CKD equations performed comparably to the original publications different. The arithmetic mean between creatinine-based and cystatin C-based eGFR yielded similar results to the complex CKD3 equation while the Lund model did not improve the diagnostic performance. This may be due to the higher bias of CKD2.
PUB161

Evaluation of Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI), Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) Equations to Assess Glomerular Filtration Rate (GFR) in Kidney Cancer Patients

Marialva, Sao Paulo, Brazil.

Background: To estimate kidney function.

Methods: Prospective evaluation of 124 outpatients with kidney cancer admitted to treatment at Sao Paulo State Cancer Institute between September 2012 and February 2015. Estimated (e) GFR was calculated using CG, aMDRD and CKD-EPI equations and compared to 1/Cr-EDTA radioisotopic (r) clearance. The bias was given as the mean difference between the eGFR and rGFR values and the precision as the SD of the differences. Accuracy was described as the number of eGFR studies within 10 and 30% of the rGFR values.

Results: Patients were 59.0 ± 10.3 years old, 50.2% were women, rGFR (ml/min/1.73 m^2) was 78.7 ± 24.6 and eGFRs (ml/min/1.73 m^2) using the CKD-EPI, aMDRD and CG (ml/min) equations were respectively 80.7 ± 22.1, 83.4 ± 25.3 and 87.8 ± 26.5. Equations bias is detailed on table 1.

<table>
<thead>
<tr>
<th>Mean bias of differences</th>
<th>CKD-EPI</th>
<th>aMDRD</th>
<th>CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Bias (ml/min)</td>
<td>2.0</td>
<td>4.7</td>
<td>9.1</td>
</tr>
<tr>
<td>SD</td>
<td>21.5</td>
<td>21.5</td>
<td>24.1</td>
</tr>
<tr>
<td>p</td>
<td>0.306</td>
<td>0.017</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The accuracy of eGFR equations within 10% of rGFR were 31.4%, 27.4% and 19.4% with CKD-EPI, aMDRD and CG, respectively. Within 30% of rGFR, the accuracy of eGFR equations were 75.8%, 78.2% and 68.5% with CKD-EPI, aMDRD and CG, respectively.

Conclusions: CKD-EPI equation showed smaller bias and satisfactory accuracy when compared with the GFR assessed by 1/Cr-EDTA in this group of kidney cancer patients.

PUB162

Correlation Between Equation for Estimating Glomerular Filtration Rate: CKD-EPI, Cockcroft-Gault -CG- and MDRD in Colombia

Carlos H. Mejia, Nephrology, Cuenta de Alto Costo, Bogota, Cundinamarca, Colombia.

Background: The determination of the GFR has been recommended the calculation from different equation , namely Cockcroft-Gault (CG) or the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboraton (CKD-EPI); we have found differences of over and underestimation of renal function by these function.

Methods: Between July 1, 2013 and June 30, 2014, 3,055,568 patients diagnosed with hypertension, diabetes mellitus and chronic kidney disease of all members of the general social security system in health in Colombia were reported. The inclusion criteria for this analysis was older than 18 years. Quantitative variables were described by their mean and standard deviation and qualitative variables using frequency distribution. They were compared equation pairs of CG -MDRD4, CG-CKD-EPI and CKD-EPI-MDRD by calculating and plotting, prediction limits for differences between pairs and the values of the correlation coefficient r.

Results: 1,348,214 patients were included, 832, 129 women (61.7%). The mean age was 64.3 years (standard deviation (SD) 13.2), 50% of patients were 60 - 74 yo. 94% had diagnosis of HTA and 26% had diagnosis of DM. The mean creatinine was 0.95 mg/dl for population. The correlation coefficient between interclass (ICC)CG and MDRD is 0.704 ICC95% (0.703, 0.705) and limits of agreement of Bland and Altman from -31.65 to 43.83; ICC being CG and CKD-EPI is 0.728 CI 95% (0.729-0.730) and limits of agreement of Bland and Altman from -37.26 to 40.62 and the correlation coefficient being intraclass CKD-EPI and MDRD is 0.855 ICC 95% (0.855, 0.856) and limits of agreement of Bland and Altman between -26.61 and 21.89.

Conclusions: General population studies have reported a good correlation comparison between MDRD and CKD-EPI, our results show a good correlation between them, rather than between CKD-EPI and CG. A higher GFR greater are the limits of agreement, both the overall and in the analysis stages, similar findings have been observed in other reports. Despite some limitations MDRD4 and CKD-EPI remain the most comparable and used to estimate kidney function.

PUB163

Family Caregivers in Chronic Kidney Disease: A Missed Opportunity to Improve Overall Care

Jason Christopher George, Andrea Lynn Berger, Christyle A. Green, Dept of Medicine, Geisinger Medical Center, Danville, PA; Center for Health Research, Geisinger Medical Center, Danville, PA; Center for Clinical Innovation, Geisinger Medical Center, Danville, PA; Dept of Nephrology, Geisinger Medical Center, Danville, PA.

Background: Many patients with chronic illness rely on the assistance of loved ones to adequately manage their disease. While there is increased recognition of the role of family caregivers in end-stage renal disease, little attention has been given to this role among patients with chronic kidney disease (CKD) not on dialysis. The aim of this study was to assess CKD patients’ degree of dependency on non-professional caregivers for their self-management needs.

Methods: We conducted a survey-based study of 208 patients with non-dialysis dependent CKD stages 3-5 to identify 1) whether they receive help from an informal caregiver to perform health-related activities and 2) the nature of this relationship. We evaluated patients residing in as many homes as those with an assigned formal caregiver, since their self-management needs are different.

Results: Mean age of participants was 72, 57% were male, 98% were white, and 53% had a high school or lower level of education. Overall, 65% (133/205) of patients reported receiving help from another individual with at least one health-related task. Help with activities included medical decision making (51%), medication management (32%), scheduling medical appointments (30%), attending office visits (43%), understanding medical providers (23%), and activities of daily living (13%). The majority stated that the main person who helped them was their spouse (70%) or adult child (16%) vs. other family members (6%). Nearly half (46%) reported that another individual had access to their electronic health information through the online health portal to assist with their care.

Conclusions: A significant number of independently functioning CKD patients rely on the help of family members to navigate their care. Efforts are needed to acknowledge and supppport these informal caregivers in the medical management of complex patients with kidney disease in order to provide optimal care.

PUB164

Impacts of Chronic Kidney Disease on Other Non-Communicable Chronic Diseases – The Burden in the Health System of China

Lucia Zhang, Jinwei Wang, Ming Hui Zhao. Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.

Background: The spread of non-communicable diseases (NCDs) presents a global crisis, and accumulating evidence based on individual disease reveals that major NCDs including heart disease and stroke have a worse prognosis in the presence of chronic kidney disease (CKD). However, there is neither large-scale study quantitatively evaluating the burden of CKD on various NCDs, nor study comparing the burden of CKD with other NCDs, especially among low- and middle-income countries like China.

Methods: A national in-patient database involving 19.5 million patient-records was used. Diagnoses of CKD and other major NCDs, including hypertension, coronary heart disease, stroke, chronic obstructive pulmonary diseases, and cancer, were extracted from International Classification of Diseases-10 codes of the discharge diagnoses. The effect of CKD on costs, length-of-stay, and in-hospital mortality were analyzed for each NCD. Then the effect of CKD on those outcomes was compared with other major NCDs.

Results: For each NCD, the presence of CKD was associated with increased length-of-stay and in-hospital mortality. And the costs were also increased by 0.1-20.3%, except for coronary heart disease and diabetes. Among those NCDs, CKD was associated with the highest length-of-stay, and with in-hospital mortality only lower than that of cancer.

Conclusions: Using database with large sample size and broad geographic coverage in China, we found that the presence of CKD was associated with substantial increased healthcare resources utilization and increased risk of in-hospital mortality.

Funding: Government Support - Non-U.S.

PUB165

Patient Empowerment in a Multi-Disciplinary Chronic Kidney Disease Clinic

Therese T. Adamowski, Jonathan H. Segal, Jamie Alton Green. Internal Medicine, Univ of Michigan, Ann Arbor, MI.

Background: Existing research shows economic and health gains associated with multi-disciplinary CKD care, but there is little data examining associations with patient-centric measures. We collected patient-centric measures on perceptions related to care in a multi-disciplinary CKD clinic.

Methods: Our multi-disciplinary CKD clinic includes a pharmacist, physician assistant, social worker, dietician and RN educator-with oversight by a medical doctor. Patients see each provider during visits. Most patients have an eGFR ≤ 40 ml/min/1.73m^2.

Results: Data were available on 51 patients. The mean (SD) age was 62 (15) years. 53% were male, 65% Caucasian, and 53% African American. Patients reported being comfortable asking their doctor questions, mean (SD) 5.5 (0.97). The mean (SD) of the confidence / empowerment measure was 4.3 (0.74). In univariate analysis, higher ratings...
Trends in Access to Care in Adults with Kidney Disease, United States 2002-

Background: Use of healthcare services by medically underserved minority populations varies by ethnicity and cultural factors. Healthcare providers may address ethnicity-specific barriers to healthcare service usage to decrease disparities in healthcare use. Through free community health screenings provided by the Kidney Disease Screening and Awareness Program (KDSAP), we seek to elucidate ethnicity-specific differences and sociocultural barriers to healthcare service use.

Methods: A questionnaire available in English, Chinese, and Spanish was administered to KDSAP participants in Massachusetts, New Jersey, and Toronto from 2012 to 2014. Participants were asked to provide their ethnicity, health insurance, primary care physician, and difficulties and alternatives to receiving care.

Results: Of the 4,399 adults age ≥18 from the Medical Expenditure Panel Survey were analyzed. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute education, followed renal failure; 158 - chronic renal failure; 160 - calculus or urinary tract; and 161 - other diseases of kidney and uraters. Patient-centered care was ascertained if the usual care provider asked about prescription medications and treatments others doctors may give them; showed respect for medical, traditional and alternative treatments that the patient was happy with; asked the person to help make decisions between a choice of treatments; presented and explained all options to the person; and spoke the person’s language or provided translator services if person is uncomfortable speaking in English. We used unadjusted and adjusted poison regression to examine the association of patient-centered care outcome. Covariates included demographics and comorbidities.

Conclusions: Patient-centered care is a quality of personal, professional, and organizational relationships. There no studies on factors associated with patient-centered care in patients with kidney disease (KD). This study examines trends in factors associated with patient-centered care (PCC) in people with KD.

Methods: Data on 3,868 adults with KD aged 18 from the Medical Expenditure Panel Survey (MEPS) Household Component were analyzed. Individuals with KD were identified with Clinical Classification Codes: 156 - nephritis, nephrosis, renal sclerosis; 157 - acute education, followed renal failure; 158 - chronic renal failure; 160 - calculus or urinary tract; and 161 - other diseases of kidney and uraters. Patient-centered care was ascertained if the usual care provider asked about prescription medications and treatments others doctors may give them; showed respect for medical, traditional and alternative treatments that the patient was happy with; asked the person to help make decisions between a choice of treatments; presented and explained all options to the person; and spoke the person’s language or provided translator services if person is uncomfortable speaking in English. We used unadjusted and adjusted poison regression to examine the association of patient-centered care outcome. Covariates included demographics and comorbidities.

Results: Of the 3,868 adults with KD, 3%, 7%, 22%, 63% and 4% reported a positive response to 1, 2, 3, 4, and 5 out 5 questions on patient-centered care respectively. Patient-centered care was significantly reported in 2010/2011. Hispanic race was significantly associated with decreased access to prescription medication. Women and those with lower income were associated with decreased patient-centered care. Compared to 2000/2003, year 2004/2005 and 2010/2011 were significantly associated with increased patient-centered care in the poison regression analysis.

Conclusions: Patient-centered care in people with kidney disease has improved in recent years. Prospective studies examining the impact of patient-centered care on kidney disease outcomes especially end stage renal disease is imperative.

Funding: Private Foundation Support

2

Hypertension and Correlating Factors in a Minority-Rich Population

Background: Analysis of demographic variations in hypertension (HTN) in minority-populations presents a major opportunity for understanding the factors that influence chronic kidney disease (CKD). This study analyzes the influence of various factors in BP control in a minority-rich-population.

Methods: Data from 417 participants from minority populations in the Boston area (38.4% Black, 37.0% White, 5.0% other races) were sampled via Kidney Disease Screening and Awareness Program screenings from 2012-2014. Participants were assessed via questionnaire for awareness of their BP, healthcare, and insurance, and an assessment of their own health as well as their race, gender, age, & education. Participants then had their systolic (SBP) & diastolic (DBP) blood pressure measured, which was in turn classified according to American Heart Association guidelines & analyzed via T-tests & one-way ANOVA.

Results: Of the 417 participants 28.8% had normal BP, 47.2% were pre-HTN (130/80-139/89), 18.5% had stage I HTN (140-149/90-99), & 5.5% had stage II HTN (>160/100). Participants aware of their HTN had higher SBP (p<0.0001) & DBP (p<0.007) than those who self-reported no HTN. Men had significantly higher SBP & DBP than women (p=0.002, p=0.003, respectively), & individuals with little/no education had higher SBP than those with college (p=0.005) or post-graduate degrees (p=0.001). Younger age groups (below 30 years: mean BP 125/76) had significantly lower BP than older age groups (60-69+ years: mean BP 136/81); p<0.0001 & p<0.037 for SBP & DBP. Notably, no significant differences in SBP among ethnicities emerged.

Conclusions: Our results revealed that awareness of HTN status, gender, education level & age influence BP variations in minority-rich communities. Services tailored to these factors may help reduce HTN prevalence among minorities.

Funding: Private Foundation Support

Veterans Affairs (VA) eKidneyClinic: A Freely-Available Online Tool to Help Close the Chronic Kidney Disease (CKD) Patient Education Gap

Background: Patient education remains an important tool in the management of CKD and end stage renal disease (ESRD)-diseases with significant patient and economic burden. Patient knowledge and understanding of CKD are dismal, particularly amongst highly-selected populations (e.g. African Americans). For Veterans with CKD, limited health literacy is prevalent, and varied, fragmented, and unclear presentation of patient education materials (PEMs) compound the gap in understanding CKD.

Methods: To address these deficiencies, VA developed a comprehensive web tutorial, VA eKidneyClinic (http://ckd.vacloud.us). This freely-available, Veteran-centered, virtual education tool is designed to help close the knowledge and understanding gap between CKD patients and providers. This tool is designed to address patient education gaps by using evidence-based educational content, providing clear and concise messaging, and demonstrating the tools and techniques that can be used in the day-to-day clinical setting, particularly in the virtual care environment.

Conclusions: The VA eKidneyClinic is a free, user-friendly, web-based educational tool that can be integrated into the usual care of CKD patients. This tool is designed to improve patient education and understanding of CKD and its implications.

Funding: Private Foundation Support

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

Underline represents presenting author.
Should All Patients with Diabetic Nephropathy Be Treated in a Joint Renal Diabetic Clinic? Jonathan P. Wong, Tara Lee, Tracy Maryan, Jocelyn Berdeprado, Suresh Mathavakkannan. *Lister Renal Unit, United Kingdom.*

**Background:** The natural history of diabetic nephropathy is variable. Some patients have rapidly declining kidney function and would benefit from close monitoring in a joint renal-diabetic clinic, however joint renal-diabetic clinics are not widely available in the UK health system. We studied outpatient attendance patterns, rate of eGFR decline and other clinical parameters in patients with diabetic nephropathy to determine potential need for development of a joint renal-diabetic clinic at our unit.

**Methods:** A cross-sectional survey of all patients with CKD and diabetes mellitus (DM) at our unit was performed. Demographic, diabetic clinic attendance and clinical parameters including HbA1c, BP, urine protein:creatinine ratio (uPCR) and eGFR for the previous 5 years were collected. Patients who had a rate of decline in eGFR 2ml/min/1.73m2 were defined as having progressive CKD.

**Results:** 630 CKD patients with DM attending CKD clinic at our trust were identified. 195/630 (31%) of patients had diabetic nephropathy. 54.6% (100/195) had progressive CKD, but only 57% (37/100) of these patients attended a diabetic clinic. Conversely, 45.4% did not have progressive CKD, potentially representing a group of patients who could be safely monitored by general physicians. Patients with progressive diabetic nephropathy were more proteinuric than those with stable CKD (161 vs 46mg/mmol, p=0.004) but did not significantly differ in terms of age, weight, glycemic control or BP. 9.2% (58/630) were lost to follow-up from nephrology services, 31% (18/58) of this subset of patients continued to attend the diabetic clinics and 69% (40/58) were lost to follow-up from both diabetic and renal services.

**Conclusions:** Not all patients with diabetic nephropathy develop progressive CKD. Identifying patients (e.g. low level proteinuria) who could be safely monitored by general physicians may relieve pressure on CKD clinic and reduce hospital visits for patients. However, many patients with progressive CKD were not being monitored in a diabetic clinic, potentially missing out on specialist interventions. Development of a joint diabetic-renal clinic could streamline care and improve management for these patients.

**Funding:** Clinical Revenue Support

Leveraging Predictive Modeling to Improve the Participant Identification Process Transition to Dialysis Support Programs Meghan Martin Cockrell, Yanting Dong, Huyl Hines, Gilbert Haugh, Vipin Gopal, Roy Beveridge, Todd Prewitt. *Humana, Louisville, KY.*

**Background:** Evidence demonstrates that renal care management is beneficial to patients suffering from late-stage chronic kidney disease (CKD) and end-stage renal disease (ESRD), especially around the time of transition to dialysis. Integrated care management solutions provide assessment, education, and care coordination. Engagement in these programs improves health outcomes, including compliance with dialysis schedules and vascular access, and also reduces costs.

**Methods:** Traditionally, patients are identified for renal care management programs via a qualified estimated glomerular filtration rate (eGFR) lab value of <20mL/min/1.73 m2. However, since eGFR is not always available, there may be a gap in identifying people who could benefit from this type of support. A predictive model (PM) was developed to identify candidates for a transition to dialysis program. The PM identifies individuals with CKD over the prior 12 months and determines their likelihood of starting dialysis within the subsequent 12 months. It is based on claims, demographics, and lab and consumer data. To assess the effectiveness of the PM, a random portion of individuals scored in the top 2% were followed up from nephrology services, 31% (18/58) of this subset of patients who continued to attend the diabetic clinics and 69% (40/58) were lost to follow-up from both diabetic and renal services.

**Results:** Thirteen percent of people referred by the PM ultimately transitioned to dialysis and all were invited into a renal care management program. Seventeen percent of the people referred were observed to see if they would be referred by the PM at a 12 month follow-up. Of those referred, 27% (n=68) were never identified for the renal care management program. Hence, the model is effective in identifying those who will get identified via the standard referral process.

**Conclusions:** Application of advanced predictive modeling permitted identification of participants who may not have otherwise had the opportunity to benefit from renal care management.

Oxidative Stress: Dual Pathway Induction in CKD Pathogenesis Grazia Maria Virzì, Alessandra Brocca, Massimo di Cal, Claudio Ronco. *Nephrology Dept-IRRIV, San Bartolo Hospital, Vicenza, Italy.*

**Background:** Oxidative stress is defined as the imbalance between excess formation and insufficient removal of highly reactive molecules (Reactive Oxygen Species-ROS and Reactive Nitrogen Species-RNS) that attack DNA, protein and lipids, either denaturing or altering their structure. The variations and the correlation of inflammation and oxidative stress in CKD have not been thoroughly understood. In this study, we examined the putative role of ROS and RNS in the pathogenesis of CKD and the interaction with inflammation.

**Table 1. Adjusted rate of decline in GFR across time**

<table>
<thead>
<tr>
<th>Year</th>
<th>CKD cases</th>
<th>Controls</th>
<th>% change in eGFR</th>
<th>% change in eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>53.166</td>
<td></td>
<td>-</td>
<td>72.481</td>
</tr>
<tr>
<td>2007</td>
<td>51.104</td>
<td>2006-2007</td>
<td>3.88%</td>
<td>72.543</td>
</tr>
<tr>
<td>2008</td>
<td>50.224</td>
<td>2007-2008</td>
<td>1.72%</td>
<td>67.368</td>
</tr>
<tr>
<td>2009</td>
<td>47.449</td>
<td>2008-2009</td>
<td>5.43%</td>
<td>61.982</td>
</tr>
<tr>
<td>2010</td>
<td>47.651</td>
<td>2009-2010</td>
<td>-0.32%</td>
<td>67.539</td>
</tr>
<tr>
<td>2011</td>
<td>42.846</td>
<td>2010-2011</td>
<td>10.08%</td>
<td>73.864</td>
</tr>
<tr>
<td>2012</td>
<td>41.294</td>
<td>2011-2012</td>
<td>6.4%</td>
<td>84.218</td>
</tr>
</tbody>
</table>

**Results:** Suggest that GFR decline may not be attributed to aging only. Each episode of AKI related to contrast or nephrotoxic drugs increases risk for CKD progression/GFR decline in elderly. Pre-existing CKD is a strong predictor of GFR decline after adjustment for other co-morbidities.
Methods: 25 patients with CKD5 (for each stage) and 18 healthy subjects (CTR) were included in the study. Determinations for IL6, Myeloperoxidase (MPO), Nitric Oxide (NO), and Endogenous Peroxidase Activity (EPA) were performed by ELISA. A p-value of <0.05 was considered statistically significant.

Results: CKD patients displayed significant augmentation in circulating ROS and RNS, as well as expression of inflammatory cytokines, as IL6 (all, p<0.01). There is a positive correlation between IL6 and all oxidative stress markers and an inversely correlation with eGFR (all, p<0.05). We divided CKD patients in CKD1-2 (n=10) and CKD3-5 (n=15): a significant higher level of oxidative stress was observed in CKD3-5 (p<0.008).

Conclusions: CKD is characterized by ROS and RNS dissequilibration and inflammation that promote additional damage to the kidney and to distal tissues with development and progression of concomitant diseases. This pilot study demonstrates the significantly heightened presence of dual oxidative stress pathway induction in CKD patients that increase with the progression of CKD: each stage of CKD could be characterized by differing levels of ROS/RNS dissequilibration. Our findings indicate that oxidative stress is a potential therapeutic target, as it promotes inflammation by ROS/RNS-linked pathogenesis. Future research should focus on interventions that aim to reduce oxidative stress and inflammation in patients with various stages of CKD and slow the progression of CKD during its early stages.

PUB175
Comparative Biomarker Analysis Reveals Serum and Urine sTNFR1 Correlate with eGFR and Albuminuria in Man

Diana L. Donnelly-Roberts, Marian T. Namovic, Mark T. Houser, Murali Gopalakrishnan, Timothy A. Esbenshade. Renal Discovery, Abbiev, North Chicago, IL.

Background: It has been demonstrated that soluble tumor necrosis factor receptors (sTNFR1 & sTNFR2) are elevated in serum of patient cohorts with various renal disease etiologies with a strong association to early renal decline with or without proteinuria. The current study was designed to gain further insight into the relationship of renal function to sTNFR1 and sTNFR2 (MPO, NO) from a recently completed clinical study in high-risk subjects undergoing non-cardiac surgery. A subset of baseline serum and urine samples from patients with and without CKD (mean age of 70, 64% male, mean eGFR of 58 ml/min/1.73 m³, and mean total urinary protein concentration 70 g/l) were evaluated to assess sTNFR1 and other select BMs reflective of progression of DN, CV risk, inflammation, fibrosis or renal injury.

Methods: Samples were selected based on medical history (DM, DN, other CKD, or no renal disease) and stratified for analysis based on eGFR values. All samples examined were from baseline/pre-dose collections prior to drug administration or surgery and analyzed in an blinded manner.

Results: In serum, several BMs correlated with eGFR with sTNFR1 (P <0.0001) and uric acid (P=0.0004) being significant but moderate for MPO-23 (P=0.01), and ADMA (P=0.01). In urine, results revealed that several BMs correlated with eGFR with a strong significant correlation for sTNFR1 (P <0.0001) as well as for complement C9 (P=0.011) and IC3b (P=0.013). Significant correlations were also observed for qualified biomarkers such as NGAL (P<0.01), albumin (P<0.01), and cystatin C (P<0.05). sTNFR1 in urine also strongly correlated with albuminuria (P<0.0002) and UA/CR (P<0.0001).

Conclusions: Our studies demonstrate that sTNF1 correlates with renal functional decline across a wide eGFR range (22 to 116 ml/min/1.73 m³) regardless of renal disease, which was assessed in both serum and urine. Limitations of this preliminary study are small sample size and use of static eGFR values. Additional correlation analyses in longitudinal cohorts can shed further light into the relationships of sTNF1 and other BMs to CKD.

Funding: Pharmaceutical Company Support - Abbiev

PUB176
The Association of Plasma Uric Acid with Renal Vascular Lesions and Intertstitial Fibrosis in Biopsy-Confirmed Kidney Disease

Anand Srivastava,1 Venkata Sabbisetti,2 Isaac Ely Stillman,1 Helmut G. Rennke,2 Sushrut S. Waikar.1 1Renal Div, Brigham & Women’s Hospital, Boston, MA; 2Dept of Pathology, Brigham & Women’s Hospital, Boston, MA, 3Dept of Pathology, Beth Israel Deaconess Medical Center; Boston, MA.

Background: Elevations in plasma uric acid (PUA) have been hypothesized to play a pathogenic role in the development of chronic kidney disease (CKD) through multiple mechanisms, including mitochondrial damage, oxidative stress, endothelial dysfunction, vascular smooth muscle proliferation, and intra-renal inflammation.

Methods: We measured PUA in plasma samples obtained from 272 patients on the day of native kidney biopsy at three tertiary care hospitals in Boston, MA. We compared PUA against measures of kidney function and pathology, including estimated glomerular filtration rate (eGFR) and adjudicated semi-quantitative measures of kidney pathology using Spearman correlation coefficients. Arterial and arteriolar sclerosis/hyalinosis were classified as none (1), mild (2), moderate (3), or severe (4). Fibrosis was classified as 0% (1), 1-10% (2), 11-25% (3), 26-50% (4), and > 50% (5) of cortical volume.

Results: The primary indications for kidney biopsy were proteinuria in 61%, hematuria in 33%, abnormal eGFR in 35%, and nephrotic syndrome in 14% (sum exceeds 100% due to multiple indications). Mean age was 51.2 ± 16.0 yrs, 53% were women, 18% were black, and median eGFR was 50 (IQR 30-80) ml/min/1.73 m². Median PUA was 6.3 (IQR 5.1-7.5) mg/dl, and was inversely correlated with eGFR (r=-0.43) and positively correlated with arterial sclerosis (r=0.21), arteriolar hyalinosis (r=0.23), and interstitial fibrosis (r=0.28) for all CKD stages. The association with proteinuria was weaker and no longer statistically significant after adjustment for eGFR. Findings were generally consistent in subgroup analyses of those with diabetes, glomerulonephritis, vascular disease, and tubulointerstitial disease.

Conclusions: We found no independent associations between PUA and semi-quantitative measures of kidney pathology. The cross-sectional associations of PUA with renal vascular lesions and interstitial fibrosis appear to be confounded by eGFR.

Funding: NIDDK Support

PUB177
Association of Plasma Sphingomyelins and Ceramides with Chronic Kidney Disease and Glomerular Filtration Rate

Maria Lourdes Gonzalez Suarez,1 Vesna D. Garovic,2 Norman James Haughey,2 Veera Venkata Ratnam Bandaru,2 Susan Resnick,2 Luigi Ferrucci,3 Michelle M. Mielke,4 Div of Nephrology, Hypertension, Mayo Clinic, Rochester, MN; 5Dept of Neurology, Johns Hopkins Univ School of Medicine, Baltimore, MD; 6Dept of Psychiatry, Johns Hopkins Univ School of Medicine, Baltimore, MD; 7Intramural Research Program, NIA/NIH, Baltimore, MD; 8Dept of Health Sciences Research, Mayo Clinic, Rochester, MN.

Background: Sphingolipids are a class of bioactive lipids linked to insulin resistance and diabetes. Ceramides have been implicated in acute renal failure and diabetic nephropathy. We cross-sectionally examined the associations of plasma ceramides and sphingomyelins (SM) with glomerular filtration rate (GFR) and Chronic Kidney Disease (CKD).

Methods: Baltimore Longitudinal Study of Aging participants (N=486) with plasma lipids and GFR were included (median age 63, 58% men); 23 had CKD defined as GFR<60 ml/min. Ceramides and SM were quantitatively measured using a HPLC-coupled electrospray ionization tandem mass spectrometer. Logistic regression was used to determine the association between the log transformed sphingolipids and odds of CKD, adjusting for age, sex, and race. Among participants without CKD, linear regression was used to examine the association between the sphingolipids and GFR adjusting for age, sex, race, BMI, and hypertension.

Results: Higher levels of all SM were associated with increased odds of CKD: each log unit increase in SM C18:1 was associated with six-fold increased odds of CKD (OR=6.92, p=0.002). Among individuals without CKD, higher SM were also associated with lower GFR. This association was most pronounced among the 290 individuals without diabetes or pre-diabetes: each log unit increase in SM C18:1 was associated with lower GFR (b=-8.40, p=0.002).

Conclusions: These results suggest that elevated plasma SM are associated with CKD. Likewise, among those without CKD, elevated SM are associated with lower GFR. The cross-sectional study design limits specific conclusions on the mechanisms and temporality of these associations but suggests that further research is warranted.

Funding: Other NIH Support - U01 AG37526 (National Institutes of Health/National Institute on Aging)

PUB178
Clinical and Pathologic Predictors of Progression to End Stage Renal Disease following Renal Biopsy

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Background: The value of renal biopsy in prognosis of chronic kidney disease remains unclear. Irreversible, chronic changes such as interstitial fibrosis and glomerulosclerosis are thought to provide prognostic information. We sought to define the relative prognostic value of biopsy pathology and clinical factors for predicting progression to end stage renal disease (ESRD).

Methods: Retrospective, single center review of renal biopsies performed between 2004-2014 in four kidney diseases. Cox regression was used to evaluate nine pathologic findings on light microscopy and 21 clinical variables as potential predictors of progression to ESRD.

Results: 231 cases were reviewed (34% IgA nephropathy, 29% focal segmental glomerulosclerosis, 19% tubulointerstitial disease, 18% diabetic nephropathy). 83/231 (36%) subjects progressed to ESRD within 5 years follow-up. Median estimated glomerular filtration rate (eGFR) at time of biopsy was 32 (IQR: 18-54) ml/min. Median percent interstitial fibrosis was 20% (IQR: 10%, 40%). In multivariable Cox regression adjusting for pathologic diagnosis and eGFR at the time of biopsy, independent predictors of progression to ESRD within 5 years of biopsy were: interstitial fibrosis > 20% (HR 2.35 [1.22, 4.53]; p = 0.01), presence of endocapillary inflammation (HR 5.92 [1.95, 17.86]; p = 0.01). Presence of arteriosclerosis (HR 2.03 [1.01, 4.05]; p = 0.05), history of liver disease (HR 3.44 [1.53, 7.71]; p = 0.02), presence of arterial hypertension (HR 3.44 [1.53, 7.71]; p = 0.02), and congestive heart failure (HR 1.85 [0.99, 3.48]; p = 0.06).
index (BMI, 29 vs. 30 kg/m²), higher mean baseline eGFR (99 vs. 94 mL/min/1.73 m²) and lower prevalence of diabetes (10% vs. 18%); p<0.05 for all. In the overall study population, eGFR was stable without any decline (mean change: 0.1 mL/min/1.73 m²), while 189 participants experienced an eGFR decline ≥3% per year. Lower dietary magnesium intake was associated with higher risk of eGFR decline ≥3% per year (tertile 1 vs. 3, hazard ratio 1.9, 95% confidence interval: 1.1, 3.3) adjusted for socio-demographics, baseline eGFR, prevalent diabetes and hypertension status, BMI, serum magnesium, total energy intake, and dietary intake of calcium, potassium, and phosphorous.

Conclusions: Among persons with preserved eGFR, we detected a significant association between lower dietary Mg intake and increased risk of rapid kidney function decline independent of traditional CKD risk factors. These results highlight the importance of magnesium intake in the overall diet for the preservation of kidney function.

Funding: NIDDK Support, Other NIH Support - NIA

PUB181

Renin-Angiotensin System: A Possible Mechanism for AKI-CKD Continuum

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Background: Based on many clinical observations and studies, acute kidney injury (AKI) was now regarded as an important risky factor causing chronic kidney disease (CKD). Not only does CKD lead to end-stage renal disease (ESRD), but also increases the risk of cardiovascular disease or even death. Clinical studies often observe that the higher the AKI severity of a patient is, the more likely her/his kidneys progress into CKD. To this day, the mechanism underlying the progression of kidneys into CKD after AKI remains unclear. Since the higher severity of the AKI leads to more reduction of nephron numbers, we propose that activation of renin-angiotensin system (RAS) may be involved in the progression to CKD after recovery from AKI.

Methods: Severe AKI was induced in male adult CD-1 mice by right unilateral nephrectomy (Nx) followed by ischemia-reperfusion injury of left kidney 2 weeks later. Drinking water with or without type 1 angiotensin II receptor blocker losartan or direct vasodilator hydralazine was administered to mice from 4 weeks after surgery. Mice with Nx only were served as the control. Blood pressure, urinary albumin-to-creatinine ratio (ACR) and plasma levels of creatinine were evaluated.

Results: Compared to Nx group, AKI mice showed acute rise of plasma creatinine levels on day 2 after Nx+IRI surgery, which decreased to baseline on day 7. Moreover, elevated systolic blood pressure and increased urinary ACR were noted since 4 weeks after Nx+IRI. During the 4-month experimental period, progressive increase of urinary ACR and plasma levels of creatinine were noted. On the contrary, systolic blood pressure, urinary ACR and plasma creatinine level were normalized in mice administered with losartan since 4 weeks after Nx+IRI surgery. However the increase of urinary ACR and plasma creatinine level were not prevented in mice administered with hydralazine despite similar normalization in blood pressure.

Conclusions: These data suggest that RAS activation may underlie the mechanism for development of CKD in mice after recovery from AKI. Future studies are needed to explore the effect of RAS blockade in prevention of CKD and its pressure in patients recovered from AKI.

Funding: Government Support - Non-U.S.

PUB182

The Renal Effects of Neprilysin Inhibition in Heart Failure and Hypertension


Background: Neprilysin inhibitors (NEPi) represent an emerging therapeutic option for treatment of hypertension (HTN) and heart failure (HF) through enhancement of natriuresis. While these agents have shown promising results with regards to lowering blood pressure (BP) and HF events, their impact on the kidney remains largely unknown. The aim of this study is to evaluate the currently available evidence on the effect of NEPi use on kidney-related parameters in patients with HTN or HF.

Methods: A search of articles cited in PubMed database from 1995 to 2015 using key words “neprilysin”, “heart failure” and “hypertension” found 237 articles. Animal studies were excluded. Those studies containing kidney-related parameters such as serum creatinine, glomerular filtration rate (GFR) or ACR were selected. Relevant data including changes in renal function, blood pressure and mortality were extracted and compared.

Results: A total of 42,487 patients from 12 randomized controlled trials with data pertaining to NEPi use were included (8 in HTN and 4 in HF). Seven studies used NEPi combined with ACE-i, 4 with ARB, and 1 with endothelin converting enzyme inhibitors. The follow up periods ranged between 7 days and 27 months. All studies in HTN (including 27,401 patients) reported significantly better BP lowering effect for NEPi compared to control group, while 94% of the patients in the HF studies presented with improvement in renal function and mortality. Although there is limited evidence, at endpoint all HF studies (including 15,086 patients) showed less frequent renal impairment (expressed as an adverse event, incidence of worsening renal function, change in GFR, or serum creatinine) compared to the control group. In contrast, only 3 HTN studies (including 466 patients) explored the impact on renal function and reported no significant benefit.

Conclusions: Current evidence suggests that in patients with HF, NEPi can lower HF-related events and mortality while potentiating favorable impact on renal function. In patients with HTN, although NEPi have been shown to reduce BP, there is no conclusive evidence of their role in improvement of renal function in this setting.

Funding: None

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

928A
PUB183

The Differences of Renal Protective Effect by Hyperuricemia Treatment Using Febuxostat in Various CKD Subgroups  Akinori Yamaguchi, Makoto Harada, Yosuke Yamada, Koji Hashimoto, Makoto Higuchi, Yuji Kamijo.  

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Background: We often experience the CKD cases exhibiting the attenuation of eGFR decline by hyperuricemia treatment using febuxostat. However, renal protective effect of the hyperuricemia treatment has not yet been established. We hypothesize that the therapeutic response of febuxostat treatment might differ among various subgroups of CKD patients.  

Methods: To investigate the difference of the therapeutic response in CKD patients, 272 outpatients with hyperuricemia who were treated by febuxostat from May 2011 to March 2015 were enrolled. Patients undergoing hemodialysis and/or peritoneal dialysis treatment, and patients lacking essential clinical data were excluded. Finally, 178 patients were analyzed. Correlation coefficient between the average of serum uric acid level and the eGFR variation during 6 months after the treatment were statistically investigated in various clinical subgroups.  

Results: In all patients, significant correlation between the average of serum uric acid levels and the eGFR variation was detected (Spearman’s correlation coefficient: r=0.163, p<0.019). This significant correlation was also detected in each patient groups as follows: male patients (n=121, r=0.211, p=0.020), non-elderly (below 70 years old) patients (n=107, r=0.261, p=0.007), patients whose systolic blood pressure were below 130 mmHg (n=72, r=0.238, p=0.044), patients without dyslipidemia (n=133, r=-0.316, p=0.005) and non-diabetic-nephropathy patients (n=133, r=0.184, p=0.034). However, the significant correlation was not detected in each opposite subgroup.  

Conclusions: The current study suggest that therapeutic response of febuxostat treatment might be well in each CKD subgroups, including male, non-elderly, non-hyperuricemia, non-dyslipidemia and non-diabetic-nephropathy. It is possible that various risk factors of atherosclerosis conceal the beneficial renal protective effects of hyperuricemia treatment using febuxostat.

PUB184


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Background: The current search for new biomarkers in CKD is intense, with particular emphasis on hard endpoints, such as ESRD, creatinine duplication and cardiovascular and overall mortality. In this analysis, we sought to evaluate which baseline clinical and laboratorial variables were related to ESRD/mortality in 56 patients with albuminuric diabetic nephropathy after mean follow-up time of 5 years.  

Methods: Baseline clinical and laboratory data of 56 participants of a clinical trial were evaluated as predictors of major outcomes (primary outcome: ESRD, creatinine duplication or mortality). Mann-Whitney and chi-square tests were used for univariate analyses. Several univariate and multivariate COX regression models were built on the risk of PO. Kaplan-Meier curve and LOG rank test were also performed.  

Results: PO occurred in 39 participants after a mean follow-up time of 5 years (70%). In univariate analyses, sex, creatinine clearance, 24h proteinuria, uRBP, urinary VEGF and serum TGF-beta were related to the event group. In univariate COX regression models, sex, proteinuria, creatinine clearance, VLDL-cholesterol, ferritin, PTH, RBP and uMCP-1, uVEGF and tGFP-beta were significantly associated to the risk of the PO. However, after adjustments for creatinine clearance and proteinuria, only uRBP and uMCP-1, tGFP-beta and uVEGF remained significantly associated to PO. In a stepwise model, only creatinine clearance (HR 0.98, 95%CI 0.97 - 1.00, P=0.06) and uRBP (HR 1.13, 95%CI 1.07 - 1.20, P<0.0001) were left as independent predictors of PO in this population. KM curve for uRBP is shown in figure 1.  

Conclusions: Urinary RBP is an independent predictor of PO in albuminuric diabetic nephropathy. Its role as a risk biomarker should be further explored in larger studies of CKD patients.  

Funding: Government Support - Non-U.S.

PUB185

Association Between Urinary RBP and Renal and Cardiovascular Risk Factors in a Population with CKD: The Progrider Study  Maria Alice Muniz Domingos, 1 Alessandra C. Goulart, 2 Paulo Lotufo, 2 Isabel B. M. Benson, 3 Silvia M. Titan.  

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Background: Urinary RBP (uRBP) has been related to the risk of ESRD in general nephrologists and renal transplant. However, its role in CKD is not well established.  

Methods: Baseline clinical and laboratorial data on 454 participants of the Progrider Study was analyzed. uRBP was measured by an immunoenzymatic assay with monoclonal antibody. Descriptive data is presented according to tertiles of uRBP, and correlation coefficients were calculated. Several univariate and multivariate linear regression models were built. Lastly, binary regression models were built on the risk of presenting more advanced CKD (class IV-V or class II-III).  

Results: In the descriptive data, the tertiles of uRBP were significantly related to sex, diabetes, renal function, SBP, glycated hemoglobin, HDL, proteinuria, WHR, phosphorus, aciddosis, albumin, pulse-wave velocity (PWV), left atrium diameter (LAD), systolic and diastolic left ventricular diameters and ejection fraction. These results were confirmed by correlation. In the univariate regression models, diabetes, SBP, WHR, renal function, proteinuria, phosphorus, albumin, lipids, glycated hemoglobin, PWV and echocarography variables remained related to uRBP. However, after adjustments, only renal function, proteinuria, SBP, bicarbonate and LAD remained associated to uRBP.  

Table: Stepwise multivariate linear regression models on log of urinary RBP.  

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>Std. Error</th>
<th>95.0% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h proteinuria</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>eGFR-MGDR</td>
<td>0.02</td>
<td>0.03</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>2h proteinuria</td>
<td>0.09</td>
<td>0.03</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>eGFR-MGDR</td>
<td>0.02</td>
<td>0.03</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>SBP</td>
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<td>0.02</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>LAD</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0.07</td>
<td>0.03</td>
<td>0.03</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*MGDR = estimated glomerular filtration rate using MDRD; SBP = systolic blood pressure; LAD = left atrium diameter.  

Lastly, uRBP was associated to an increased risk of class IV-V CKD (OR 1.16, 95%CI 1.08 - 1.25, p=0.0001), even after adjustments for age, sex, diabetes, proteinuria and SBP.  

Funding: Government Support - Non-U.S.

PUB186

Treatment of Subclinical Hypothyroidism and the Progression of Chronic Kidney Disease  Padmavathi Mali, 1 Sudheer Muduganti.  

1 Internal Medicine, Marshfield Clinic, Marshfield, WI; 2 Nephrology, Univ of Wisconsin Hospitals and Clinics, Madison, WI.  

Background: Evidence suggests that treatment of subclinical hypothyroidism may slow the progression of chronic kidney disease (CKD) and delay or prevent development of end stage renal disease (ESRD). The goal of this study was to provide additional evidence regarding the same.  

Methods: Patients with subclinical hypothyroidism and CKD stages 3 or 4 were identified by retrospective chart review over a period of 6 years. Subjects were grouped based on L-thyroxine treatment. Subjects treated with L-thyroxine before first elevated thyroid stimulating hormone (TSH) were excluded. Index date was defined as the date of first L-thyroxine for treated patients. Index dates for untreated patients were assigned by correlation. In the univariate COX regression models, sex, proteinuria, creatinine clearance, VLDL-cholesterol, ferritin, PTH, RBP and uMCP-1, uVEGF and tGFP-beta were significantly associated to the risk of the PO. However, after adjustments for creatinine clearance and proteinuria, only uRBP and uMCP-1, tGFP-beta and uVEGF remained significantly associated to PO. In a stepwise model, only creatinine clearance (HR 0.98, 95%CI 0.97 - 1.00, P=0.06) and uRBP (HR 1.13, 95%CI 1.07 - 1.20, P<0.0001) were left as independent predictors of PO in this population. KM curve for uRBP is shown in figure 1.  

Conclusions: Urinary RBP is an independent predictor of PO in subclinical diabetic nephropathy. Its role as a biomarker of hard clinical end-points should be further explored.  

Funding: Government Support - Non-U.S.
Vitamin D Deficiency Is a Cause and a Result of Renal Dysfunction in Rheumatoid Arthritis
Suad Ma Hannawi, Issa AL Salmi.

**Background:** Asymptomatic kidney dysfunction is common in RA. Low vitamin D(VD) increases susceptibility to development of RAA disease activity. Sequential hydroxylation occurs in liver & kidney to form active,1,25-VD & patients with kidney failure are often resistant to VD & suffer from 25-hydroxylipidosis & renal osteodystrophy. In addition to its role in maintaining Ca&PO4 homeostasis, VD is important for maintaining maximum muscle strength & prevention of chronic diseases. Our objective is to evaluate eGFR & VD status in RA.

**Methods:** RA diagnosed by ACR 1998 criteria. 25-VD level obtained & GFR calculated by MDRD at Rheumatology clinic visit. Univariate linear regression analysis carried out to determine the relation between 25-VD & eGFR, other renal parameters & RA inflammatory markers.

**Results:** In an analysis of 52 RA(47.5M) with mean age 46±13 years(46±12, M±SD), 25.5-VD level was 40±29 nmoI/(NR=50-80) & GFR is 134±49 ml/min. Univariate linear regression showed a negative relationship between 25-VD level & eGFR(p=0.041,CI=0.23-0.01), micro-albuminuria(p=0.046,CI=0.63-0.01), CRP(p=0.011,CI=1.16-0.11), neutrophil count (p=0.033,CI=1.67-0.11) . A positive linear relationship between GFR & weight (p=0.03,CI=0.66,1.04), HAg(p=0.02, CI=11.19&BMP(p=0.009,CI=0.65-4.05), Ca(p=0.03, CI=7.24, 13.12 nmoI/l).

**Conclusions:** Negative relationship between eGFR & 25-VD indicating a higher 25-VD as failure to convert to active form as GFR decreases. Extra-renal formation of active VD requires a level of 25-VD >78 nmol/L & is necessary for maximal extra-renal production of 1,25VD. 1,25-VD is one of the most potent regulators of cellular growth & very effective modulator of the immune system. VD receptors are present in most cells & tissues including atheroma body including activated T & B lymphocytes. Surveillance for VD deficiency, should be part of follow-up as it may be linked to underlying kidney dysfunction in RA. On the other hand, reduced VD might worsen RA & hence, increase the possibility of renal deterioration. VD supplementation may be needed early in management for prevention of kidney dysfunction & to reduce RA severity.

**PUB199**

Associations Between the Progression of Chronic Kidney Disease and Patient Demographics
Danieque Xu, 1 Mark Stuart, 1 Barbara Cannon, 2 Chad Sowers, 3 John W. Larkin, 4 Sophia Rosen, 4 Carly R. Van Zandt, 4 Len A. Usvyat, 4 Yuedong Wang, 2 Danqing Xu, 2 Seble Kassaye, 1 Georgetown Univ Medical Center, Washington, DC; 2 Georgetown Howard Univ Center for Clinical & Translational Science, Washington, DC; 3 MedStar Health Research Inst, Hyattville, MD.

**Background:** It is well known if demographic factors are related to the progression of chronic kidney disease (CKD). Our study aimed to investigate whether age, sex, race, marital status and geography are associated with significant changes in kidney function determined by linear slopes of mean annual glomerular filtration rate (GFR).

**Methods:** We analyzed data from 90,240 CKD patients (Pts), who had significant declines in GFR, in the Fresenius Medical Care CKD Data Registry. Annual average decline in GFR was estimated on a per pt basis using linear regression with time as the predictor and GFR as the outcome variable. Univariate linear models were fitted for age groups (15-30, 31-40, 41-50, 51-60, 61-75, and 76+ years), sex (female vs. male), race (African American, Caucasian, or other), marital status (married, unmarried) and geography (10 divisions of zip codes); a multiple linear regression model was utilized to investigate associations in mean annual GFR slope and demographics.

**Results:** This analysis identifies significant associations between mean annual GFR slope & Pt demographics. CKD Pts age 15-30 years old were found to decline faster in GFR versus Pts of African American or Caucasian race (p<0.001). The geographical location of Pts by zip code was observed to be associated with differences in GFR slope (p<0.001). The marital status of Pts was not found to be related to differences in slopes of GFR (p=0.218).

**Conclusions:** This study identifies that during the progression of CKD, younger Pts tend to have faster declines in GFR, as compared to older Pts; males have slower declines in GFR, as compared to females; Pts with a race of “other” have slower declines in GFR, as compared to Pts of African American or Caucasian race; and declines in GFR are related to Pt geography.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

**PUB191**

Correlation of Increased Th17 to Treg Cell Ratio with Endoplasmic Reticulum Stress in Chronic Kidney Disease
On Yan.

**Kidney Dept, Second Affiliated Hospital of Xi an Jtolong Univ, Xi’an, Shaanxi Province.**

**Background:** The study aimed to investigate the relationship between the regulatory immune network and endoplasmic reticulum stress (ERS) in patients with different stages of chronic kidney disease (CKD).

**Methods:** A total of 91 patients diagnosed with CKD were divided into different groups according to the stage of disease. Routine blood and biochemical tests were performed in patients. The levels of cytokines in healthy controls were measured according to the protocol (n=20). The frequencies of T helper cell type 17 (Th17) and regulatory T (Treg) cells in the overall T cell population was measured by flow cytometric analysis. Levels of Th17 cell (IL-17) and Treg cell (IL-10) cytokines and the ERS markers

**Results:**
- **Th17 and Treg Cell Counts:**
  - Th17 cell count (IL-17): IL-17 levels were significantly increased in patients with CKD compared to healthy controls.
  - Treg cell count (IL-10): Treg cell counts were lower in patients with CKD compared to healthy controls.

**Conclusions:** The study showed a significant correlation between Th17/Treg cell ratio and endoplasmic reticulum stress (ERS) in patients with different stages of chronic kidney disease (CKD).
CHOP and GRP78 were measured by ELISA in serum samples collected from controls and patients of the different CKD groups. Correlations between each parameter and serum creatinine, an indicator of renal function, were analyzed by Spearman’s rank correlation and regression test. 

**Results:** CKD stage showed a positive correlation with serum creatinine level, and increased values of Th17 and Treg cells, respectively, increased the levels of ERS markers. There was no correlation with serum creatinine levels in patients with the non-dialysis group. 

**Conclusions:** We found that an increased Th17/Treg cell ratio and increased serum levels of ERS markers correlate with the progression of CKD. Our results indicate that the interplay between the immune network and management of ERS is closely associated with the pathogenesis of CKD. Although hemodialysis and peritoneal dialysis treatment manage chronic kidney conditions and prevent further deterioration of renal function, they have limited effects on improving the immune disorder and relieving ERS. 

**Funding:** Government Support - Non-U.S.

**PUB192**

Metabolic Phenotyping in Thin Basement Membrane Nephropathy

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**Background:** Thin basement membrane nephropathy (TBMN) is the commonest cause of familial microscopic hematuria in children and adults, usually associated with benign clinical presentations i.e. minimal proteinuria and normal renal function. In a Greek-Cypriot cohort of TBMN patients, 35% of patients were shown to develop ESRD by age 70-years while ~50% of patients over 50-years developed CKD of variable degree. 40% of TBMN patients in the different CKD groups, 35% of patients were shown to develop ESRD by age 70-years while ~50% of patients over 50-years developed CKD of variable degree. 40% of TBMN patients in the different CKD groups. Correlation analysis showed that serum levels of CHOP and GRP78 were independently and positively correlated with the ratio of Th17/Treg cells. 

**Conclusions:** We have found that an increased Th17/Treg cell ratio and increased serum levels of ERS markers correlate with the progression of CKD. Our results indicate that the interplay between the immune network and management of ERS is closely associated with the pathogenesis of CKD. Although hemodialysis and peritoneal dialysis treatment manage chronic kidney conditions and prevent further deterioration of renal function, they have limited effects on improving the immune disorder and relieving ERS.

**Funding:** Other NIH Support - Financial support: ExplDTP-FT0/1792/2013; PID/BD/105892/2014 (CGD)

**PUB195**

Association of hsCRP and Kidney Damage Indicators in 5667 Adults Receiving Physical Examination

Hao Zhang, Juan Mao, Bin Yi, Guo Xu, Wei Li. The Third Xiangya Hospital of Central South Univ.

**Background:** Chronic kidney disease and cardiovascular disease share many risk factors. Injury to the vascular endothelium, measured by elevated levels of serum high-sensitivity C-reactive protein (hsCRP), may play a role in kidney disease. Therefore we examined the association of hsCRP with kidney damage indicators (uACR,cgiFR) among 5667 participants receiving physical examination in the Third Xiangya Hospital.

**Methods:** We conducted a cross-sectional analysis of 5667 adults who received health physical examinations in 2014. Spearman correlation analysis, multiple linear regression and multivariable logistic regression models were used to analyze the correlation between hsCRP with uACR,cgiFR. ROC curves was drawing to explore the statistically significant intercept point of hsCRP in predicting the occurrence of albuminuria and declining in eGFR. Multivariable logistic regression analysis was used to calculate the ORs for albuminuria, declining in eGFR according to the quartile of hsCRP levels and other risk factors.

**Results:** Spearman correlation analysis showed that uACR was positively correlated with serum hsCRP (r=0.233,p=0.01). While eGFR showed negative correlation with hsCRP (r=-0.135,p<0.01). Multiple linear regression analysis showed that hsCRP was independently correlated with uACR (B=0.205,β=0.156, P<0.01). While hsCRP didn’t enter the multivariable linear regression model of eGFR. Multivariable logistic regression analysis showed that male, central obesity, hypertension, diabetes and high hsCRP levels were independent risk factors for albuminuria. Based on the ROC curve, the 0.5mg/L of hsCRP was the best numerical value to predict the risk of albuminuria. Multivariable logistic regression analysis showed that the risk of albuminuria significantly increased in male, central obesity, hypertension, diabetes or combined with high hsCRP levels.
Conclusions: HoCRP was correlated with kidney damage indicators, and hoCRP was an independent risk factor of albuminuria. The 0.85mL of CRP was the best numerical value to predict the risk of albuminuria. Male, central obesity, hypertension, diabetes accompanying high serum hoCRP levels are more likely to have albuminuria.

**PUB196**

**Serum Non-Protein Bound Homocysteine Levels Are Related with Chronic Kidney Disease Progression in HIV-Infected Patients**  
**Carlos Díaz, 1 Nelson Casimiro, 1 Nuno Coelho, 1 Ana R. Lemos, 1 Pedro Pereira Campos, 1 Ana Luisa Papolla, 1 Sara Maia, 2 Karina Soto, 2 Sofia Pereira. 1 Centro de Estudos de Doenças Crônicas, NOVA Medical School/Faculdade de Ciências Médicas (NMS/FCM), Univ Nova de Lisboa; 2Centro de Estatística e Aplicações da Univ de Lisboa (CEAUL), NOVA Medical School/Faculdade de Ciências Médicas, Univ Nova de Lisboa; 3Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal.

Background: Homocysteine (Hcys) is present in serum in two major forms: disulfide protein-bound (PB) (70-80%, mostly albumin) and non-protein bound (NPB) (20-30% combined thiol dimers + 1% thiol free). Only the NPB-fraction of Hcys is able to enter into the cell and accumulate in both kidney failure and HIV-infected patients, hyperhomocysteinemia is a common feature. The present study was aimed to explore the relationship of Hcys fraction and chronic kidney disease (CKD) progression in HIV-infected patients.

Methods: As part of an on-going prospective study of HIV+ population, a cross-sectional analysis was performed in a cohort of HIV-infected patients under combined antiretroviral therapy. Serum NPB-fraction of Hcys was quantified by HPLC with fluorescence detection. Glomerular filtration rate (eGFR) was estimated by CKD-EPI equation. The fractional excretion of phosphate (FePi) was also assessed.

Results: A total of 141 HIV-infected patients were included, 65% men, 73% non-Black, and 55 years old (IQR44-63). Median values of eGFR and FePi were 85 ml/min/1.73m² (66-95) and 19% (13-25) respectively. Univariable analysis was performed for eGFR, FePi and age. Only eGFR remained in the multivariable model (r=-0.332, p<0.0001).

Conclusions: Serum NPB-Hcys fraction was independently related with kidney dysfunction. The present data suggest that monitoring this sub-fraction of Hcys could be a tool for early kidney dysfunction detection in HIV-infected patients.

Funding: Other NIH Support - Financial support: EXPLOD/FTO/1792/2013; PD/BD/105892/2014 (CGD)

**PUB197**

**Diabetic Foot Ulcers and Acute Kidney Injury Are Associated with a Decline in Renal Function**  
**Huda Mahmoud, 1 Maarten W. Taal, 1 Frances Game, 2 Laura M. Proctor, 2 Heather Sherriff, 2 Christina Udani Peter, 2 Hana Baig, 2 Faaiza Asma, 2 Emma J. Lincoln, 2 Nicholas M. Selby. 1 1Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; 2Diabetes, Royal Derby Hospital, United Kingdom; 3Div of Medical Sciences and Graduate Entry Medicine, Univ of Nottingham, United Kingdom.

Background: There is an increased incidence of foot ulcers in patients with diabetes in the period immediately prior to the initiation of chronic dialysis; this may be explained if chronic foot ulcers accelerate a decline in renal function. We sought to examine this further by describing changes in renal function associated with hospitalisation for diabetic foot ulcer management.

Methods: All patients admitted to our centre during 2013 with ICD10 coding for diabetic; 18.6% m and 11.4% f were hypertensive; 2.2% m and 0.7% f had heart disease; 3.7% m and 6.8% f had dyslipidemia; 5.9% m and 3.0% f were obese; 18.6% m and 11.4% f were hyperglycemic; 2% m and 0.7% f had heart disease; 0% m and 3.5% f had hypothyroidism; 1.5% m and 1.2% f had CKD. Gender differences in SBP, DBP, overhydration, FTI, LITI and BMI are shown (Table).

Results: Waist circumference was higher than normal (i.e. >88 cm for f and >102 cm for m) in 38.4% (m) and 51.6% (f).

Conclusions: In a large sample of apparently healthy persons, males had more CVD and CKD risk factors than females, such as SBP, overhydration, and FTI. In association with other CVD risk factors, these increase morbidity and mortality. Evaluation of body composition is important in the general population for identification of CVD and CKD risk.

**PUB198**

**Gender – An Additional Cardiovascular and Chronic Kidney Disease Risk Factor in an Apparently Healthy Population**  
**Anttillo Di Benedetto, 1 Annalisa Ciotola, 1 Fabrizio Cerino, 1 Annamaria Colao, 2 Daniele Marcelli, 1 Bernard J. Canaud, 3 NephroCare Italy, Naples, Italy; 2Medicina Clinica e Chirurgia, Univ Federico II, Naples, Italy; 3Fresenius Medical Care, Bad Homburg, Germany.

Background: Cardiovascular disease (CVD) is on the rise, presenting significant social and economic burden. Early detection of CVD and chronic kidney disease (CKD) risk factors may prevent related complications. We report results of a CVD and CKD risk factor screening program in an apparently healthy population.

Methods: Participants and spectators of the “Prevention Races” held in 2013/2014 in Naples/Salerno (Italy) were screened for CVD and CKD risk factors by different specialists, including nephrologists. Parameters assessed were: systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, waist circumference, BMI, and body composition. Lean (LITI) and Fat (FTI) tissue indexes and overhydration were evaluated by Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany) using multi-frequency bioimpedance spectroscopy at 50 different frequencies.

Results: 701 subjects (38.5% m; 61.5% f) were evaluated. Mean age was 54.54 ± 15.6 (m) and 50.06 ± 15.2 (f). 3.7% m and 6.8% f had dyslipidemia; 5.9% m and 3.0% f were obese; 18.6% m and 11.4% f were hyperglycemic; 2% m and 0.7% f had heart disease; 0% m and 3.5% f had hypothyroidism; 1.5% m and 1.2% f had CKD. Gender differences in SBP, DBP, overhydration, FTI, LITI and BMI are shown (Table).

Conclusions: These data add strength to the hypothesis that an active diabetic foot ulcer may contribute to a decline in renal function, particularly when associated with an episode of AKI. This decline may also be under-estimated due to loss of muscle mass and subsequent over-estimation of eGFR in the post hospitalisation period. These results support additional prospective epidemiological and mechanistic studies to further explore the relationship between diabetic foot ulcers, AKI and CKD progression.

**PUB199**

**Potential Effect of Treatment of Metabolic Acidosis on Reducing the Risk of End Stage Renal Disease in Chronic Kidney Disease**  
**Solomon Daledern, Candace D. Grant, Vladimir Liberman, Alejandro Pepen Romero, Shayan Shirazian, Nobuyuki (Bill) Miyawaki, Joseph Mattana. Medicine, Winthrop-Univ Hospital, Mineola, NY.

Background: There is increasing evidence that low serum bicarbonate levels impact adversely on the progression of chronic kidney disease (CKD) to end stage renal disease (ESRD). It is plausible that treatment could result in a significant reduction in ESRD incidence though the potential impact in a CKD population and number needed to treat (NNT) are incompletely understood. We carried out the present study to estimate the potential impact of treatment of metabolic acidosis on the incidence of ESRD in a population of CKD patients.

Methods: We evaluated a cross section of 623 Stage 3 and 4 CKD patients at our institution. Their risk of developing ESRD at 2 and 5 years was estimated using the method of Tangri et al (JAMA 2011;305:1553-1559) which incorporates age, gender, eGFR, urine albumin to creatinine ratio, calcium, phosphorus, albumin, and bicarbonate. ESRD risk was then recalculated after assuming correction of all serum bicarbonate levels to 28 mEq/L.

Results: The population had a mean serum bicarbonate level of 24.3 mEq/L, with 79.5% having levels below 28 mEq/L. When ESRD risk was calculated following correction of low serum bicarbonate levels to 28 mEq/L, 16 fewer patients were predicted to develop ESRD at 2 years and 27 fewer at 5 years (relative risk reductions of 0.31 and 0.23 respectively). This effect was greatest for patients with CKD stage 4, accounting for 13 fewer ESRD patients predicted at 2 years and 20 fewer at 5 years. For the population as a whole, the NNT to prevent one case of progression from CKD to ESRD was 40 and 23 at 2 and 5 years respectively, while for those with CKD stage 4 the NNT was only 16 and 11.

Conclusions: Our findings suggest that in a population of CKD patients correction of metabolic acidosis could potentially result in a substantial reduction in the number who reach ESRD given the large numbers of patients with low serum bicarbonate levels. Prospective studies are needed to determine whether sodium bicarbonate therapy in populations of CKD patients could prevent many cases of ESRD.
The Impact of Vascular Disease on Risk of Development of End Stage Renal Disease in Patients with Chronic Kidney Disease

Vladimir Liberman, Sairah Sharif, Candace D. Grant, Alejandro Pepen Romero, Shanza Mujeeb, Nobuyuki (Bill) Miyawaki, Shayan Shirazian, Joseph Mattana. Medicine, Winthrop-Univ Hospital, Mineola, NY.

Background: Patients with chronic kidney disease (CKD) are not only at higher risk for development of end stage renal disease (ESRD) but also suffer disproportionately from vascular disease (VD), with associated high cardiovascular mortality. VD can plausibly impact progression of CKD and increase the risk of ESRD. However, VD also shortens survival, and may therefore reduce the risk of ESRD by increasing the competing risk of death. In the present study we evaluated the relationship between VD and the risk of development of ESRD in patients with CKD.

Methods: We carried out a retrospective cross sectional study of 623 CKD patients and recorded demographic, clinical and laboratory variables. We divided them in two groups based on presence or absence of VD and stratified them into different age groups. We estimated the risk of ESRD progression using the method of Tangri et al (JAMA 2011;305:1553-1559) and compared the risk levels between each group.

Results: Out of 623 patients with CKD 285 had VD (coronary artery disease and or peripheral vascular disease) documented in the record. Patients with VD were significantly older than patients with no VD (76 vs 70 years), had lower serum albumin (4.0 vs 4.1 g/dL) and lower eGFR (33.8 vs 36.4 ml/min/1.73 m²). We found that older patients with VD had significantly higher risk of developing ESRD. For the 70 to 79 year age group the 2 year risk was 2.45 vs 1.50 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03) in patients with and without VD. For patients ≥80 years the 2 year risk of developing ESRD was 2.18 vs 1.35 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03).

Conclusions: Our findings suggest that older patients with VD may be at increased risk for the development of ESRD despite the higher competing risk of death. This may be partly due to shared pathophysiological mechanisms between atherosclerosis and CKD progression. If validated in an ongoing prospective study this finding would suggest that VD should be partly due to shared pathophysiological mechanisms between atherosclerosis and CKD risk for the development of ESRD despite the higher competing risk of death. This may be partly due to shared pathophysiological mechanisms between atherosclerosis and CKD progression. If validated in an ongoing prospective study this finding would suggest that VD should be considered a risk factor predisposing to an increased risk of developing ESRD.

Management of Renal Artery Stenosis Post-ASTRAL and CORAL: Outcome of Patients with Radiologically Confirmed Atherosclerotic Renal Artery Stenosis Treated Conservatively

Moheen Mohammed Ahmed, Nicholas John Railton, Abdelgail Abdelrahman Ali, Anthony Chan. Renal Medicine, Mid Essex NHS Trust, Chelmsford, United Kingdom; Radiology, Mid Essex NHS Trust, Chelmsford, United Kingdom.

Background: Following the publications of ASTRAL and CORAL trials, the use of percutaneous renal artery angioplasty and stenting (PRAS) in the treatment of atherosclerotic renal artery stenosis (ARAS) has fallen dramatically. We report the outcomes of patients with radiologically confirmed diagnosis of ARAS who did not undergo PRAS and were managed medically.

Methods: Retrospective review of all patients undergoing CT/MRI angiography for suspected ARAS from 2008-2014 in Broomfield Hospital, Essex. Patients with more than >50% stenosis in a renal artery who were medically managed and did not undergo PRAS were included in analysis. They were followed for blood pressure control, renal events and mortality.

Results: 29 patients were identified, all Caucasians with a median age of 78 (49-85 years) of which 59% were males. None underwent PRAS. They were followed up from diagnosis till December 2014 or date of death with a mean period of 51 months. Systolic BP at end of study was <140 mmHg in 48%, 140-200 in 48% and >200 in 4% of patients. 69% were on 3 or more antihypertensives with 34% on renin angiotensin system blockade. 20 patients were CKD 3 and 8 with CKD 4 at baseline, with 3 patients progressing from CKD 3 to CKD 4. For the 70 to 79 year age group the 2 year risk of developing ESRD was 2.45 vs 1.50 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03) in patients with and without VD. For patients ≥80 years the 2 year risk of developing ESRD was 2.18 vs 1.35 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03). We found that older patients with VD had significantly higher risk of developing ESRD. For the 70 to 79 year age group the 2 year risk was 2.45 vs 1.50 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03) in patients with and without VD. For patients ≥80 years the 2 year risk of developing ESRD was 2.18 vs 1.35 (p=0.029) and 5 year risk was 6.80 vs 4.31 (p=0.03).

Conclusions: Our findings suggest that older patients with VD may be at increased risk for the development of ESRD despite the higher competing risk of death. This may be partly due to shared pathophysiological mechanisms between atherosclerosis and CKD progression.

From this study of patients with ARAS not indicated for PRAS, only a small number progressed to higher grades of CKD. Blood pressure control appeared adequate in a significant proportion of patients. This is in keeping with the findings from ASTRAL/CORAL trials and may be of significant benefit in terms of cost and reducing patient morbidity.

Clinical, Laboratory and Immunological Characteristics of Membranous Nephropathy in Kidney Transplantation Patients

Artur Quinteriano Silva, Juliana Busato Mansur, Marisa Petrucelli Doher, Gianna Mastroianni-kirsztajn. Dept of Nephrology, UNIFESP, Sao Paulo, Brazil.

Background: Membranous nephropathy (MN) is one of the more common causes of nephrotic syndrome in the adult population and may occur in the transplanted kidney. The goal of this study was to describe clinical and laboratory characteristics of membranous nephropathy in kidney transplantation patients. A total of 41 patients was studied. The first proteinuria was with 48 months and time at diagnosis was 57.9 months. Eleven patients had a secondary cause of MN. Independently of the immunosuppressive regimen occurred MN.

Methods: The characteristics evaluated were graft survival, time to onset of symptoms, patient profiles, treatment evolution , time from onset of symptoms to graft loss, immunosuppression used before and after the diagnosis of membranous nephropathy post transplant (MNPT), blockers of the renin-angiotensin-aldosterone system, proteinuria levels and time of biopsy x beginning of the onset of symptoms with disease progression.

Results: The mean age of the receptor was 49.4 years and 58.5% were males. The most common comorbidities were HBP (96.7%), dyslipidemia (22%), neoplasia (12.2%), diabetes (9.1%), SLE (7.3%) and hepatitis (7.3%). Induction therapy to prevent acute rejection during the early post transplant period was used in 9 (21.9%) patients (8 antithymocyte and 1 basiliximab) followed up by initial immunosuppression with PRED+CNI+AZA (56.1%) and PRED+CNI+MPA (34.1%). The end immunosuppression was Pred+CNI+AZA (29.2%), Pred+CNI+MPA (41.1%). Secondary MN causas had a more benign course (graft function) than the primary causes. Death censored graft survival in 10 years was 58.6%.

Conclusions: About 50% of grafts which develop de novo MGN eventually fail. This rather poor outcome may not represent the natural history of de novo MGN per se but rather the consequences of associated chronic rejection. Evidence is presented that many of the cases of so-called de novo MGN may be a complication of transplant glomerulopathy rather than being caused by mechanisms totally independent from rejection. The beneficial effects of immunosuppression agents have not been validated.
Factors Influencing Initiation and Choice of Immunosuppressive Therapy in Primary FSGS

Louis-Philippe Laurin,1* Bethany J. Foster,4* A. Gasim,2 Caroline J. Poulton,1* J. Charles Jennette,1,2 Ronald J. Falk,3 Patrick H. Nachman,1 1 Div of Nephrology, Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 2 Dept of Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 3 Div of Nephrology and Hypertension, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; 4 Div of Nephrology, McGill Univ Health Center, Montreal, QC, Canada.

Background: The treatment of patients with primary focal segmental glomerulosclerosis (FSGS) may include immunosuppressive therapy in patients not responding to conservative treatment or considered at high risk of progression to renal failure. We sought to determine the patient and disease characteristics associated with choice of therapy early in disease course.

Methods: Inception cohort of biopsy-proven patients with primary FSGS diagnosed between 1980 and 2012. Factors influencing choice of therapy were identified using multiple logistic regression; we report odds ratios (OR) with 95% confidence interval (CI).

Results: 458 patients met criteria; 183 on no immunosuppressives; 173 treated with glucocorticoids [GC] alone; 90 with calcineurin inhibitors [CNIs] ± GC; 12 with other immunomodulatory agents.

<table>
<thead>
<tr>
<th>No immunosuppression</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=183</td>
<td>N=275</td>
</tr>
<tr>
<td>Median age (yr)</td>
<td>48 (32-63)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>48.1</td>
</tr>
<tr>
<td>Black race (%)</td>
<td>45.1</td>
</tr>
<tr>
<td>Median eGFR (mL/min/1.73m²)</td>
<td>43.8 (27.2-69.9)</td>
</tr>
<tr>
<td>Median proteinuria (g/d)</td>
<td>3.8 (2.4-6.6)</td>
</tr>
</tbody>
</table>

Tip lesion variant (OR 3.00; 95% CI 1.23-7.32), eGFR <30 mL/min/1.73m² (OR 1.89; 95% CI 1.01-3.45) and hypouricemia (OR 2.22 per g/dl lower; 95% CI 1.59-3.13) were associated with a higher likelihood of any immunosuppressive treatment. Only tip lesion was associated with choice of GC alone vs. CNIs (OR 0.17; 95% CI 0.05-0.53).

Conclusions: Presence of tip lesion, preserved renal function at baseline and more severe hypouricemia are associated with immunosuppressive therapy in primary FSGS, but only tip variant appears to influence choice of GC alone over CNIs.

A Performance-Enhancing Drug and Its Depressing Effects

Waidi Bader, Internal Medicine, John Stroger Hospital of Cook County, Chicago, IL.

Background: Anabolic steroid use is a habit with a global 3.3% lifetime prevalence rate and is well known for its adverse effects on the renal, endocrine, hepatic, and hematologic systems. We bring a case of focal segmental glomerular sclerosis (FSGS) in a known user of anabolic steroids.

Methods: A previously healthy 28 year old male had presented to our hospital after being told he had kidney damage during a recent routine check up. On presentation, he complained of generalized weakness of one month’s duration; the social history was significant for use of Mutant Plexx, a bodybuilding supplement that contained an anabolic substance. On admission, his vital signs were normal for body mass of 189/109 and a heart rate of 82. His physical exam noted a muscular male with normal cardiovascular, respiratory, and abdominal exams. On labs the patient had a BUN of 59, a creatinine of 5.6, and a hemoglobin of 13.1. A urinalysis showed 1+ protein. Nephrology team was consulted for further workup. Urine microscopy was performed and showed no dysmorphic RBCs. Spot urine protein/creatinine ratio was 2.2 grams. Hb was negative; HbA1c, HbA1c, and hepatic C antibody were negative. Three days into his admission, the patient had an ultrasound guided kidney biopsy. On biopsy, half of the glomeruli had segmental scars, some with collapsing features. The interstitium was noted to have areas of fibrosis and the arteries showed mild sclerosis and arterioles with hyalinosis. The patient was diagnosed with collapsing FSGS secondary to anabolic steroid use; he was educated on control of hypertension and was advised to stop using anabolic steroids.

The patient was diagnosed with collapsing FSGS secondary to anabolic steroid use; he was educated on control of hypertension and was advised to stop using anabolic steroids.

Results: The pathophysiologic cause of FSGS secondary to anabolic steroids is thought to be due to several reports indicated that hyperuricemia might be independent risk factor for renal worsening, but about the effect of hyperuricemia itself upon progression of kidney diseases, especially in IgA nephropathy patients. Aim is to reveal effect of uric acid upon renal progression in IgA nephropathy patients.

Methods: This study is retrospective cohort study. Subjects were 923 IgA nephropathy patients who had not been treated uric acid lowering drugs, from 1001 IgA nephropathy patients who were diagnosed by renal biopsy, and over 15 years old in Osaka University Hospital, Osaka general medical center, Osaka Rosaki Hospital. Outcome was 1.5 times of serum creatinine. Exposure is uric acid at renal biopsy. Exploratory variables included sex, age, BMI, blood pressure, baseline eGFR, proteinuria, smoking status.

Results: Mean age was 34[23-46] years, proteinuria was 0.40[0.18-0.89] g/day. Uric acid was 6.5+1.3mg/dl in male patients, and 4.8+1.3mg/dl in female patients. Multivariate Poisson regression analysis revealed that uric acid was significant risk for progression of renal disease [Hazard Ratio 1.30[1.01-1.65] UA per 1mg/dl] in female patients along with proteinuria(g/day) [HR 1.27[1.08-1.47],p<0.001], Creatinine(mg/dl) [HR 2.73[1.84-3.74]]. In male patients, uric acid was not independent risk factor.

Conclusions: Hyperuricemia is independent risk for progression of kidney disease in female IgA nephropathy patients.

Long-term H.P. Acthar® Gel Treatment of Relapsing Idiopathic Membranous Glomerulopathy: A Case Study

Firas Marwani, Southwest Kidney Inst, Gilbert, AZ.

Background: Long-term treatment with H.P. Acthar® Gel (repository corticotropin injection, Questa Pharmaceuticals, Inc., Hayward, CA), an FDA- approved treatment for remission of proteinuria associated with nephrotic syndrome, was examined in a patient with biopsy-confirmed idiopathic membranous glomerulopathy (mM). Methods: A retrospective clinical record review examined Acthar Gel treatment over 2 years and 6 months in a patient with mM who received prescription-based treatment in a clinical practice. Outcomes included proteinuria level (mg/g), serum creatinine (SCr), serum albumin and treatment-related side effects. Complete remission was defined as proteinuria <500 mg/g. Partial remission was defined as ≥50% reduction in proteinuria from baseline and proteinuria 500-3500 mg/g.

Results: The 54-year-old Vietnamese patient with mM was treated over 7 years. At diagnosis, the patient’s proteinuria was 8000 mg/g, SCr 0.7 mg/dL, and serum albumin 2.1 g/dL. Initial treatment included prednisone, cyclophosphamide, mycophenolate mofetil, tacrolimus, and rituximab over 4.5 years. The patient showed partial complete remissions followed by relapse. At 1 Aktch Gel initiation, proteinuria was 3400 mg/g, SCr 0.6 mg/dL, and serum albumin 4.2 g/dL. The patient did not tolerate 80 U twice weekly but did tolerate 40 U twice weekly. At 4 months, she showed complete remission (proteinuria <150 mg/g). Dose reduction to 20 U twice weekly resulted in relapse 7 months later (proteinuria 2350 mg/g). Dose increase to 40 U twice weekly led to complete remission 4 months after that. Loss of insurance and cessation of Acthar Gel for 4 months led to relapse (proteinuria 7700 mg/g). Acthar Gel was re-started at 32 U twice weekly followed by 24 U twice weekly. Partial remission occurred 4 months later (proteinuria 2100 mg/g) with greater improvement at 10 months (proteinuria 800 mg/g). The patient has maintained partial remission (proteinuria 970 mg/g) 4 months post-therapy. Side effects over the course of Acthar Gel therapy included fatigue, myalgia, hyperglycemia, and weight gain.

Conclusions: Long-term treatment with H.P. Acthar Gel may help meet an important treatment need in patients with treatment-resistant and frequently-relapsing mM.

Outcome of Steroid Dependent (SDNS) and Frequent Relapsing Nephrotic Syndrome (FRNS) in Children

Isabel Robert, Shefali Vyas, Children’s Kidney Center, Saint Barnabas Medical Center, Livingston, NJ.

Background: Management of SDNS and FRNS in children can be frustrating. With the goal of minimizing steroid toxicity while achieving a sustained remission multiple regimens have been used with variable results. We reviewed our cases of SDNS/FRNS who had kidney biopsy (Rx) after failing MFM, for the past 12 yrs.

Methods: Charts of children with Rx due to SDNS or FRNS (after failure of MFM) were reviewed. Congenital and secondary causes of NS were excluded. Demographics, medications, side effects and response to therapy were studied. IV cytotoxin (CYP) was considered in non-FSGS cases with suspected non-adherence (400 mg/m2/dose monthly.

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

Underline represents presenting author.

934A
x 3). Others received tacrolimus (TAC) (0.1 mg/kg BID; trough up to 6 ng/mL). Rituximab (750 mg/m2 x 2 doses IV) was given if child became TAC dependent or resistant. Response to therapy was classified as: complete remission (CR), partial remission (PR), infrequent relapse (IR) (<2/yr), failure (F).

Results: 32 children had kidney biopsy (Bx) for primary SDND/FRNS. 14 females; 14.4 yrs, 6 AA, 6 other race. Age at presentation: 2-14 yrs (median = 3 yrs). Bx: 15 MCNS (4 diagnosed later with FSGS), 9 IgMN, 5 FSGS, 3 C1QN, 1 idiopathic immune mediated GN. All children had normal GFR at the time of the bx. 24 children received TAC; 21 CR (13 became TAC dependent with IR), 2 PR, 1 F. 15 received CYP: 6 CR, 9 F (5 diagnosed later with MCNS but bx had FSGS), 7 received rituximab: all had CR (5 IR). The rates of CR were significantly higher for TAC (87.5%) and rituximab (100%) as CYP had a failure rate 60% (p<0.01), including 4 cases with MCNS. However, those who had CR from CYP didn’t have further relapses. Rate of IR among those who initially had CR was similar between rituximab and TAC. Follow-up time: 2-12 yrs, including 6 discharged due to stable CR and 3 ESRD (all with FSGS). Side effects: 4 AKI with TAC (reversible), 2 respiratory distress/allergy in rituximab group (IV D/C). Late TAC resistance was seen in 3 patients.

Conclusions: Children with SDND/FRNS despite failure to respond to MMF had an excellent outcome. Some required sequential use of tacrolimus and rituximab after failure of CYP with a rate of CR/IR = 88% with minimal side effects.

Figure 1: Bar diagram showing frequency of glomerular diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus nephritis</td>
<td>12</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>26</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>26</td>
</tr>
<tr>
<td>FSGS</td>
<td>32</td>
</tr>
<tr>
<td>Membrane-proliferative</td>
<td>32</td>
</tr>
<tr>
<td>Stippled glomerulonephritis</td>
<td>32</td>
</tr>
</tbody>
</table>

Conclusions: This survey highlights the histopathological patterns of glomerular disease in southern Arizona. The data suggest regional and ethnic variations in glomerular disease that may suggest genetic or environmental influence in the pathogenesis of glomerular diseases.

PUB210

Use of Rituximab to Induce Remission in Frequently Relapsing Pediatric Nephrotic Patients Jason Peter Thomas, Teri L. Crumb, Alejandro Quiroga.

Results: Use of rituximab may be an effective agent for inducing remission for pediatric patients with frequently relapsing nephrotic syndrome (NS) with a reported 82% response rate. We evaluated the clinical response of pediatric nephrotic patients for induction of remission following one dose of rituximab.

Methods: This is an IRB approved, prospective clinical research trial. Informed consent was obtained from each family. Four pediatric patients with NS were enrolled prior to their clinically indicated rituximab infusion. Urine Protein/Creatinine ratio and albumin blood levels were collected.

Results: Urine Protein/Creatinine ratios obtained post infusion of rituximab decreased between 37-93% from pre infusion levels. 50% of patients identified had resolved edema noted on physical exam post infusion.

Conclusions: Rituximab may be an effective agent for inducing remission for pediatric patients with frequently relapsing nephrotic syndrome, warranting further investigation.

Funding: Private Foundation Support

PUB211


Results: There were 38 respondents to our survey: 12 rheumatologists and 26 nephrologists. Work setting: 81% academic, 19% non-academic. Management of abnormal UA findings in an asymptomatic lupus patient: 33% of rheumatologists versus 76% of nephrologists chose to biopsy. Induction regimen of ISN Class III LN: 79% of all providers chose MMF and 21% chose IV cyclophosphamide.

Choice of Induction Regimen in ISS Class III LN per Specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate Mofetil</td>
<td>18</td>
</tr>
<tr>
<td>IV Cyclophosphamide</td>
<td>30</td>
</tr>
</tbody>
</table>

Results: There were 38 respondents to our survey: 12 rheumatologists and 26 nephrologists. Work setting: 81% academic, 19% non-academic. Management of abnormal UA findings in an asymptomatic lupus patient: 33% of rheumatologists versus 76% of nephrologists chose to biopsy. Induction regimen of ISN Class III LN: 79% of all providers chose MMF and 21% chose IV cyclophosphamide.
Maintenance regimen of ISN Class III LN: all surveyed rheumatologists chose MMF as a sole maintenance agent compared to 32% of nephrologists who elected the addition of low-dose corticosteroids to MMF. Choice of an adjunctive agent in refractory ISN Class IV LN: 68% of providers chose rituximab, 14% chose tacrolimus, 5% chose CTLA-4 IgG, and 14% elected not to add any agents listed.

Conclusions: The results of this survey suggest a significant difference among rheumatologists and nephrologists on the decision to perform initial kidney biopsy and management of ISN Class III LN. The results suggest that perception of side effect profiles play an important role in the choice of therapeutics. This study emphasizes the need for a multi-disciplinary approach toward renal disease in lupus patients. We continue to recruit subjects to complete this survey.

**Results:** Two groups- group which had immune deposits (group 1) and group with no immune deposits (group 2). A1: 9.5% patients (2 FSNGS, 2 MjLN, 1 MPGN) with initial partial remission maintained partial remission during the follow-up period from a minimum of 2 months up to 19 months post-Achater Gel treatment of treatment-resistant NS in clinical practice.

**Methods:** Nine cases of patients with partial remission (500-550 mg/d proteinuria) (≥50% reduction from baseline), 1 patient with clinical response (≥30% reduction without meeting remission criteria), and 1 patient with clinical response and ongoing treatment following initial prescription-based Achater Gel treatment for NS, and who had follow-up clinical care, were included. Medical charts were reviewed for proteinuria levels. Follow-up ranged from 2 to 19 months.

**Results:** Biopsy-confirmed NS etiological diagnoses included focal segmental glomerulosclerosis (FSGS, n=3), membranous lupus nephritis (MLN, class V, n=2), membranoproliferative glomerulonephritis (MPGN, n=1), and diabetic nephropathy (DN, n=1). 5.5 patients (2 FSNGS, 2 MjLN, 1 MPGN) with initial partial remission maintained partial remission during the follow-up period from a minimum of 2 months up to 19 months post-Achater Gel treatment. The patient with MPGN and 1 with FSNGS showed increased proteinuria with relapse at 12 months and 19 months post-treatment, respectively. The patient with DN received ongoing Achater Gel treatment and maintained a proteinuria clinical response during the 11-month follow-up period. The patient reported fatigue but did not require cessation of Achater Gel treatment. The patient with FSNGS who showed an initial clinical response had further improved proteinuria at 2 months post-Achater Gel treatment and showed partial remission at 12 months post-therapy without intervening immunosuppressive medications.

**Conclusions:** These follow-up proteinuria outcomes in 7 patients treated with H.P. Achater Gel® for varied etiology NS suggest the proteinuria treatment response can be maintained long-term in some patients during treatment and beyond treatment cessation.

**Results:** A fifty year old male presented with increasing weight loss, night sweats and shortness of breath of 3 months duration. Additionally he noted some swelling of his lower limbs and frothy urine. He was extensively investigated with urinalysis, blood tests, imaging and histopathology till a novel diagnosis was made. The patient was found to have rheumatoid arthritis with subclinical inflammatory bowel disease (IBD) and was promptly started on infliximab 5 mg/kg IV, with subsequent improvement. The patient was maintained on infliximab for 18 months with complete remission and eventual remission of IBD. Unfortunately, he has been found to relapse when an attempt at a steroid wean was made and is thus maintained on a low dose of prednisone.

**Results:** We describe a novel pulmonary-renal syndrome and provide an approach to its investigation and management. This case opens the way for further research into eosinophilic pulmonary-renal syndromes.

**Results:** In this study, 25 patients with IMN with heavy proteinuria defined as ≥ 6 g/day were evaluated for the effect of a partial remission (50% reduction in baseline proteinuria to ≤ 3 g/day and ≥ 25% increase in baseline creatinine) and complete remission (creatinemia ≤ 0.5 g/d and serum creatinine ≤123 µmol/l) on renal outcomes compared with patients who did not attain a remission. Worse renal outcomes was defined as doubling of creatinine mg/dl and shortness of breath of 3 months duration. Additionally he noted some swelling of his lower limbs and frothy urine. He was extensively investigated with urinalysis, blood tests, imaging and histopathology till a novel diagnosis was made.

**Results:** These are patients who might benefit from plasmapheresis in addition to standard treatment.

**Results:** Eosinophilic pulmonary renal syndromes are well established and can be either vasculitic or infectious in aetiology. We describe a novel case of a patient whose presentation could not be fitted into either category.

**Results:** These are patients who might benefit from plasmapheresis in addition to standard treatment.
Comparison of Short- and Long-Term IgA Nephropathy Clinical Remission Rates Between Tonsillectomy plus Consecutive and Intermittent Steroid Pulse Therapies


Background: Tonsillectomy (Tx) plus steroid pulse therapy (TSP) is widely performed across Japan for clinical remission (CR) of IgA nephropathy (IgAN) but treatment protocol lacks consensus. We used both TSP (methylprednisolone 0.5 g/day iv for 3 days*) thrice/3 consecutive weeks (TSP-C) and intermittent pulse (* thrice/5 high-power field. Oral prednisolone (oPSL) between pulse therapies began at 0.5 mg/kg on alternate days. After the third pulse, oPSL was tapered over 1 and 0.5 years in TSP-C and TSP groups, respectively. Tx was performed before or during steroid therapies. We compared the effects of two regimens for CR.

Methods: This is a retrospective cohort study of 169 patients newly diagnosed with IgAN during January 2007 to December 2013 in our institute. We enrolled 90 patients we could follow-up after oPSL cessation and compared short- and long-term CR rates in both groups.

Results: Before treatments, there were no significant clinical [TSP-C (n = 57) vs. TPS-I (n = 33); age, 31.0 ± 11.2 vs. 34.0 ± 11.9 years; male/female, 17/40 vs. 12/21; eGFR, 82.2 ± 29.9 vs. 77.4 ± 28.7 ml/min; blood pressure, 121 ± 17.7/12 ± 12 vs. 120 ± 17.7/6 ± 13 mmHg; urinary protein, 0.41 (0.18, 1.19) vs. 0.79 (0.20, 1.08) g/lc; and positive occult blood, 91.2 vs. 90.9%) and histological grade stratification differences between the groups. At oPSEL cessation, short-term CR rates were equivalent between the groups (TSP-C vs. TPS-I: 68.4 vs. 61.0%). Long-term CR rates at 1, 2, and 3 years after oPSEL cessation were equivalent between the groups (TSP-C vs. TPS-I: 1 year, 64.1 (n = 39) vs. 59.1 (n = 22); 2 years, 64.0 (n = 25) vs. 80.0% (n = 10); 3 years, 73.7 (n = 19) vs. 66.7% (n = 6)). CR continuation rates by Kaplan–Meier method also revealed no significant differences between the groups.

Conclusions: Tx plus other consecutive or intermittent steroid pulse therapies may be equally beneficial for short- and long-term IgAN CR. IgAN patients can flexibly choose therapies.

Clinical Characteristics of Multiple Myeloma Patients Diagnosed by Nephrologist Byoung Geun Han, Jae seok Kim, Hyeon-Chool Park, Shinhdan Song, Jae Won Yang, Seung-Ok Choi. Internal Medicine, Yonsei Wonju College of Medicine, Wonju, Korea.

Background: Early diagnosis of multiple myeloma (MM) that is in early phase or has atypical presentation may be difficult. Even though MM is a hematologic malignancy, clinicians in different departments can make a diagnosis with a suspicious eye. In our department, we routinely performed protein electrophoresis in the patients with renal failure for the early diagnosis of MM.

Methods: We reviewed the medical records of 151 patients and examined the data of 117 patients diagnosed with MM in our hospital between January, 2003 and December, 2014. The patients were divided into three groups: group I presented to nephrologist prior to diagnosis (n=31), group II presented to hemato-oncologist directly (n=53), and group III presented to the other departments of our institute. The age, sex, initial symptoms, hematologic and biochemical parameters, and survival data were retrospectively analyzed.

Results: The main findings were anemia (n=30), renal failure (n=25), back pain (n=17), paraproteinemia (n=10), rib pain (n=7), mass (n=7), deficit (n=5), infection (n=4), bleeding (n=3), etc. Osteolytic bone lesion, survival rate, % of plasma cell in bone marrow study, Hb, platelet, CRP, serum albumin and calcium were not significantly different between three groups. 24 hours urine study (amount of proteinuria, plasma cell in bone marrow study, Hb, platelet, CRP, serum albumin and calcium were not significantly different between three groups. Complete remission defined as stable or improved renal function with final proteinuria of <500 mg/day; partial remission as stable or improved renal function with ≤50% reduction in proteinuria and final proteinuria 500 to 3500 mg/day. Failure to meet this criteria was classified as treatment failure.

Conclusions: In a substantial amount of newly diagnosed AA V patients, screening for AA V patients and to identify differences between hospital departments.

Methods: Retrospective case series of 7 Adults patients with nephrotic syndrome, treated with ACTH gel. Data was gathered by chart review, from the clinic EMR and paper based records. ACTH was given in the form of ACTHAR gel 80 USP units/ml SC twice a week for 6 months. Complete remission defined as stable or improved renal function with final proteinuria of <500 mg/day; partial remission as stable or improved renal function with ≤50% reduction in proteinuria and final proteinuria 500 to 3500 mg/day. Failure to meet this criteria was classified as treatment failure.

Results: Table 1. Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Diagnosis</th>
<th>eGFR (ml/ min/1.73 m²)</th>
<th>Proteinuria pre-ACTH (mg/g)</th>
<th>Proteinuria post-ACTH (mg/g)</th>
<th>Outcome</th>
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<tr>
<td>2</td>
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<td>M</td>
<td>Hispanic</td>
<td>MGN</td>
<td>Prednisone, MMF</td>
<td>104</td>
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<td>290</td>
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<tr>
<td>3</td>
<td>62</td>
<td>F</td>
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<td>Prednisone</td>
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<tr>
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<td>MGN</td>
<td>MMF</td>
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</tbody>
</table>

Conclusion: ACTH is a promising treatment for the nephrotic syndrome, associated with significant improvement in clinical status and relatively few adverse effects. We present our experience using natural ACTH gel for nephrotic syndrome in patients with diverse diagnosis.

Screening for Renal Involvement in Newly Diagnosed ANCA-Associated Vasculitis Patients in Clinical Practice – Differences Between Hospital Departments Eline Houben, Willem A. Bax, Bastiaan Van Dam, Valentina A. Sliker, Gideon Verhave, Fenneke C.P. Frerichs, Erik Lars Penne. Dept of Nephrology, MCA-Gemini Group, Alkmaar, Netherlands; Laboratory of Clinical Chemistry, Hematology and Immunology, MCA-Gemini Group, Alkmaar, Netherlands.

Background: Kidney involvement occurs in a majority of ANCA-associated vasculitis (AAV) patients and requires early and aggressive immunosuppressive therapy. The aim of the present study was to evaluate screening procedures for renal involvement in newly diagnosed AAV patients and to identify differences between hospital departments.

Methods: All AAV patients with a positive ANCA (PR3 and/or MPO) between 2005 and 2015 in a secondary care hospital in the Netherlands were included. Patient demographic data and the department making the diagnosis were recorded, as well as whether or not a complete screening for renal involvement had been made. The latter was defined as assessment of serum creatinine, analysis for erythrocyturia and proteinuria within two weeks before or after the diagnosis AAV.

Results: We included 110 newly diagnosed AAV patients (age 62±14 years; mean±SD; 63% male). 81 patients (68%) had renal involvement (defined as: rise in creatinine >30%, >10 RBC/hpf and/or proteinuria ≥500mg/24h). Complete screening was performed in 90 patients (82%), depending on department: Nephrology 100% (21 of 21), Internal Medicine 88% (29 of 33), Pulmonology 68% (15 of 22), Ear Nose Throat 62% (8 of 13), other departments 81% (17 of 21). Of the 20 patients with incomplete screening, assessment of proteinuria was missing in 100% (20 of 20), erythrocyturia in 55% (11 of 20) and serum creatinine in 5% (1 of 20). Serum creatinine was higher in patients with complete renal screening (72 versus 109 μmol/l, p=0.1). Screening was completed within 2 months (n=12), 4 years (n=3), or never (n=5). One patient was found to have erythrocyturia 6 weeks after the diagnosis, but had not been treated accordingly.

Conclusions: In a substantial amount of newly diagnosed AAV patients, screening for renal involvement was incomplete, especially in patients with a normal creatinine level outside the renal department. Incomplete screening may have led to suboptimal treatment in some patients.
Conclusions: ACTH gel is an effective therapy in patients with nephrotic syndrome, as significant reductions in proteinuria were seen in the majority of patients, it was not only patients with nephrotic syndrome who responded to treatment with ACTH but also patients who were nephrotic due to other diagnosis such as IgA nephropathy; this data highlights a need of further studies on natural ACTH gel in the treatment of nephrotic syndrome.

PUB220

Efficacy of Rituximab in Severe Lupus Nephritis in Children: A Case Series
Julien Hogan, Véronique Baudouin, Georges Deschenes. Pediatric Nephrology, Robert Debre Hospital, Paris, France.

Background: The association of cyclophosphamide or Mycophenolate Mofetil (MMF) with prednisolone is the treatment of reference of lupus nephritis(LN), both in adults and children but is associated with major side effects. Rituximab (RTX) failed to demonstrate an improvement of patient outcome when associate with MMF and prednisolone. However, recent data suggest that it might allow to spare prednisolone. We report our experience of the use of RTX in first LN flare in children.

Methods: We included patients treated by RTX for a first flare of LN class III to V between 2006 and 2014. Treatment associated methylprednisolone (500mg/m2) was followed by RTX (1000mg/1.73m2) at day one and 15 and MMF 1200mg/m2/day. Tapered down and withdrawal of prednisolone was left to each physician appreciation. Complete remission (CR) was defined as a proteinuria over creatinine ratio (Pu/creat) <50mg/mmol and normal serum creatinine and partial remission (PR) as a Pu/creat<300mg/mmol and no relapse within 1 year renal and 4 years disease free. Significant association of cFLCs with pathologic classification was observed.

Results: Between July 2003 and December 2013, 48 patients were diagnosed with biopsy-proven LN. Among 48 patients, 13 had IgA nephropathy, 19 had LN secondary to SLE, 12 had LN secondary to Henoch-Schönlein Purpura, and 4 had LN secondary to other immune diseases. CR was achieved in 11 (22.9%) patients, PR in 31 (64.6%) and 6 (12.5%) had failure to achieve remission and relapses were associated with poor renal outcomes in SLE patients.

Conclusions: Although the proportion of ANCA negative pNCGN was not high in our study population, poor 1-year renal survival was noted among these patients. We believe that particular caution should be exercised while treating ANCA negative pNCGN.

PUB222

Clinical Implication of Serum Free Light Chain in Patients with IgA Nephropathy
Woo Jin Jung,1 Sang Heon Song,1 Su Min Park,1 Jong Man Park,1 Il Young Kim,1 Dong Won Lee,1 Soo Bong Lee,1 Harin Rhee,1 Eun Young Seong,2 Ihm Soo Kwak,1 Min Jung Kim,1 Joo Hui Kim.1 1Dept of Internal Medicine, Pusan National Univ School of Medicine, Busan, Republic of Korea; 2Dept of Internal Medicine, Pusan National Univ School of Medicine, Busan, Yansung, Republic of Korea.

Background: Free light chains (FLCs) are produced in excess during immunoglobulin synthesis by plasma cells and other cells of the B-cell lineage. Recent studies demonstrated that elevated polyclonal FLCs are associated with increased mortality in chronic kidneys disease. But little is known about the clinical implication of FLCs in patients with IgA nephropathy which is caused by the overproduction of an aberrant form of IgA1 and the activation of B-cells responding to mucosal infection. Therefore, we investigated the relationship between the serum levels of combined FLCs (cFLCs) and prognostic markers in IgA nephropathy.

Methods: This retrospective study analyzed consecutive 42 patients with biopsy-proven IgA nephropathy without renal function impairment (estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m2) at the Pusan National University Hospital from January 2010 to December 2013. cFLCs was defined as a sum of kappa and lambda FLCs and clinical and laboratory data were collected by medical records reviewing.

Results: The mean (SD) age were 41.4 (14.9) years and the median (inter-quartile range) of cFLC and urinary protein-to-creatinine ratio (uPCR) were 40.5 (32.6 – 47.8) mg/L and 666.3 (364.8 – 1306), respectively. In correlation analyses, log-transformed cFLCs was positively related to age, serum cystatin C, IgG and log-transformed uPCR, and negatively associated with serum albumin and hemoglobin levels. In multivariate regression models, increased cFLCs was significantly associated with higher log-transformed uPCR (R2=0.042, p=0.045) after adjusting confounding factors. However, no significant association of FLCs with pathologic classification was observed.

Conclusions: We found a significantly higher level of cFLCs in patients with IgA nephropathy. Further longitudinal studies are needed to clarify the role of cFLCs as a prognostic maker in IgA nephropathy.

PUB223

Long Term Renal Outcomes in Lupus Nephritis in a Multi-Racial Asian Population: A Retrospective Study
Hui Zhan Tan, Cynthia Ciwei Lim, Jason Choo Chon Jun, Chan Choong Meng. Dept of Renal Medicine, Singapore General Hospital, Singapore, Singapore.

Background: Lupus nephritis causes significant morbidity with racial predilection affecting prognosis and treatment responses. We aimed to evaluate risk factors for progressive CKD in lupus nephritis (LN) in a multi-racial Southeast Asian population.

Methods: We retrospectively reviewed 113 consecutive patients with newly diagnosed biopsy-proven LN diagnosed between 10 May 2001 to 30 May 2009. Demographics, indices of renal function and disease activity, histopathologic data and pharmacotherapy were evaluated. Primary endpoint was progressive chronic kidney disease (CKD) defined by doubling of serum creatinine or end stage renal failure.

Results: Median age was 41.6 (IQR 29.2, 51.6) years, predominantly Chinese (76.1%) and female (81.4%). Twelve patients (10.6%) had Class I or II LN, 13 (11.5%) Class III LN, 62 (54.9%) Class IV LN and 25 (22.1%) isolated Class V LN. Eight patients (7.1%) had mixed proliferative and membranous LN. Most patients received either angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (100 patients, 88.5%). Induction immunosuppressants included glucocorticosteroids in 109 patients (96.5%), cyclophosphamide 26 (23.0%), mycophenolate mofetil or mycophenolate sodium 91 (81.5%), cyclosporine 9 (8.0%), and azathioprine 14 (12.4%). Median follow up was 79.0 (61.5, 104.0) months. One hundred and eight patients (95.6%) achieved remission, with complete remission in 89 patients. Among patients who achieved remission, 61 patients had disease relapse. Thirteen patients had progressive CKD at last clinic visit, with ESRD occurring in 5 patients at median 12.0 (1.0, 59.5) months from biopsy. Patients with progressive CKD tended to be non-Chinese (53.8% vs. 20.0%, p=0.01), with higher serum complement levels [median C3 0.66 (IQR 0.48, 0.87) vs. 0.38 (0.29, 0.60), p=0.04 and C4 0.17 (0.12, 0.22) vs. 0.06 (0.05, 0.12), p=0.004], fewer remissions (69.2% vs. 99.0%, p<0.001) and more relapses (100% vs. 52.5%, p=0.005).

Conclusions: In this multi-racial Asian cohort, race, higher serum complement levels, failure to achieve remission and relapses were associated with poor renal outcomes in lupus nephritis.
The Clinical Predictors for Outcome of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis Patients with Renal Involvement
Pr Lej, Guisen Li, Li Wang, Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: Primary anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is chronic multisystem autoimmune diseases and result in dysfunctions of multi-system. Renal involvement is the most common manifestation and is closely associated with the outcome of patients with vasculitis. We investigated the clinical determinants of the early mortality of patients with vasculitis-related renal injury followed up 2 years in a single west Chinese center to study the factors associated with patient outcome.

Methods: A total of 123 consecutive patients with AAV-related renal injury diagnosed in our center were recruited and in our study data were collected retrospectively. All the patients were followed up for 2 years after diagnosis. The predictive variables of values associated with mortality were analyzed.

Results: During 2 years follow up duration, 54 (43.9%) died, of whom 41 died within the first year after diagnosis. Compared with surviving patients, the deceased patients had higher BVAS scores and higher incidence of pulmonary hemorrhage. They also had higher serum creatinine and ESR, lower hemoglobin and complement C3, more patients accepting renal replacement therapy than surviving patients during hospitalization. Higher BVAS scores and serum creatinine–400μmol/L were the predictors of death in patients with AAV-related renal injury independently.

Conclusions: the incidence of early mortality in patients with AAV-related renal injury was higher. Prudent monitoring and therapy should be given to patients with active vasculitis and serious renal dysfunction to reduce adverse events.

Significance of Resistive Index in Renal Arterial Ultrasonography as a Clinical Parameter for Tubulo-Interstitial Nephropathy
Mimori Hatano,1 Kazumi Takayama,1,2 Taisuke Shimizu,1 Hiroaki Hara,1 Nobuyuki Onizawa,1 Koki Ogawa,1 Yuka Tanaka,1 Kunihiko Yasuda,1 Tomonari Ogawa,1 Akihiko Matsuda,1 Hajime Hasegawa.1 'Nephrology and Hypertension, Saitama Medical Center, Saitama Medical Univ, Kawagoe, Saitama, Japan; 2Ishikawa Kinokai Kawagoe Ekimae Clinic, Kawagoe, Saitama, Japan.

Background: Renal arterial ultrasonography (RA-US) has been principally applied to evaluate the stenosis of the renal artery and the indication of catheter intervention by the measurement of peak systolic velocity (PSV). Resistive index (RI) is calculated as PSV/EDV, where EDV indicates end-diastolic velocity, and is reported to be related to the renal function. In this study, we aimed to investigate the possible clinical benefit of RI for the assessment of tubulo-interstitial nephropathy (TIN).

Methods: We studied 51 patients (51:62.3 years old) who underwent RA-US and sufficient laboratory tests for the analysis in the past 10 years in our hospital. PSV and RI were measured at both main renal arteries (RA-measurement) and intra-renal arteries roughly corresponding to the interlobular arteries (IRA-measurement). NAG index (urine excretion ratio of N-acetylglucosaminidase (NAG) to creatinine) was used as a conventional clinical parameter for the assessment of TIN.

Results: Stratified analysis by median value of RI (0.69) showed significant difference in eGFR in the RA-measurement (43.4±4.7 vs 60.3±4.2), but not in the IAR-measurement. In contrast, the analysis showed significant difference in NAG index in IRA-measurement (median: 11.6 vs 5.4), but not in RA-measurement. When the patients showing NAG index ≥ 15, indicating advanced renal insufficiency, would be excluded from the analysis, NAG index significantly correlated with RI of IRA-measurement (R=0.50, p<0.05), but not RA-measurement. In addition, ROC analysis revealed that the cut-off value of RI to NAG index was 0.65.

Conclusions: In addition to the previous report showing the relevance of RI to the histological severity, the present study demonstrated the correlation of RI with the conventional parameter of TIN, NAG index. Particularly, for the assessment of TIN, RI value measured at intra-renal artery would be more beneficial.

Recovery of Renal Function with Eculizumab in a Girl with Dense Deposit Disease and Normal Soluble C5b-9 Levels
Marianne Linhof,1 Arjan Diepstra,2 Marc Maj Seelen,1 Coen A. Stegeman,1 Valentina Grachi.1 'Pediatrics, UMCG, Groningen, Netherlands; 2Pathology, UMCG, Netherlands; 3Nephrology, UMCG, Netherlands.

Background: Dense Deposit Disease (DDD) is a rare glomerulopathy characterized by electron-dense deposits in the glomerular basement membrane (GBM) and glomerular complement deposition. 50% of patients progress to ESRD and have recurrences after kidney transplantation. Dysregulation of the alternative complement pathway plays a key role in the pathogenesis. Increased soluble C5b-9 in blood is considered to predict response to eculizumab, an anti-C5 monoclonal antibody.

Methods: We report the case of a previously healthy 15-year-old girl who presented with acute kidney injury, hypertension, nephrotic syndrome (10.8 gr protein /24 hours) and microscopic hematuria.

Results: Biochemical (C3 &4, C5b-9, factors H & I, C3 nephritic factor and anti-FH) and genetic workup of the complement system (CFI, CFB, C3 and MCP) showed normal results, except for a slightly increased C3d and a risk allele in the CFH gene. Renal biopsy showed cellular crescents and electron-dense deposits in the GBM. Glomerular C3 and C5b-9 immunofluorescence staining was positive. Despite escalating therapy, including methylprednisolone pulses followed by oral prednisolone, cyclophosphamide and plasma exchange (PE), the renal function further deteriorated and hemodialysis was started. Eculizumab was administered. This led to a rapid improvement of renal function (discontinuation of dialysis and increase of endogenous creatinine clearance from 11 to 53 ml/min/1.73m2). Three months later the girl is in a good clinical condition but proteinuria is still in the nephrotic range (3.6 gr/24 hours). Treatment with eculizumab is ongoing. Up to now no side effects have been observed.
Conclusions: Manifestations of IgAN vary widely. The mainstay of therapy consists of supportive measures, which the majority of our cohort received. Immunosuppressive regimens are reserved for a select group, and in our cohort both mycophenolate and steroid based regimens yielded a reduction in proteinuria.

Effect of Rituximab on Immunoglobulin Levels and Infection Risk in ANCA Associated Vasculitis

Shivani Shah,1 M-Hatifur Rahman,2 Duvuru Geetha.1
1Div of Nephrology, Dept of Medicine, Johns Hopkins Hospital, Baltimore, MD; 2Bloomberg School of Public Health, Johns Hopkins Univ, Baltimore, MD.

Background: Rituximab (RTX), a B cell depleting anti-CD20 monoclonal antibody, is approved for treatment of ANCA associated vasculitis (AAV). Low immunoglobulin (Ig) levels are a consequence of RTX treatment. The association between the degree of Ig deficiency and infection risk is unclear in AAV patients.

Methods: AAV patients treated with RTX in a single center with available serum Ig measurements were included. The rates and types of infection after RTX administration were correlated with Ig level using correlation matrix and logistic regression analysis.

Results: Our cohort of 27 patients had a median age of 68 years, eight males, 15 GPA patients, and 17 with a new diagnosis of AAV. Twenty five received four doses of RTX 375 mg/m² weekly and two received RTX 1000 mg biweekly for two doses. Nine received concomitant cyclophosphamide. Twenty three patients had low serum IgG levels (<751 mg/dL) greater than one month following RTX treatment. Ten out of these 23 developed infections over the median follow up time of 338 days. Pneumonia was the most common infection. The odds of having an infection with IgG level ≤500 mg/dL is 3 times higher than with IgG level between 501-750 mg/dL, though p = 0.26. There is a significant association between infection and IgM level ≤20 mg/dL (p = 0.047).

Conclusions: Severely low Ig levels due to RTX therapy may increase the risk of infection in AAV patients, and these patients may benefit from IVIG therapy. Further investigation is warranted given our study is limited by small sample size, concomitant cyclophosphamide use, and variable timing of Ig measurement.

Lipoprotein Glomerulopathy

Hostensia M. Beng, Basema I. Dibas, Hsiao Ling Lai, Guillermo Hidalgo. Pediatrics, ECU, Greenville, NC.

Background: Lipoprotein glomerulopathy has been associated with mutations in the Apolipoprotein E (APOE) gene. The average age of reported cases is 32 years and the youngest patient described to date is 4 yrs old. Here we present the first case of a 3 years old AA male with right hemihypertrophy, malignant hypertension, severe proteinuria & lipoprotein glomerulopathy, with a heterozygous mutation on APOE gene.

Methods: 3 year old African American male presented to pediatrician complaining of hemihypertrophy, short stature, polydipsia & hypertension. Physical examination remarkable for right leg soft tissue hemihypertrophy. Echocardiogram revealed left ventricular hypertrophy likely secondary to chronic hypertension. Hypertension and proteinuria persisted despite adequate treatment. Renal US showed persistent echogenic kidneys. Kidney biopsy showed Lipid vacuolization of podocytes, endothelial cells, tubular epithelial cells, and glomerular capillary lumens. Labs & imaging studies AFP and abdominal US have been normal with exception of proteinuria and increased lipid profile. Patient currently on a trial treatment with fibrin acid and dietary modification.

Results: The case is the first in all monocyte subpopulations: classical (CD14++CD16-CCR2highCXCR1-), intermediate type 1 (CD14++CD16+CCR2highCXCR1-) and intermediate type 2 (CD14+CD16+CCR2lowCXCR1high). This was the case in all monocyte subpopulations: classical (CD14++CD16-CCR2highCXCR1-), intermediate type 1 (CD14++CD16+CCR2highCXCR1-) and intermediate type 2 (CD14+CD16+CCR2lowCXCR1high).

Conclusions: Toll like receptors seem to be down regulated in monocytes of patients with primary untreated glomerulonephritis during the active phase. The pathophysiological significance of these findings is unclear and remains to be elucidated.

Proliferative Lupus Nephritis (LN) – 60 Month Evolution of an Argentinian Cohort

Gabriel Pedro Alvarez, Marcelo Alejandro De Rosa, Luis Alberto Tobasc.1 Hospital San Martin. La Plata, Buenos Aires; 2Univ of Buenos Aires, Argentina.

Background: Remission of proteinuria predicts good evolution in many glomerular diseases; we describe the behavior of the proteinuria, renal function and flare up in a group of patients with proliferative LN in a 60 month period.
Methods: Data from 55 patients were obtained. Proteinuria and Creatinine were shown at 0 time of the biopsy, 6 and 60 months; renal biopsies were classified using ISN-RPS 2003. All patients received an induction with at least 6 gr. of cyclophosphamide plus prednisone and a maintenance treatment with sodium mycophenolate 1440 mg/d and low doses of prednisone for at least 5 years. Flares was considered in case of 50% proteinuria increase or an acute urinary sediment.

Results: Results are in table

<table>
<thead>
<tr>
<th>N</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>31.2 range 18-64</td>
</tr>
<tr>
<td>Sex</td>
<td>52/3</td>
</tr>
<tr>
<td>Bx class II</td>
<td>1 2</td>
</tr>
<tr>
<td>Bx class III</td>
<td>7 12</td>
</tr>
<tr>
<td>Bx class IV</td>
<td>40 72</td>
</tr>
<tr>
<td>Bx class V</td>
<td>1 2</td>
</tr>
<tr>
<td>Bx class V+ III/IV</td>
<td>7 12</td>
</tr>
<tr>
<td>Proteinuria gr/d (median)</td>
<td>3.04 (0.2-28) 1.2 (0.1-16.6) 0.2 (0.1-3.8) &lt; 0.05</td>
</tr>
<tr>
<td>Creatinine mg/dl (median)</td>
<td>0.94 (0.54-2.4) 0.9 (0.6-6.2) 0.91 (0.55-7.22) NS</td>
</tr>
<tr>
<td>Flares up</td>
<td>17/32</td>
</tr>
<tr>
<td>Treatment months</td>
<td>36 (30-60)</td>
</tr>
</tbody>
</table>

Conclusions: We observed a sustained decline in proteinuria and a preservation of renal function in most of patients; Treatment was well tolerated and flares up were in a high number of patients.

Treatment

PUB232

A Case Study Comparing Cyclophosphamide plus Methylprednisolone versus Cyclophosphamide Alone in Idiopathic Membranous Nephropathy

Basel Jaafar Alhayki, Dept of Nephrology and Renal Transplant, Salamania Medical Complex, Manama, Bahrain.

Background: In the treatment of high risk idiopathic membranous nephropathy the modified Ponticelli protocol with the use of alternative month Cyclophosphamide and steroids is the most used treatment protocol. The scientiffic bases for the use of intermittent alternating month Cyclophosphamide and Methylprednisolone versus Cyclophosphamide alone in the treatment protocol is not well established and in many studies showed that steroid alone has limited role in the treatment of idiopathic membranous nephropathy. Weather this intermittent use of Cyclophosphamide and Methylprednisolone lead to a fluctuating response to therapy and prolong the recovery or not need to be investigated.

Methods: This is a case study of a 26 years old male with idiopathic membranous nephropathy and a positive AntiPLA2R antibody who needed to be started on Modified Ponticelli protocol with alternative month Cyclophosphamide and Methylprednisolone for his persistent massive Proteinuria of 16 gram per day and who failed cyclosporine in the past. Initially the patient was given the six month the modified Ponticelli protocol but he failed to reach a complete or a partial remission with persistent Proteinuria of more than 6 gram per day and high Anti-PLA2R antibody titer and later he was given an extra three months of Cyclophosphamide alone.

Results: There was a fluctuating antibody titer during the course of therapy with increase Anti-PLA2R antibody titer at the end of the Methylprednisolone month and reduce level after the months of Cyclophosphamide use. After the start of the extra three months of continues Cyclophosphamide the anti-PLA2R antibody titer was reducing in each month and at the end of the extra three months it disappeared completely with a remission of the Proteinuria.

Conclusions: This case shows that the use of Cyclophosphamide is more effective in the treatment of idiopathic membranous nephropathy than Methylprednisolone and it might provide a better control of the disease activity. Future study to evaluate this with the use of novel biomarker like Anti-PLA2 R antibody is recommended.

PUB233

Plasma Cytokines and Chemokines Profile in Patients with Systemic Lupus Erythematosus: Its Potential Use as Biomarkers of Kidney Damage

Gustavo Aroca Martinez, D Lisandro Pacheco, E Elkin Navarro Navarro, Y Irisy Diaz, T Henry J. Gonzalez torres, T Gloria Garavito, T Eduardo Egea bermejo, T Eduardo I. Navarro, T Lisneth Almendares, T Antonio De Jesus Iglesias-Gamarr, T Medicina, Univ Simon Bolivar, Carranquilla, Atlantico, Colombia; T Nephrology, Clínica de la Costa, Barranquilla, Atlantico, Colombia; T Medicine, Univ del Norte, Barranquilla, Atlantico, Colombia; T Medicine, Univ Nacional de Colombia, Bogotá DC, Cundinamarca, Colombia.

Background: Systemic lupus erythematosus is an autoimmune disease in which the innate and adaptive response plays a significant role, mainly mediated by cytokines. Lupus nephritis-LN is the most severe complication associated with SLE. Objective: To identify differential expression of cytokines profiles and circulating chemokines in plasma of SLE patients with different degrees of Caribbean region.

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

Underline represents presenting author.

941A
Acute Tubulo-Interstitial Nephritis (ATIN): Predicting Long Term Outcomes

**Acute Tubulo-Interstitial Nephritis (ATIN): Predicting Long Term Outcomes** Victoria C. Robins,1 Aravind Cherukuri,2 Padmini Prasad,1 Richard J. Baker.1 1SJHH; Pittsburgh.

**Background:** ATIN is a relatively common potentially reversible cause of acute kidney injury. It has become clear over the last 2 decades that the disease is not always reversible, particularly in the elderly. We present a large contemporary single centre retrospective series concentrating on factors that predict poor outcomes.

**Methods:** 62 cases retrospectively diagnosed histologically via pathology records as primarily ATIN were included. An experienced histopathologist, blinded to outcomes, graded biopsies according to the presence, absence and degree of 8 different parameters: Interstitial inflammation, tubulatr atrophy, eosinophilia, plasma cell infiltration, chronic vascular lesions, hyalinosis, granulomas + oedema. Patients were classified as a poor outcome if eGFR (4 variable MDRD) after 12 months was less than 30 ml/min/1.73 m² or they died.

**Results:** 62 patients with biopsy proven ATIN were identified. 15 had a poor outcome. Baseline demographics are presented in Table 1.

<table>
<thead>
<tr>
<th>Good (eGFR&lt;30)</th>
<th>Poor (eGFR&lt;30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>age</td>
<td>56.2±16.8</td>
<td>56.6±19</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>19/28</td>
<td>6/9</td>
</tr>
<tr>
<td>Creatinine-diagnosis</td>
<td>366±/245</td>
<td>545±/334</td>
</tr>
<tr>
<td>Creatinine-6 months</td>
<td>130±/40</td>
<td>220±/90</td>
</tr>
<tr>
<td>PCR-diagnosis</td>
<td>103±/72</td>
<td>126±/90</td>
</tr>
<tr>
<td>Treatment: prednisolone</td>
<td>87%</td>
<td>80%</td>
</tr>
<tr>
<td>Serum eosinophil count</td>
<td>0.4±/1.0</td>
<td>0.4±/0.5</td>
</tr>
<tr>
<td>Biopsy degree of interstitial inflammation</td>
<td>2.1±/0.8</td>
<td>2.1±/0.7</td>
</tr>
<tr>
<td>tubular atrophy</td>
<td>1.2±/0.4</td>
<td>1.3±/0.6</td>
</tr>
<tr>
<td>eosinophilia</td>
<td>0.9±/0.8</td>
<td>1.3±/1.0</td>
</tr>
<tr>
<td>plasma cell infiltration</td>
<td>2.0±/0.9</td>
<td>2.0±/0.8</td>
</tr>
<tr>
<td>chronic vascular lesions</td>
<td>1.3±/0.5</td>
<td>1.6±/0.5</td>
</tr>
<tr>
<td>hyalinosis</td>
<td>0.6±/0.7</td>
<td>0.6±/0.7</td>
</tr>
<tr>
<td>granulomas</td>
<td>0.3±/0.6</td>
<td>0.9±/1.1</td>
</tr>
<tr>
<td>oedema</td>
<td>0.3±/0.5</td>
<td>0.5±/0.8</td>
</tr>
</tbody>
</table>

Aetiology was difficult to definitively ascertain but consisted of drug induced, infectious, sarcoid or jologens. Parameters significantly associated with poor outcomes include higher creatinine at presentation & 6 months, presence of granulomas and chronic vascular lesions on biopsy at diagnosis. The effect of steroid treatment was difficult to assess since most patients were treated at the outset.

**Conclusions:** ATIN usually carries a good prognosis but some patients experience poor outcomes. Poor renal function at diagnosis and the presence of granulomas and chronic vascular lesions are predictive of poorer outcomes.

Cotreatment of Olmesartan and Caterpillar Fungus Attenuate Albuminuria in Patients with Glomerulonephritis

**Cotreatment of Olmesartan and Caterpillar Fungus Attenuate Albuminuria in Patients with Glomerulonephritis** Hua Zhou, Ye Zhang, Ya Li, Hairong Tang, Congqong Jiao, Lining Wang. Nephrology Dept, 1st Hospital of China Medical Univ, Shenyang, China.

**Background:** Angiotensin II receptor blockers (ARBs) were demonstrated to reduce proteinuria since a decade ago. However, proteinuria still remains as the top of clinical symptoms in glomerulonephritis (GN). We aim to investigate the effect of cotreatment with olmesartan (Olm), an ARB and caterpillar fungus capsule (CF) on proteinuria.

**Methods:** 491 patients with GN were retrospectively studied. GN was diagnosed by positive ANCA with high titer in at least one specific serum sample from each patient. ANCA subtypes were determined in each patient. Descriptive and analytical epidemiological studies may improve our understanding of environmental influences on the disease. Seasonal variations in AAV have been previously described, mainly related to Wegener’s disease, showing an increased number of cases during the winter months. It has been hypothesized the infection could be the underlying factor for these observations. Our goal is to study seasonal variations of AAV diagnosed in the city of Barcelona.

**Results:** Of the 209 patients, 160 (76.5%) were MPO-positive, 28 (13.3%) were PR3 positive and 21 (10%) were ANCA negative. Regarding the onset of symptoms, we found a greater number of cases in the months of January, February and March, compared with the rest of the year. This data correlates positively with the higher incidence of symptoms in Barcelona between 2009 and 2013.

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

**PUB235**

**PUB237**

**PUB238**

Seasonal Variations of Renal ANCA Associated Vasculitis

**Seasonal Variations of Renal ANCA Associated Vasculitis** Juliana Bordignon Drabig, Joan Torres, Xavier Fulladosa. Nefrologia, Hospital Univ de Bellvitge, Barcelona, Spain.

**Background:** Filling the gaps in the genetic research of etiological factors related with ANCA associated vasculitis (AAV) is a major challenge in the current investigation. Descriptive and analytical epidemiological studies may improve our understanding of environmental influences on the disease. Seasonal variations in AAV have been previously described, mainly related to Wegener’s disease, showing an increased number of cases during the winter months. It has been hypothesized the infection could be the underlying factor for these observations. Our goal is to study seasonal variations of AAV diagnosed in the city of Barcelona.

**Methods:** Our study included 209 AAV patients diagnosed between 2001 and 2013 in 5 different University Hospitals of Barcelona. We analyzed their medical records, including the date of diagnosis and the approximate date of the first symptoms in 194 patients. We have also analyzed data related to ANCA subtypes in each patient. Descriptive and analytical epidemiological studies may improve our understanding of environmental influences on the disease. Seasonal variations in AAV have been previously described, mainly related to Wegener’s disease, showing an increased number of cases during the winter months. It has been hypothesized the infection could be the underlying factor for these observations. Our goal is to study seasonal variations of AAV diagnosed in the city of Barcelona.

**Results:** Of the 209 patients, 160 (76.5%) were MPO-positive, 28 (13.3%) were PR3 positive and 21 (10%) were ANCA negative. Regarding the onset of symptoms, we found a greater number of cases in the months of January, February and March, compared with the rest of the year. This data correlates positively with the higher incidence of symptoms in Barcelona between 2009 and 2013.
Considering the date of diagnosis we found a greater number of cases in two periods of the year; the months of May, June and July, and the months of October, November and December.

Conclusions: In our population, predominantly ANCA-MPO-positive related vasculitis, we found a higher incidence of the disease in the winter months, being diagnosed more frequently in May, June and July or October, November and December. One potential environmental factor, influenza disease, may explain this finding.

PUB239

Background: This meta-analysis was performed to investigate the efficacy and safety of mycophenolate mofetil (MMF) in treating idiopathic nephrotic syndrome.

Methods: We searched MEDLINE, EMBASE, the Cochrane Library database, the Database for Chinese Technical Periodicals, Wanfang, Chinese National Knowledge Infrastructure and the Chinese Database of Biology and Medicine for randomized controlled trials compared MMF with the other immunosuppressive agents for the treatment of idiopathic nephrotic syndrome. Weighted mean difference (WMD) and summary estimates of relative risk (RR) reductions with 95% CIs were calculated.

Results: We identified 36 trials that included 2007 patients, mainly on membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and refractory nephrotic syndrome without clearly pathological diagnosis (RNS). Overall, MMF therapy showed lower level of serum albumin and higher rates of use of diuretics, renin-aldosterone system (RAS) inhibitors, and NSAIDs. Logistic-regression analysis showed that use of these drugs before presentation at our institution could predict the development of AKI (odds ratio, 2.8, 95% CI, 2.2 to 3.2). Furthermore, use of these drugs could determine the time to remission (Hazard ratio, 2.4, 95% CI, 1.8 to 3.0), as well as the initial serum creatinine. All cases were initially treated with steroid, and there was no difference in the time to remission between oral and parenteral administration of steroid.

Conclusions: There is a high incidence of AKI in adult-onset MCD. The use of several drugs such as diuretics could influence the onset of AKI and clinical course of MCD.

PUB241
Expression of HLA-G Molecule in Crescentic Glomerulonephritis and Its Clinical Significance  Guoqian Li, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, Sichuan, China.

Background: In recent years, human leukocyte antigen-G (HLA-G) was found to be an important immune-regulatory molecular. Our purpose of this study is to assay the concentrations of serum soluble HLA-G (sHLA-G) in patients with CGN and to analyze its clinical significance.

Methods: 48 patients with CGN from 2009 to 2014 were involved in this study. The clinical data were collected, include demographic characteristics, laboratory parameters, pathological examinations, prognostic information and immunosuppressive therapy. Analyze if oliguria or anuria, serum creatinine levels, the crescent formation ratio and therapy would affect the prognosis of patients.22 patients with CGN, 15 patients with MCD, and 30 healthy adults in control group were enrolled with serum levels of sHLA-G measured by ELISA. The relationship between the clinical or pathological features and sHLA-G was studied and the value of the HLA-G in crescentic glomerulonephritis was analyzed.

Results: 3-years kidney survival rate was only 38% with one case of death. Cox regression analysis showed higher serum creatinine was associated with the patients with a poor prognosis(HR=4.04,95%CI:1.584-10.544, P=0.004). Serum level of sHLA-G in CGN was significantly higher than in healthy control(2198.8± 1924.17pg/ml vs.1311.86 ± 448.84pg/ml, P=0.046), while higher than in MCD, (2198.8± 1924.17 pg/ml vs. 1181.33 ± 320.10 pg/ml, P=0.023). Kaplan Meier survival analysis showed elevated levels of HLA-G was associated with poorer patients.

Conclusions: High serum creatinine level(>5mg/dl) at admission is an independent risk factor for the development to be ESRD. sHLA-G was significantly elevated in the serum of patients with CGN, and the level of sHLA-G had relationship with the prognosis of the patients with CGN. sHLA-G may be used as a new biomarker in CGN with clinical value in the early diagnosis and prognosis.

PUB242
A Treatment of Nutcracker Syndrome Leads to a Resolution of Unexplained Proteinuria  Badamkhund Batarkhuu, Raymond Raut, Winston Y. Shih, Panupong Lisawat. Nephrology and Hypertension, WCHN Danbury Hospital, Danbury, CT.

Background: The nutcracker syndrome is rare and can be a cause of unexplained proteinuria. We report a case of nutcracker syndrome related proteinuria and resolution of the proteinuria is observed after the enrapment was surgically corrected.

Methods: This is a 22-year-old male with a history of unexplained proteinuria since he was 17 years old. He has moved to a new location and presented to our clinic with proteinuria. The patient’s initial work up at an outside hospital revealed 1.4g proteinuria per 24 hours. A left kidney biopsy showed mesangial hypercellularity and preserved foot processes. The patient at that time was treated with prednisone, cyclosporine and lisinopril. His proteinuria decreased to 196 mg per 24 hours. Due to intolerance, lisinopril was stopped and urine protein subsequently rose. At the time of evaluation, the patient’s 24-hour urine protein was 700 mg and the autoimmune and infectious work up was negative. Upon reviewing the medical record from 2 years ago, he had inferior venacavagram as a part of the varicocele treatment. It showed compression of the left renal vein between the aorta and superior mesenteric artery. Nutcracker syndrome was suspected. Subsequently, he was referred to vascular surgery, and underwent an open recomstructive surgery. Postoperatively the patient remained off lisinopril and repeated 24 hour urine protein was 100 mg.

Conclusions: Nutcracker syndrome can cause significant proteinuria. Although it is rare, an early recognition could lead to a definitive treatment, help avoid unnecessary medications and invasive procedure such as a kidney biopsy.
Parvovirus B19 Immune Complex Glomerulonephritis
Beth Lynne Braunhut
Erika R. Bracamontes. Pathology, Univ of Arizona College of Medicine, Tucson, AZ.

Background: A 14 year old girl underwent a cadaveric renal transplant due to end-stage renal disease from obstructive uropathy and developed Parvovirus B19 viremia and graft dysfunction. Renal biopsy showed de novo immune complex glomerulonephritis with parvovirus B19 DNA detected in renal tissue by PCR. We herein review of B19-associated glomerulonephritis.

Methods: A search of the English-language medical literature was conducted. PubMed, Medline, and Google scholar were used. Adult and pediatric cases were included. Sources included case reports and series, including prior reviews. Articles were evaluated for description of demographics, clinical data, findings, laboratory data, and renal biopsy results.

Results: 67 cases were identified. 51 involved native kidneys and 16 transplants. 66 of 67 cases had serologic evidence of B19 infection (98.5%). B19 DNA testing by PCR of various samples was positive in 82.9% of cases. Biopsy results were reported in 52 cases. Of native cases, 92.3% reported a proliferative glomerulonephritis. Allografts most commonly showed TMA (66.7%). IF showed C3 in 84.4%, IgM in 68.8%, IgG in 62.5% and IgA in 40.6%. IF was negative in all transplant cases, save for our patient who showed IgG, IgM, C1q and C4d. EM results were reported in 24 cases with subendothelial deposits being most common (91.7%).

Conclusions: The findings in B19-associated glomerular disease are different in the native kidney versus transplant setting. In a native kidney, proliferative immune complex glomerulonephritis is most common. In the transplant setting, most cases showed TMA. The pathogenesis of this discrepancy remains unclear. To our knowledge, this is the first report of B19 immune complex glomerulonephritis in a renal transplant patient. Our patient showed findings more commonly seen in native-kidney B19 disease. We believe this discrepancy may be explained by insufficient immunosuppression in our patient, as evidenced by concurrent AMR. B19 infection in a transplant patient has practical implications. B19 glomerular disease represents a largely reversible form of renal injury. But, adverse outcomes have been reported. Management may require a balancing act with the risk of rejection on one hand and B19 disease on the other.

A Case of ANA-Negative Systemic Lupus Erythematosis
Ankur Shah, Rachel Criner, Jean Lee. *Internal Medicine, Temple Univ Hospital, Philadelphia, PA; †Nephrology, Temple Univ Hospital, Philadelphia, PA.

Background: Systemic Lupus Erythematosis is a chronic autoimmune disorder hallmarked by several autoantibodies targeting intracellular antigens. The most sensitive of these antibodies is the anti-nuclear antibody. Various studies show that this antibody is present in 95-98% of individuals with the disorder. As methodology improves, the incidence of ANA-negative Lupus has been decreasing.

Methods: We report a case of a 53 year old female whose known past medical history included only hypertension who presented to the outpatient clinic with arthralgias, pancytopenia, alopecia, proteinuria and skin rash whose labwork to this point included an elevated ESR of 115, negative ANA, neg HIV, Hep B, and Hep C serology. She was then lost to followup until presenting to the hospital with anisocoria and acute kidney injury. Her further workup confirmed a negative ANA but also revealed positive Anti-SSa, and anti-SSB antibodies. On serologic testing, the patient had circulating anti-anti-Phospholipid. Her C3 and C4 were decreased as low as 43 and 66 respectively. She had a renal biopsy performed revealing focal proliferative and membranous lupus nephritis, Class III/V. The patient was started on mycophenolate, plaquenil, and prednisone.

Conclusions: Once a byproduct of a technically variable laboratory test, the entity of ANA-negative Lupus has been decreasing in its frequency. The adoption of the human epithelial substrate has brought standardization to this assay and also increased its sensitivity. Nonetheless, the entity still exists, and has been described before. The majority of ANA- Negative Lupus cases will present with antibodies to cytoplasmic components – SSA or SSB, as did our case. ANA negative cases of SLE have been shown to have a decreased incidence of renal manifestations, with our case being an interesting exception. Our case serves as a reminder that the entity of systemic lupus erythematosis remains a clinical one, and that while the ACC criteria do include immunologic studies, the absence of the hallmark antibody does not rule out the disorder.

Patients with Combined Membranous Nephropathy and Focal Segmental Glomerulosclerosis Have Comparable Clinical and Autoantibody Profiles with Primary Membranous Nephropathy
Qiu-hua Gu, Zhao Cui, Jing Huang, Gang Liu, Minghui Zhao. Renal Div, Peking Univ First Hospital, Inst of Nephrology, Peking Univ, Beijing, China.

Background: Patients with combined membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS) have been reported with different clinical significance. Investigation on the possible mechanisms of the combined glomerular lesions is necessary before treatments and better renal outcome during follow-up. These were comparable to the primary MN, but differed from the patients with primary FSGS. Among patients with combined lesions showed higher stages of MN, no cellular variant on FSGS classification and more common (100%) tubulointerstitial injury than both primary MN and primary FSGS patients. In the patients with combined lesions, 80% had circulating anti-PLA2R antibody and 68.4% had IgG4 predominant deposition in glomeruli, which were comparable to primary MN. No circulating antibody or IgG4 deposition was detected in primary FSGS patients. The patients with combined lesions had significantly lower urinary sPAR concentration, compared to the primary FSGS patients (315.6±302.0 vs. 691.3±1223.5pg/ umol, P=0.014), but similar to primary MN patients (275.7±253.4pg/umol).

Conclusions: We conclude that patients with combined MN and FSGS may share the same underlying pathogenesis with primary MN. The FSGS lesion might be secondary to primary MN.

Funding: Government Support - Non-U.S.

Glomerulosclerosis Is Prevalent but Not Associated with Kidney Function in Healthy Japanese Elderly
Koiti Sato, Tsukasa Nagamuna, Daisuke Ichikawa, Sayuri Shirai, Yugo Shibagaki. Div of Nephrology and Hypertension, St. Marianna Univ, Kawasaki, Kanagawa, Japan.

Background: Previous western studies have shown that global glomerulosclerosis (GS) is common in healthy elderly but is not associated with kidney function. We here conducted a study to determine whether healthy Japanese elderly, whose glomerular filtration rate (GFR) is much lower than that of western counterparts, have also same relationship among kidney function and prevalence of GS.

Methods: We analyzed 81 kidney biopsy specimens from Japanese living donors obtained at donor nephrectomy between 2009 and 2014. Using the 2007 Banff classification system, GS, tubular atrophy (TA), interstitial fibrosis (IF), and arteriosclerosis (AS) on kidney samples were evaluated. Donor characteristics such as age, serum creatinine (SCr), C4-based estimated GFR (eGFR), proteinuria, and the prevalence of hypertension, were also evaluated. GS was expressed as a percentage of the standard deviation from the mean range (IQR). We performed univariate and multivariate analyses to identify the relationship between the parameters.

Results: Average age was 59.5 ± 9.1 years, male accounted for 38 (46.9%), with sCr 0.68 ± 0.15 mg/dl (eGFR 80.0 ± 12.9 ml/min/1.73m²), proteinuria 125.5 ± 61.0 mg/gCr, and hypertensive 28 (34.6%). Each kidney sample had the average of 16 glomeruli (IQR, 12 to 23) and 1 GS (IQR, 0 to 2), so the proportion of GS among total glomeruli was 0.25% (IQR, 0 to 1.43). The prevalence of any GS was 65.4%, any TA, 51.9%, IF greater than 5%, 48.1%, and any AS, 91.4%. Statistical analyses revealed that donor age was the only independent factor related to GS, and also to TA, IF, and AS. Among kidney biopsies of our 53 normotensive donors, 5 (9.4%) had more GS than the 95th percentile of the number of GS in western studies.

Conclusions: Although Japanese healthy adults had lower GFR and a higher number of GS than western counterparts, GS was still not associated with kidney function. Pathological significance of GS in otherwise healthy Japanese is not supported as in western counterparts.

Funding: Government Support - Non-U.S.

241 Case of Monoclonal Gammopathy with Renal Biopsy Analysis
Yuqing Chen, Beini Lv, Yan Wang, Yu Xiaojuan, Ming Hui Zhao. Renal Division, Dept of Medicine, Peking Univ Frist Hospital, Beijing, China.

Background: Patients with monoclonal gammopathy can accompany various renal lesions related or un-related to the monoclonal gammopathy. We aim to describe the renal lesions with monoclonal gammopathy in china.

Methods: Data of renal biopsy and clinical presentation of patients with monoclonal gammopathy on serum and/or urine immunofixation electrophoresis in our center from 1999 to 2014 were collected.

Results: 241 patients met the inclusion criteria and were classified as renal disease related to multiple myeloma (MM) (n=18, 7.5%), monoclonal gammopathy of renal significance (MGRS) (n=85, 34.9%) and monoclonal gammopathy of undetermined significance (MGUS) (n=138, 57.4%). Among patients with MGRS, Amyloidosis (n=69, 28.6%) is the most common diagnosis, followed by Light Chain Deposition Disease (LCDD) (n=7, 2.9%), Cryoglobulinemic glomerulonephritis (n=6, 2.5%), and 56 cases (22.9%) received no further treatment. Among patients with MGUS, a variety of renal lesions were found, including membranoproliferative nephropathy (n=48, 20.2 %), IgA nephropathy (IgAN) (n=17, 7.05%), interstitial nephritis (n=13, 5.4%), membranous proliferative glomerulonephritis (MGN) (n=9, 3.3%) and so on.

Conclusions: We analyzed the data of mononclonal gammopathy with renal biopsy in china for the first time. A growing number of renal diseases were found to be associated with monoclonal gammopathy, MGUS is the most common diagnosis of patients with monoclonal gammopathy, while membranous nephropathy and IgAN are most common among MGUS.

Further work are in need to determine whether some MGUS are truly and intertemine or with renal significance and whether or not early treatment is in need for these patients.

Funding: Government Support - Non-U.S.
Stella. In Membranous Nephropathy angiopathy. Specific diagnosis and treatment. Kidney biopsy was always gold standard and a combination embolization. Because of this complication we waited start oral anticoagulant till 7 days we obtained rapidly recovery of diuresis that resulted in a progressive recovery of renal with plasma-exchange (total 4 sessions) with plasma sostitution and corticosteroids (500 and the biopsy result, suggestive of antiphospholipid syndrome (APS), we start treatment proliferative glomerulonephritis associated to thrombotic microangiopathy with sub positive LAC screening. Urinalysis showed microhaematuria and proteinuria 2.5 g/24 h, VES augmented, positive low title anti

Acute Renal Failure in Thrombotic Microangiopathy and C3 Glomerulopathy? Tiziana Stellato,1 Paolo Fabbrini,1 Sonia Sirtori,2 Andrea Stella,1,2 Dept of Nephrology, San Gerardo Hospital, Monza, Italy; Univ of Milano Bicocca, Milan, Italy.

Methods: RBC casts are important component of rapid and early diagnosis of RPGN. RBCs in a cast are almost always pathological and marker of acute glomerular injury. Our case represents an unusual finding of RBC casts in myeloblastic ATN. We purpose extensive renal glomerular injury secondary to severe rhabdomyolysis as possible etiological involvement such as acute renal failure associated with haematuria and proteinuria.

In conclusion, we present an unusual case of ANCA positive, ANA negative full house nephropathy. ANA negative lupus nephritis is very rare presentation that biopsy does not meet any other diagnostic criteria for SLE classification established by American Rheumatism Association. Our patient was 60- year-old woman with past medical history of only hypothyroidism, presented with new onset of acute kidney injury and hypertension. Laboratory data showed BUN and creatinine of 74mg/dl and 30.3mg/dl respectively, decreased complement C3 and C4, hypocomplementemia and nephrotic range proteinuria and hematuria. Serology tests including serum ANA, anti ds DNA, anti-smith and smooth muscle antibodies, anticoagulipin IgG and IgM titers, C1Q binding assay were negative. HIV, hepatitis B and C viruses serologies were negative too. C-ANCA (0.7 U) and P-ANCA (1.5U) were positive. Renal biopsy showed proliferative crescentic and membranous glomerulonephritis with a full house immuno-fluorescence pattern with extra-glomerular tubular basement deposits suggestive of Lupus like glomerulonephritis. Patient required hemodialysis for her renal failure and was treated with oral cyclophosphamide and corticosteroids. Seven months into treatment, patient still requires twice a week hemodialysis with only minimal recovery of renal function and has not yet experienced any clinical symptoms of SLE.

In conclusion, we report an unusual presentation of seronegative SLE diagnosed is a rare disease characterized by arteriolar and capillarly thrombosis with endothelial damage. Clinical manifestations include renal involvement such as proliferative membranous glomerulonephritis and proteinuria.

Pathological and Clinical Analysis of the Kidney Puncutation Biopsy in 1,551 Patients Mei Li,1 Qiong-li Yin,1 Zhenda Zheng,2 Cai-Lian Cheng,1 Xin Liu,1 Cheng-gang Shi,1 VIP Healthcare Center, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou;2 Cardiovascular Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou; Nephrology Dept, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.

Background: To summarize all the renal biopsy cases in the past ten years in the Third Affiliated Hospital of Sun Yat-sen University; analyze the pathological type distribution, and their relationship with clinical manifestations.

Methods: Pathological and clinical data in 1,551 cases with renal biopsy with complete clinical data were analyzed retrospectively from January 2005 to December 2014. Results: Among 1,551 cases, including primary glomerular disease (63.8%), secondary glomerular disease (33.5%). The first third pathomorphological types of primary glomerulonephritis are IgA nephropathy (38.6%), membranous nephropathy (25.9%) and membranoproliferative glomerulonephritis (19.3%). The third most common clinical manifestations for male versus female, the ratio is 1.32:1 in the primary glomerulonephritis, while 0.73:1 in the secondary glomerulonephritis. Conclusion: Primary glomerulonephritis is still the most common form of renal disease, and almost in male. IgA nephropathy is the most common pathological type of primary glomerulonephritis followed by glomerular minor lesion. While for the secondary glomerulonephritis, female is more than male, and LN is the most common pathological type followed by DN. And Chronic nephritis syndrome is the most common clinical manifestations of renal biopsy.
Iodine-123 MIBG Imaging of Renal Cell Carcinoma with Pathological Correlation

Ken Hiratsuka,1 Isao Kurihara,1 Sayuri Suzuki,2 Shintaro Yamaguchi,3 Toshiaki Monkawa,1 Koichi Suzuki,2 Hiroshi Itoh.1 1Dept of Internal Medicine, Keio Univ School of Medicine, Japan; 2Dept of Mycobacteriology, Leprosy Research Center, National Inst of Infectious Diseases, Japan.

Background: The incidence of renal cell carcinoma has continuously increased during the last fifty years. Despite the increase in number, the five year survival rate has been reduced by the advances in renal imaging. Chromophobe renal cell carcinoma (ChRCC) is an uncommon variant of RCC, accounting for approximately 5% of renal cancer. Although its prognosis is usually favorable, preoperative diagnosis is difficult because there is no marker for this variant. Here, we reported a novel method to distinguish ChRCC from other RCC (especially, clear cell carcinoma).

Methods: We experienced a case of ChRCC with adrenal pheochromocytoma in a 69-year-old Japanese female. We noticed that iodine-123 MIBG scintigraphy showed uptake in ChRCC in addition to pheochromocytoma; uptake was not observed in other RCC cases.

Results: The protein expression of pendrin, the candidate transporter, which related to iodine-123 uptake, was highly detected in ChRCC compared with clear cell carcinoma.

Conclusions: We identified specific transporter, pendrin, which is highly expressed in ChRCC. Our results indicates that iodine-123 MIBG scintigraphy may be a useful tool for the diagnosis of ChRCC and represents a substantial advance in the diagnosis of ChRCC.

Clinical Significance of Glomerular IgG Deposits in IgA Nephropathy

Anthony Alvardo,1 Nicole K. Andeen,2 Sergey V. Brodsky,3 Alice Hinton,4 Tiber Nadasdy,1 Charles E. Alpers,2 Christopher D. Blosser,1 Belzhad Najafian,2 Brad H. Rovin.1 1Faculty of Medicine, Nephrology Div, The Ohio State Univ, Columbus, OH; 2Pathology Dept, Univ of Washington, Seattle, WA; 3Pathology Dept, The Ohio State Univ, Columbus, OH; 4Div of Biostatistics, College of Public Health, The Ohio State Univ, Columbus, OH.

Background: IgAN is characterized by IgA dominant or IgA-IgG co-dominant mesangial deposits. It is not clear whether IgG deposits in IgA Nephropathy affects disease prognosis. We evaluated the significance of IgG co-deposits in IgAN.

Methods: Consecutive IgAN biopsies (n=80) from Ohio State University and University of Washington (2001-2013) were retrospectively classified into IgA only and IgA-IgG (IgG > trace). The presence or absence of IgG was correlated to the combined primary outcome of renal replacement therapy, death, OR doubling of serum creatinine.

Results: The change in estimated GFR (eGFR) was also assessed. Covariates were age, sex, primary outcome of renal replacement therapy, death, OR doubling of serum creatinine.

Conclusions: The presence or absence of IgG was correlated to the combined primary outcome of renal replacement therapy, death, OR doubling of serum creatinine.

Renal Biopsy

Figure 1. (a) H&E Crescentic GN (1b) Jones Silver: MPGN with Crescents. Trichrome staining (1c) reveals eosinophilic intra-glomerular deposits with collagen deposition and obliteration of Bowman’s space.

Substantial mesangial (2a: 30000x) and subendothelial (2b: 30000x) electron dense deposits of randomly arranged, slightly curved microtubular/fibrillar structures of approximately 20-25nm in diameter (2c: 120000x), and fingerprinting (2d: 30000x).

LM: crescents and endocapillary proliferation. EM showed subendothelial, subepithelial and paramesangium 20.5-25nm microtubular fibrils. IF: only C1q 2+ granular GHM and mesangial deposits. Labs: UPCR: 2.1 grams/day, ESR and CRP levels were markedly elevated. Viral hepatitis/HIV PCR, ANA, anti-DNA, anti-RNP, anti-Smith, SSA/SsB, anti Sm and Rh factor/CCP, C3, C4, ASO, cryocrit, SPEP/UPEP/free light chains/Immunofixation, peripheral flow cytometrywere negative. Patient was treated with IV methylprednisolone pulse and rituximab with improvement of renal function and proteinuria.

Conclusions: The uniqueness of this case is underscored by a variety of factors; clinical presentation, laboratory, serologies, and pathology. Laboratory and serological studies in cryoglobulinemia generally follow a characteristic pattern, detection of circulating cryoglobulins, low levels of complement, viral, autoimmune or lymphoproliferative etiology—yet a limited number of cases have presented with normal serological results, similar to the case presented here.

Development of a Clinicopathologic Kidney Biopsy Database Using Billing and Diagnosis Codes: A Descriptive Study

Anju A. Oommen,1 Jason Cobb,2 Jose E. Navarrete,1 Demilade Adedinnsewo,2 Oluwatolobio A. Osikoye,3 Helene B. Fevrier,4 Federic F. Rahbari-Oskouie,1 Alton Brad Farris,1 Laura Plantinga,5 Titilayo O. Iiroti.1 1Dept of Nephrology, Emory Univ School of Medicine, Atlanta, GA; 2Morehouse School of Medicine, Atlanta, GA; 3Lee Univ, Cleveland, TN; 9Dept of Epidemiology, Rollins School of Public Health, Emory Univ, Atlanta, GA; 10Dept of Pathology and Laboratory Medicine, Emory Univ School of Medicine, Atlanta, GA.

Background: A growing kidney disease population coupled with expanded use of electronic medical records (eMR) presents a unique opportunity for regional translational clinical research. We developed a comprehensive registry of all native renal biopsies at a major hospital in Southeastern US and described the pattern of glomerular diseases.

Methods: We identified all native percutaneous renal biopsies (n=2,245) performed in Atlanta (~18) between 2000 and 2011 using CPT and ICD-9 billing codes (50200 and 5523). Transplant biopsies (V42.0) and cytology were excluded. Renal pathology reports were reviewed by at least two independent clinical nephrologists. Clinical, laboratory and demographic data were extracted and validated by independent chart review. A clinicopathologic diagnosis was subsequently entered. Descriptive and bivariate statistics were used to analyze patient characteristics at biopsy.

Results: Patients in the registry had a mean age of 44.2 years; approximately half were male and majority were African American (40.7%). Overall, lupus nephritis (n=278, 12.4%) was the second most prevalent renal clinicopathologic diagnosis. Among primary glomerular diseases, FSGS (136, 9.2%) was the most prevalent, followed by IgA nephropathy (123, 8.3%), membranous glomerulonephritis (GN) (69, 4.6%), membranoproliferative GN (24, 1.6%) and minimal change disease (27, 1.8%). Diabetic nephropathy was the second most common secondary GN (97, 6.5%) followed by ANCA-associated vasculitis (31, 2.1%). Other diagnoses were all less than 2%.

Conclusions: We successfully established a kidney biopsy registry at our center, which will be instrumental to studying outcomes in this rare group of diseases, the most prevalent of which were lupus nephritis and FSGS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

946A
**PUB257**

**Is There Clinical Significance of IgM and Complement Staining in Idiopathic Focal Segmental Glomerulosclerosis**

**Vansantha M. Muthupalanpian, Kieran Mccafferty, Michael Sheaff, Muhammad M. Yaqoob**

Nephrology, Barts & The London NHS Trust, London, United Kingdom; Pathology, Barts & The London NHS Trust, London, United Kingdom.

**Background:** Experimental evidence suggests that focal segmental glomerulosclerosis with complement deposits is associated with poor outcome. Whether this is transferable or relevant in human disease is unclear.

**Methods:** We performed a proof-of-concept observational study on all patients with a diagnosis of idiopathic focal segmental glomerulosclerosis (fSGS) on native renal biopsies from January 2004 to December 2014. A total of 40 renal biopsies were identified. Clinical outcome data were obtained to seek an association with complement deposits (CD) and outcomes. Immunosuppression administered was according to the local trust policy which included prednisolone and cyclophosphamide or calcineurin inhibitor.

**Results:** See Table 1

<table>
<thead>
<tr>
<th>No CD (n= 21)</th>
<th>CD (n= 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43 (35-50)</td>
<td>39 (30.5-54.5)</td>
</tr>
<tr>
<td>Sex Male</td>
<td>11 (52)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Race Black/Asian/White</td>
<td>6 / 9 / 6</td>
<td>8 / 5 / 6</td>
</tr>
<tr>
<td>Type of lesion : Tip/Collapsing/NOS</td>
<td>2 / 2 / 17</td>
<td>3 / 0 / 16</td>
</tr>
<tr>
<td>IgM</td>
<td>0 (0)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>12 (57)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Baseline urine protein creatinine ratio (UPCR)</td>
<td>540 (330-1000)</td>
<td>1000 (560-1200)</td>
</tr>
<tr>
<td>Baseline albumin</td>
<td>29 (24-38)</td>
<td>26 (21-36)</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>49 (25-71)</td>
<td>60 (48-81)</td>
</tr>
<tr>
<td>Change in UPCR</td>
<td>-370 [-700,-140]</td>
<td>-430 [-790,-260]</td>
</tr>
<tr>
<td>Change in serum albumin</td>
<td>8.5 (2.3-13)</td>
<td>4 (0-17)</td>
</tr>
<tr>
<td>Change in eGFR</td>
<td>4.5 (5.5-21)</td>
<td>4 (-15-11)</td>
</tr>
</tbody>
</table>

CD was present in approximately 50% of the biopsies, but there was no significant association between CD and baseline clinical or demographic characteristics, furthermore, there are no association between CD and markers of disease progression (change in proteinuria, serum albumin or GFR between baseline and year 1 follow up). IgM staining was strongly co-associated with CD.

**Conclusions:** Our results indicate that, unlike animal models of fSGS, IgM and complement deposition does not alter outcomes. However, these findings will need to be confirmed in a larger study.

**PUB258**

**A Case of Intra-Occular Lucentis (Ranibizumab) Induced Minimal Change Disease**

Ashwin Reddy Ganta, Dept of Nephrology, Archbold Memorial Hospital, Thomasville, GA.

**Background:** Intravitreal monoclonal antibodies like Lucentis (Ranibizumab), Eylea and Avastin are being increasingly used for the treatment of Wet Age related Macular Degeneration (wAMD) and Diabetic Macular Edema (DME) of the eye. Though the intravitreal use of these agents is 1.7 mg/dL, hemoglobin 11 g/dL, normal platelet count and LDH.

**Methods:** This is a case of a successful use of Lucentis, in a patient with Lupus nephritis and thrombotic microangiopathy refractory to classical treatment. A putative explanation is that autoantibodies may have primed the endothelium, unmasking a complement defect that was successfully controlled by terminal complement blockade. A genetic analysis may reveal a mutation in regulator factors of the alternative complement pathway or auto-antibodies against Factor H or I. Eculizumab may be an option for the treatment of refractory lupus nephritis with thrombotic microangiopathy.

**Results:** We decided to start eculizumab and after one week, platelet count increased allowing for a renal biopsy that showed lupus nephritis class IV with thrombotic microangiopathy. After the third dose of eculizumab, there was improvement of anemia and she started to present diuresis. She was discharged from hospital one week later with creatinine of 2.3 mg/dL and off dialysis. After one year, she is on maintenance eculizumab every two weeks with low dose prednisone and mycophenolate mofetil 1per day. Creatinine is 1.7 mg/dL, hemoglobin 11 g/dL, normal platelet count and LDL.

**Conclusions:** This is a case report of the successful use of eculizumab in a patient with Lupus nephritis and thrombotic microangiopathy refractory to classical treatment. A putative explanation is that autoantibodies may have primed the endothelium, unmasking a complement defect that was successfully controlled by terminal complement blockade. A genetic analysis may reveal a mutation in regulator factors of the alternative complement pathway or auto-antibodies against Factor H or I. Eculizumab may be an option for the treatment of refractory lupus nephritis with thrombotic microangiopathy.

**PUB260**

**Diagnostic Items for Renal and Hepatic Cyst Infection – A Delphi Survey**

**Muthuppalaniappan, Neves, Barbosa, Kieran Mccafferty,**

& The London NHS Trust, London, United Kingdom.

**Background:** In common cases of autosomal dominant polycystic kidney disease (ADPKD), diagnosis is relatively simple using a combination of diagnostic imaging of the kidney and analysis of ADPKD in the patient’s family history. Therefore, in most patients, ADPKD genetic testing for ADPKD is not necessary for diagnosis. However, in ADPKD cases where a definitive diagnosis is not obtained by imaging or living related donor is identified for kidney transplantation, genetic testing may be necessary.

**Methods:** This is a case report of a female patient, 18 years old, with no past history of disease, started fever, abdominal pain and dysuria treated initially as UTI. She evolved with skin rash and a few days later, oligoanuria, nausea and vomiting. She was admitted and treated with dialysis on the same day. Initial exams showed creatinine 1.7 mg/dL, hemoglobin 11 g/dL, normal platelet count and LDH.

**Results:** This is a case of a successful use of Lucentis, in a patient with Lupus nephritis and thrombotic microangiopathy refractory to classical treatment. A putative explanation is that autoantibodies may have primed the endothelium, unmasking a complement defect that was successfully controlled by terminal complement blockade. A genetic analysis may reveal a mutation in regulator factors of the alternative complement pathway or auto-antibodies against Factor H or I. Eculizumab may be an option for the treatment of refractory lupus nephritis with thrombotic microangiopathy.

**PUB261**

**The Use of Multiplex Ligation-Dependent Probe Amplification Technology for Genetic Analysis of the Entire PKD1 Gene and PKD2 Gene**

**Tetsuhiko Yasuno,**

Estadual de Campinas, Campinas, Sã o Paulo, Brazil.

**Background:** In common cases of autosomal dominant polycystic kidney disease (ADPKD), diagnosis is relatively simple using a combination of diagnostic imaging of the kidney and analysis of ADPKD in the patient’s family history. Therefore, in most patients, ADPKD genetic testing for ADPKD is not necessary for diagnosis. However, in ADPKD cases where a definitive diagnosis is not obtained by imaging or living related donor is identified for kidney transplantation, genetic testing may be necessary.
Methods: Multiplex ligation-dependent probe amplification (MLPA) kits have been developed for genotyping using proprietary MLPA technology. We obtained informed consent from nine patients (mean age, 45 years) and collected 8 mL of blood from each patient for analysis of genetic mutations in PKD1 and PKD2 genes using the MLPA method.

Results: In case 1 (a 39-year-old man), we found deletions in exons 3 and 39 of the PKD1 gene. The kidney was extracted due to enlargement and cyst infection. Dialysis was initiated when the patient was 39 years of age. The kidney capacity was 5013 mL. In case 2 (a 32-year-old woman), we found a deletion in exon 3 of the PKD1 gene. Renal function was maintained, and the serum creatinine level was 0.7 mg/dL. She has hope of the delivery. Tolvaptan does not have the safety about the dosage to a pregnant woman. Tolvaptan was administered after delivery.

PUB263

Abstract Withdrawn

PUB264

A Rare Presentation of Acute Kidney Injury: Have a Look at the Skin Alper Ah1, Sarenur Eserc, Didar Gursoy. 1 1Nephrology, Van Education and Research Hospital, Van, Turkey; 2Dermatology, Van Education and Research Hospital, Van, Turkey.

Background: Tuberous sclerosis(TS) is a multisystem,rare,genetic disorder of autosomal dominant inheritance which can involve different organs.Most commonly involved organ system in skin.We describe a case presented with periumbilical fibromas,multiple renal cysts and Shagreen patch without other features of TS.

Methods: A 33 yo woman presented with fatigue and renal failure.On physical examination,she had multiple non traumatic periumbilical fibromas in both hands and feet. Also Shagreen patch was seen in the right lumbar sacral region.

On admission biochemical tests;urea 132 mg/dl,creatinine 4.7 mg/dl,potassium 4.7 mmol/L, pH 7.32,HCO3 18.4.Lab output was satisfactory,no uremic symptoms were present.Renal ultrasonography revealed bilateral renal cysts with normal size and parenchymal thickness.Histopathology of the Shagreen patch revealed dense collagen bundles in the dermis.Due to the skin lesions and renal cysts the patient was diagnosed as TS.Other manifestations of TS were not present.Renal biopsy was suggested but she did not accept the procedure.

Conclusions: As stated in diagnostic criterias,physical examination has a strong impact on diagnosis of TS.Hypomelanic macules(~3),Shagreen patch,forehead plaque,non traumatic periumbilical fibromas,adenoma sebaceum,facial angiofibromas should remind the physicians TS.Kidneys are involved in almost 50-80% of the adult patients.Most frequent renal lesions in TS are angiomyolipomas.Bilateral and multiple characteristics of angiomyolipomas are pathognomonic.They may progress to end stage renal disease. However in some rare cases frank renal lesions may be absent.With a detailed inspection it is possible to recognize these specific dermatological signs,making the Tuberous sclerosis diagnosis and taking these patients under nephrological follow up.

PUB265


Background: Depression occurs more commonly than in the general population and is associated with poor outcomes. The use of antidepressants (ADs) has been associated with inappropriate release of vasopressin and hyponatraemia. Since vasopressin is thought to aggravate the progression of ADPKD, AD use could be deleterious.

Methods: Examine the use of ADs in the participants of the HALT-PKD randomized clinical trials (RCTs) and whether their administration is associated with faster disease progression. Post-hoc analysis of two HALT-PKD RCTs (A and B) studying the effect of rigorous versus standard BP control (A) and of ACE inhibitor alone vs ACE inhibitor/ARB combination (A and B) on rates of change of TVK (A) and eGFR (A and B) in ADPKD patients with eGFR >60 mL/min/1.73 m2 and <25-60 mL/min/1.73 m2.

Results: Female used ADs more frequently than male participants (39.7% of 526 participants exposed for less £30% and exposure for >30% of the time: 31.7% and 28.4%, respectively). Participants with PKD1 mutations used ADs (42.4%) more frequently than those with PKD2 mutations (27.9%, P<0.0009) despite having milder disease. Ages of these using or not using ADs were similar. To assess the effect of ADs on disease progression we divided the participants into three groups, no exposure to ADs, exposure for less £30% and exposure for >30% of the time:

Conclusions: Measuring body water balance by InBody720® could be useful as predictors of hTKV and eGFR decline in short term after administration of tolvaptan in ADPKD patients.

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

Underline represents presenting author.

948A
In conclusion, this axis may be a therapeutic target in PKD. C. Craig, Mukaiyama, Nozu, in ADAMTS1 mRNA was significantly upregulated in day 21, n=12, 9.1-fold, p<0.0001) and that one of the target molecules of miR-378a-3p, identified by health professionals in the guideline working group with the exception of function, cyst growth, and nephrotoxicity. Almost all topics/outcomes had already been identified by health professionals in the guideline working group with the exception of five topics/outcomes (surgical management of cysts, patient education about end-stage kidney disease, psychosocial impact of diagnosis, need for dialysis, knowledge). Many more topics (33) and outcomes (44) were identified as priorities by health professionals than consumers. Six themes reflected reasons for consumer choices: clarifying ambiguities, resolving debilitating pain, concern for family, preparedness for the future, taking control, and significance of impact.

Conclusions: Although there was considerable concordance between the priority topics and outcomes of health professionals and consumers for guidelines of ADPKD, there was also important discordance with consumers focused on fewer issues but particularly on lifestyle, psychosocial support, caregiver management, and quality of life and renal outcomes. Funding: Government Support - Non-U.S.

PUB266

Dysregulation of miR-378a-3p and ADAMTS1 Gene in cpk Mice: A Model of ARPKD, Masashi Satō, Koichi Nakashima, Yuka Shima, Masaya Miyazima, Kandai Nozu, Shizuko Nagao, Hisahide Takahashi, Kazumoto Iijima, Norishige Yoshikawa, Pediatrics, Tokyo Women’s Medical University, Tokyo, Japan; Laboratory Animal Center, University of Tokyo, Tokyo, Japan; National Center for Child Health and Development, Tokyo, Japan.

Background: The pathophysiology of cystic epithelia in PKD is characterized by altered proliferative activity, a secretory rather than absorptive function, and an abnormal matrix microenvironment. miRNAs are clarified to be involved in PKD. However, the detail has not been fully investigated. We reported that cpk cystic epithelia partially shared cell pathophysiology with colorectal carcinoma (JASN 25:414A, 2014). Recently, dysregulation of miR-378a-3p/ADAMTS1 axis was reported in colorectal carcinoma (Kara, et al. Gene, in press). ADAMTS1 is one of the ADAMTS (A Disintegrin And Metalloproteinase) with Thrombospondin motifs) metalloproteinases family. Elevated ADAMTS1 promotes pro-tumorigenic changes such as increased tumor cell proliferation and altered extra cell matrix environment.

Methods: To identify miRNAs that are differentially expressed between cpk and control kidneys, we performed miRNA microarrays, and assessed the target molecule gene and its product expression using real-time PCR and western blotting.

Results: miRNA microarray analysis revealed that 22 (up, down 18) miRNAs were differentially expressed (more than 4-fold) in cpk (day 21, n=7) kidneys. Of 22 miRNAs, miR-378a-3p was significantly downregulated in cpk (5.1-fold). Real-time PCR confirmed that miR-378a-3p was significantly downregulated in cpk (day 14, n=14, 5.0-fold, p=0.002; day 21, n=12, 9.1-fold, p=0.0001) and that one of the target molecules of miR-378a-3p, ADAMTS1 mRNA was significantly upregulated in cpk (day 14, n=20, 1.4-fold, p=0.01; day 21, n=12, 3.5-fold, p=0.0002). Western blotting showed that ADAMTS1 was increased in cpk (day 21, n=6, 1.8-fold, p=0.03) kidneys.

Penetration Rate (%) and P-value

A

>30% (N=128)

136.4

65.8

75.1

8.81

-3.32

0.031

0.89

0.37

0.22

0.07

B

None (N=348)

139.5

50.5

168.2

-3.81

P-value

0.06

0.46

0.005

-0.98

Average of measurements for each participant during the trial

Conclusions: AD use, defined as >30% use, does not affect the progression of ADPKD. Whether a particular AD class has an effect is under evaluation. Funding: NIDDK Support

PUB267

Identifying and Integrating Consumer Perspectives in Clinical Practice Guidelines on Autosomal Dominant Polycystic Kidney Disease

David J. TumnickLiff, Allison Tong, Pamela Andrea Lopez-Vargas, Jonathan C. Craig,1 Gopala K. Rangan,2,3,4 The Univ of Sydney, Australia; 2Westmead Millennium Inst, Australia; 3Westmead Hospital, Australia.

Background: Integration of consumer perspectives into clinical practice guidelines is widely advocated as it ensures that recommendations are relevant to all stakeholders. We aimed to identify consumer perspectives on topics and outcomes to include in clinical practice guidelines on autosomal polycystic kidney disease (ADPKD).

Methods: A workshop involving three concurrent focus groups with consumers was convened. Guideline topics, interventions and outcomes were identified, and integrated into guideline development. Thematic analysis was used to analyze the reasons for their choices.

Results: Eighteen consumers (patients with ADPKD [n=15], caregivers [n=3]) participated and 22 priority topics (including interventions) were identified, with most focused on non-pharmacological management (diet, fluid intake, physical activity, complementary medicine), pain management, and psychosocial care (mental health, counseling, cognitive and behavioral training, education, support groups). They also identified 30 outcomes including quality of life, progression of kidney disease, kidney function, cyst growth, and nephrotoxicity. Almost all topics/outcomes had already been identified by health professionals in the guideline working group with the exception of five topics/outcomes (surgical management of cysts, patient education about end-stage kidney disease, psychosocial impact of diagnosis, need for dialysis, knowledge). Many more topics (33) and outcomes (44) were identified as priorities by health professionals than consumers. Six themes reflected reasons for consumer choices: clarifying ambiguities, resolving debilitating pain, concern for family, preparedness for the future, taking control, and significance of impact.

Conclusions: Although there was considerable concordance between the priority topics and outcomes of health professionals and consumers for guidelines of ADPKD, there was also important discordance with consumers focused on fewer issues but particularly on lifestyle, psychosocial support, caregiver management, and quality of life and renal outcomes. Funding: Government Support - Non-U.S.

PUB268

Urine AQP2 Is One of the Candidates for a Surrogate Marker in the Treatment of ADPKD Patients by Tolvaptan

Koichi Natsumi, Hiroshi Kanbe, Toshihiko Motomichi, Miki Nishida, Masayo Sato, Hiroshi Kitaoka, Hidekazu Sugura, Ken Tsuchiya, Kosaku Nitta. Medicine IV, Tokyo Women’s Medical Univ, Shinjuku, Tokyo, Japan.

Background: Tolvaptan, arginine vasopressin (AVP) V2 receptor antagonist is accepted for autosomal dominant polycystic kidney disease (ADPKD) patients in Japan since 2014. TEMPO study showed tolvaptan from 60 to 120 mg per day slowed renal cyst expansion and renal function decline. Tolvaptan dose is decided by preliminary study (TEMPO3), which showed the maximum dose that meet both urinary osmolality (Uosm) under 300 mOsm/kg and patient’s tolerance. So that adequate dose for individual patient has not been suggested. Moreover, tolvaptan cause polyuria, thirsty, polydipsia due to aquaresis. Thus, it is necessary to find surrogate markers for determine the maximum effects and minimum side effects for long-term administration.

Methods: Seventeen ADPKD patients initiated tolvaptan of 60 mg were investigated. Physical data, plasma osmolality (Posm), Uosm, AVP, urine cyclic AMP (UCAMP), and urine AQP2 (UAQP2) were assessed. UCAMP was measured by radioimmunoassay (Yamasa corp.) and UAQP2 was measured by a sandwich enzyme-linked immunosorbent assay method (Otsuka Pharmaceutical Co. Ltd.).

Results: After initiation of tolvaptan, average urine volume was 8621 ml/day and delta body weight was -1.42 kg/day on day 1. One month after, AVP increased from 3±3 to 7.3±11.2 pg/ml (p=0.001), Uosm decreased from 367±349 to 243±436 mOsm/kg (p<0.001). Posm and UCAMP were not statistically associated. UAQP2 decreased from 0.029±0.068 to 0.012±0.028 pmol/MgCr (p=0.0001). In our preliminary data (n=5), the serum copeptin, a precursor of vasopressin, was shown to be no consistent level.

Conclusions: It has been reported that 3% of total production of AQP2 excreted into the urine, it reflected directly the intracellular action of AVP. Thus, UAQP2 is likely to be one of surrogate markers of tolvaptan effect, moreover it could provide additional information of determination of individual dosage and monitoring for long-term use.

Funding: Private Foundation Support

PUB269

Abnormalities in the Radius of Patients with Autosomal Dominant Polycystic Kidney Disease Measured by High-Resolution Peripheral Quantitative Computerized Tomography Imaging

Danielle Diarra, Janina M. Patsch, Claudia Schueller-Weidekamm, Michael Weber, Astrid Nia, Gre Sander-Plassmann, 1 Dept of Medicine III, Medical Univ of Vienna, Austria; 2 Dept of Radiology, Medical Univ of Vienna, Austria; Dept of Medicine II, St. Vincent Hospital, Medical Univ of Vienna, Austria.

Background: ADPKD is a multi-organ disorder and the most common of all cystic kidney diseases. Mutation of the PKD1 or -2 gene causes epistaphelial ciliopathies, which lead to the dysfunction of various organs. Animal studies show that primary cilia are present in osteoblasts of mice and point mut ation of the osteoblastic PKD1 gene induces osteopenia.

Methods: In this pilot-study, we examined the bone structure in 6 ADPKD patients in comparison to 6 matched patients with glomerular disease (GD), both in CKD stages I-III, by HR-pQCT of the radius and the tibia. The aim of the study was to identify microarchitectural target parameters for a subsequent larger study in patients with ADPKD.

Results: Demographic data see Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GD Patients (controls)</th>
<th>ADPKD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27±6.4</td>
<td>26±7.6</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.81±0.17</td>
<td>0.83±0.19</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>109±18</td>
<td>108±23</td>
</tr>
</tbody>
</table>

We found reduced cortical and trabecular microstructural parameters by HR-pQCT, mainly affecting the radius. The outer trabecular density, the cortical thickness and the total density of the radius showed the biggest differences between the two groups, see Figure 1.

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949A
The total density of the radius was the best parameter to distinguish between the bone structure of ADPKD— in comparison to GD patients (AUC=0.861).

Conclusions: We provide evidence of microstructural bone deterioration of the radius in patients with ADPKD. We thus hypothesize that ADPKD is associated with microstructure bone changes in men.

PUB270
An Accurate Formula for a Quick Estimate of Total Liver Volume in Polycystic Liver Disease Patients

 Methods: The primary aim of treatment of PLD is reduction of total liver volume (TLV) as patients often suffer from hepatomegaly. The gold standard to assess TLV is CT volumetry which involves manual delineating of the liver outline. Unfortunately this is a time-consuming method (45-60 minutes per CT scan) and requires a certain level of expertise. An easily accessible and fast method to estimate TLV in routine clinical practice is needed. Therefore we aimed to develop an accurate formula for quick estimation of TLV. We collected a cohort of PLD patients in whom CT scans were available. Manual delineation of TLV served as gold standard. PLD patients were distributed in 2 cohorts, a development cohort (N=80) and a replication cohort (N=50). We measured anterior-posterior (AP), transverse (T) and cranial-caudal (CC) distance (in meters) of the liver on CT. TLVs were logarithmically transformed as data were not normally distributed. \( R^2 \) was measured as it indicates the goodness of fit of the prediction model. The prediction model was tested in a replication cohort.

Results: Median liver volumes in the development and replication cohort were 4749mL [1084-14816] and 4684mL [1287-16746] respectively. All three diameters significantly correlated with TLV (\( p < 0.0001 \)). Linear regression analysis resulted in the following formula: Logarithm of TLV = 2.540 + 0.7568 x CC + 2.522 x AP + 0.041. Our model predicted TLV accurately in the development cohort (\( R^2=0.898 \)). The correlation in the development cohort was 0.848 and validated in the replication cohort resulted in a correlation of 0.937.

Conclusions: Our model accurately and quickly (< 2 minutes) predicts TLV in PLD patients based on three liver dimensions.

PUB271
Clinical Significance of Urine NAG and L-FABP Excretion for the Assessment of ADPKD-Progression

 Methods: This study, 59 ADPKD cases with consents were retrospectively analyzed. Average age, duration of the observation, median values of kidney volume (KV) and kidney growth rate (KGR), average estimated GFR (eGFR), and urine creatinine ratio of N-acetylglucosaminidase (NAG) to Cr (NAG index) for the clinical assessment of TIN. We stratified patients by the average or median value of the parameters mentioned above, and analyzed their differences in each stratified group. KV, eGFR and KGR showed significant difference only in the eGFR-, KV-, and GFR-stratified group. However, NAG index showed significant difference in both KV-stratified (median: 7.42 vs 6.09 U/mgCr) and eGFR-stratified (8.00±5.98 vs 3.93 U/mgCr) groups. Additionally, urine liver type fatty acid binding protein (L-FABP), as a biomarker of the tubular ischemia, showed significant difference in all stratified groups (KV: 7.29±9.98 vs 1.76±1.68, eGFR: 4.15±7.76 vs 2.45±2.34, KGR: 4.46±7.68 vs 2.09±3.30, NAG index: 4.33±1.20 vs 1.88±2.10).

Conclusions: Progression of ADPKD has been primarily assessed by the kidney volume. However, the present study may show that the assessment of TIN might be more helpful to evaluate the severity and prognosis of ADPKD. It might be suggested that TIN-related markers such as NAG index or L-FABP index should be actively utilize in the clinical management of patients with ADPKD.

PUB272
Classic and Alternative Criteria for the Diagnosis of Autosomal Dominant Polycystic Kidney Disease: Genetics and Disease Progression in HALT-PKD

 Methods: Of 959 HALT-PKD patients with genetic testing 835 (87.1%) had CC, and 124 (12.9%) had AC. Three groups: Alternative (AC-NMD), Classical (CC-PKD1/ PKD2 mutation), and Intermediate (combined CC-NMD = AC-PKD1/PKD2 mutation) were compared for annual change in total kidney volume (TKV, htTKV) in early ADPKD (n=17, 410, 81, respectively), and eGFR in early/late ADPKD (n=17, 414, 375, 81/4 respectively).

Results: TKV increase was 4.21% in Alternative (AC-NMD) compared to 6.39% in Classical (CC-PKD1/ PKD2), and 6.68% in Intermediate (CC-NMD + AC-PKD1/PKD2) (InTKV P=0.0346; latinTKV P=0.0035) and was not affected by BP level.

NMD patients were 20.2% of AC but just 5.5% of CC patients which was true in both early (P<0.0001) and late ADPKD (P=0.0066). Annual eGFR change in early and late ADPKD was not significantly different in the 3 groups, and Low vs Standard BP, or lisinopril+telmisartan vs lisinopril+placebo, did not alter that.

Conclusions: AC-NMD (Alternative) patients with early ADPKD have a significantly lower annual increase in TKV/htTKV. The –FH factor in AC appears to be the clinical portal to a genetically complex population enriched 3.7-fold for NMD. Patients with AC-NMD might have mosaicism, atypical mutations, or even polycystic kidney disease(s) other than ADPKD.

Funding: NIDDK Support

PUB273
Lifestyle Counseling in Polycystic Kidney Disease Patients

 Methods: We performed a systematic chart review. Using our electronic medical record system, we identified patients with ADPKD who most recent visit at UCSF with a nephrologist occurred during the previous six months. We reviewed the notes associated with these visits to assess for nephrologists’ discussion of dietary advice, water drinking parameters, and exercise recommendations based on documentation in clinic notes.
Lipid Alterations in Murine Models of Polycystic Kidney Disease

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1Univ Vita-Salute San Raffaele, Milan, Italy; 2Dibit San Raffaele Scientific Inst, Milan, Italy.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disorder characterized by massive bilateral renal cyst formation. ADPKD results from mutation in the PKD1 or PKD2 genes, encoding Polycystin-1 (PC-1) and 2 (PC-2) proteins respectively. Previous studies have suggested that the mTORC1 cascade might play an important role in PKD. Further, mTORC1 regulates the activity of SREBP which regulate the expression of genes required for the synthesis of fatty acids and cholesterol. However, the regulation of fat synthesis in ADPKD remains poorly understood.

Methods: We analyzed newborn kidneys of Pkd1-Cre;Pkd1flox/+, mice and detected an increased expression of SREBP1 and its target genes including fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD) when compared to control, non-cystic kidneys (Pkd1-Cre;Pkd1flox/+ or Pkd1flox/+).

Results: As expected the increased expression of SREBP1 also correlated with increased transcript levels of SREPB2 concomitant with an increased transcript levels for the lipid alterations that we observed appear to be gender-specific. Of interest both have been implicated in regulating membranes trafficking and they may alter alteration of some lipid classes, particularly sphingolipids and sterol esters (cholesterol).

Conclusions: We are currently characterizing this aspect further and trying to determine which lipid alterations might be dependent and/or independent of mTORC1 upregulation.

PUB276

Baseline Renal Cysts Diameter Predicts the Erithropoietin Requirement in Autosomal Dominant Polycystic Kidney Disease

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Background: Subjects with autosomal dominant polycystic kidney disease (ADPKD) require classically low recombinant human erythropoietin (EPO) to reach haemoglobin target levels. We hypothesize that EPO requirement in subjects with ADPKD is more dependent to the enlargement of the cysts than the reduction of glomerular filtration rate. Aim: To evaluate the role of renal cyst and kidney size on EPO requirement in severe chronic kidney disease (stage 4-5).

Methods: A total of 35 pts with ADPKD and anemia treated with EPO were enrolled (14 pts with CKD Stage 4 and 21 pts Stage 5), the mean volume (V) and diameter (D) of the four largest cysts and the mean antero-posterior renal diameter (AP) were prospectively followed-up for 18 months with computer tomography.

Results: The overall mean age was 65.14±7 years. Male sex 57%. At baseline, AP was 19.7±2.2 cm, D 4.6±1.1 cm, V 749±641 cm³. During the 18 month’s follow-up, rHuEPO dose was 8543±6626 UI/week, and EPO/haemoglobin ratio (E/H) was 1983±1039. In a multivariate linear regression model, adjusted for age and sex, at baseline both AP and V were significantly associated with E/H; after 18 months, only V remains significantly associated with E/H. Baseline V (100cm³ increase: β=115UI/g week, 95%CI 65-164, P<0.001) was also associated with mean E/H during follow-up and explain 42% of E/H variability.

Conclusions: The Cysts volume is useful to predict prospecitively the EPO requirement in ADPKD in stage 4-5 CKD.
PUB278

Amniotic Fluid Stem Cells Transplantation in Fetal Kidney to Regenerate Nephrons Loss. Kathleen Labarbe, 1 Sebastian Sammut, 2 Mehrak Hekmati, 2 Agnieszka Anna Ksiazek, 3 Benedikt Weber, 4 Luc Behr. 5 Necker Hôpital-Paris 5 Univ, Paris, France; 1 IMM, Paris, France; 2 Swiss Center for Regenerative Medicine, Univ Hospital, Zurich, Switzerland.

Background: Amniotic fluid stem cells (AFSC) harbour the potential to differentiate toward renal lineages and contribute to the development of primordial kidney structures. To investigate whether AFSC can improve prenatal renal compensatory growth, cells were transplanted in a model of subtotal nephrectomy (5/6NX) in the fetal sheep.

Methods: Ovine AFSC labelled with GFP were selected using c-kit. In absence of LIF, AFSC formed embryonic bodies which cultured in an optimized medium generated a renal epithelial progenitor population (oAFSCd), expressing Pax-2. 5/6NX was performed at 70 days of gestation in 10 fetal lambs; 5 were injected with oAFSCd in the kidney poles. Sham-operated did not received oAFSCd (SHAM, n=8). At 134 days of gestation, fetuses were euthanized, kidneys removed and processed.

Results: Body weight did not differ significantly among the groups and no morphologic abnormalities were observed, in spite of a severe reduction in amniotic fluid in 5/6NX+oAFSCd. Compensatory renal growth of the remaining kidney was observed in all 5/6NX, but in spite of oAFSCd injection, catch-up kidney growth was similar in both 5/6NX groups. SHAM: 3.2±0.62; 5/6NX: 4.6±0.62; 5/6NX+oAFSCd: 5.5±1.4 K/BW. Glomeruli number/section was similar in all groups: SHAM:271±123; 5/6NX:215±69; 5/6NX+oAFSCd:196±22. In 5/6NX+oAFSCd, GFP cells were present in renal proximal tubules, and proximal tubule hypertrophy was observed.

Conclusions: Transplantation of oAFSCd predifferentiated toward renal epithelial progenitor cells during nephrogenesis increases proximal tubule mass but has no effect on the number of glomeruli (GFR) and do not restore fully kidney damage. Funding: Private Foundation Support

PUB279


Background: Low birth weight (LBW) leads to significant risk to the newborn, with many of these babies developing acute kidney failure and dying soon after birth due to underdeveloped vascular and renal systems. Surviving LBW neonates are also susceptible to a variety of health problems later in life during adulthood including hypertension, diabetes and chronic kidney disease with an associated 70% increased risk of end-stage kidney failure.

Methods: Using a maternal malnourished mouse model, we examined the causes of vascular and renal underdevelopment and impaired function in the LBW neonate. Parameters measured in the LBW offspring included nephron development, stem cell levels, apoptosis, gene expression, circulating cytokine/chemokines, renal blood flow and renal function.

Results: Within 24 hours after birth, LBW male offspring had 40% reduced weight, while only 40% of LBW neonates survived the first week after birth. Within the first week after birth, LBW neonates had an up to 40% reduction in renal blood flow and elevation of serum creatinine up to 3.0 mg/dL. Nephrogenesis was impaired in the LBW neonates with a 75% reduction in renal vesicle formation and a significant downregulation of Wnt9B (which induces differentiation of progenitor cells into tubular epithelia) at day E17.5, which ultimately resulted in a 30% reduction in glomeruli at the conclusion of nephrogenesis. During nephrogenesis, six2+ positive nephron progenitor cells were reduced by up to 70% (which induces differentiation of progenitor cells into tubular epithelia) at day E17.5, which ultimately resulted in a 30% reduction in glomeruli at the conclusion of nephrogenesis.

Conclusions: LBW impairs vascular and renal development due to underdeveloped vascular and renal systems that result from enhanced IL-1beta, increased apoptosis, altered Wntbeta expression, and reduced six2+ progenitor cells in the embryonic and neonate kidney. Funding: Private Foundation Support

PUB280

Increasing Podocyte Number in Neonatal Kidney Reduced Renal Injury in Adulthood Jianyong Zhong, 1,2 Ji Ma, 3 Taiji Matusaka, 4 Agnes B. Fogo, 1 Valentina Kon, 5 Haichun Yang. 1 Pathology, Microbiology and Immunology, Vanderbilt Univ, Nashville, TN; 2Pediatric Nephrology, Vanderbilt Univ, Nashville, TN; 3Dept of Molecular Life Science, Inst of Medical Science, Tokai Univ School of Medicine, Isehara-shi, Kanagawa, Japan.

Background: Preterm birth increases the risk of hypertension and renal disease, which has been linked to decreased Nephron number. We previously found that perinatal puromycin injection in mice at birth impairs glomerular maturation, and has renal pathology phenotype which is similar to that observed in human preterm births. In the present study, we tested the hypothesis that increasing podocyte number during glomerular maturation can rescue glomerular loss and thus reduce renal injury in adulthood.

Methods: We mated podocin-rtTA with TRE-5SV40 in mice to generate double-transgenic mice (RS), in which podocyte proliferation can be activated by doxycycline (Dox). RTA mice (R) served as controls. After a single puromycin injection, doxycycline was initiated on P7 until P8. By P18, mice under Dox (UN) and were started on a high salt diet. At 14 weeks of age, angiotensin II (Ang II) was given by minipump for the next 8 weeks. All mice were sacrificed at week 22.

Results: At week 3, there were more WT positive glomerular cells in RS than R mice (RS 10.34±4.1 vs. R 8.15±0.58 X10^3/mm^2, p<0.05), while glomerular in superficial cortex were less more (RS 2.13±0.05 vs. R 2.32±0.06, maturity scale 1-3, p<0.05). At week 6, glomerular number increased in RS (RS 909±2.6442 vs. R: 962±1.2447, kidney, P<0.05). Glomerular volume and albuminuria did not differ between groups at week 3 and 6. At week 22, after UN, high salt and Ang II, blood pressure, albuminuria and GFR were similar in both RS and R. However, RS mice had lower K/WBW ratio (RS 0.97±0.143 vs. R 1.263±0.041, p<0.05) and less mesangial expansion (0-4 scale) (RS 0.72±0.10 vs. R 1.14±0.14, p<0.05).

Conclusions: We conclude that increasing podocyte number in kidney development rescues puromycin-induced loss of glomerular growth, which in turn reduces renal injury following a second hit in adulthood.

PUB281

Exploring Ciliopathies – Cep164Tissue Expression in a Murine Model Simon Ramsbottom, Shalash Srivastava, Colin Miles, John Andrew Sayer. Dept of Genetic Medicine, Newcastle upon Tyne, United Kingdom.

Background: Nephronophthisis (NPHP) is the major cause of paediatric renal failure, yet the disease remains poorly understood, partly due to the lack of appropriate animal models. Joubert Syndrome (JBS) is an inherited ciliopathy giving rise to NPHP and neurodevelopmental abnormalities and mutations in CEP164 are one of the known genetic causes. Clinical phenotypes of patients with CEP164 mutations include NPHP with retinal degeneration and cerebellar vermis aplasia. In cultured cells CEP164 localises to centrosomes as well TIP-60 positive nuclear foci, and CEP164 has an established role in DNA damage response signalling. However, there has been no previous documentation of CEP164 spatial expression during development.

Methods: We have recently acquired heterozygous Cep164 mice from the International Mouse Phenotyping Consortium (MRC/Harwell) (B6NTac: B6-Cep164^+/-; C57BL6N). We used these animals for tissue expression studies, including X-gal staining for beta-galactosidase and whole embryo. Homozygote Cep164 animals had 100% perinatal lethality.

Results: In heterozygote Cep164 animals, specific X-gal staining representative of beta-galactosidase adults and whole embryo. Homozygote Cep164 animals had 100% perinatal lethality.

Conclusions: These data support a role for Cep164 in multiple organs throughout development and explain the wide phenotypic spectrum of JBS mutations in man.

PUB282

Specific Deletion of Early B Cell Factor 1 from Podocytes Does Not Recapitate the Developmental Defects Observed in the Globally Deficient Animals but Does Provide Protection from Injury Jackie A. Fretz, Tracy Nelson, Li Li. Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT.

Background: Globally deficient mice lacking the transcription factor Ebf1 (Ebf1 KO) are extremely sick owing to the multiple functions of Ebf1 across the body. We recently described a novel function of Ebf1 as an essential component of the latest stages of mesenchephalic development. Mice globally deficient in Ebf1 have impaired formation of peripheral glomneruli and a thinned cortex. Within the kidney Ebf1 is present within multiple cell types including distinct tubular epithelium, interstitial pericytes, glomerular mesangium, and podocytes. This investigation aimed to identify if the actions of Ebf1 in the podocyte were driving the developmental defects present in the global knockout.

Methods: In this study we made a specific deletion of Ebf1 within the podocytes using the podocin-driven cre mouse. These were mated with mice where the 3rd exon of Ebf1 (encoding part of the DNA-binding domain) is flanked by flox sites. This is the same genetic trap that is excised in the global knockout, and injury was also performed on 3 month old animals (100mg/kg, IP daily for 4 weeks).

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Results: Restricted deletion of Ebf1 from podocytes did not result in any observable decrement in GFR evaluated at the functional and histological level, glomerular number, and glomerular development were unchanged regardless of genotype. The mice were followed for up to 6 months. During this time renal function did not decline in the mice with podocyte-specific deletion of Ebf1, and in fact baseline proteinuria was reduced in Podc-eCre+/Ebf1−/− animals compared to littermate controls. To examine if Ebf1-deficient podocytes harbored differential response to injury 3 month old animals were subjected to BSA-overload and exhibited reduced proteinuria.

Conclusions: Taken together these results suggest that Ebf1 regulates metanephric development through other cell types than the podocyte. While Ebf1 does not control glomerular development through its actions in the podocyte, it appears to participate in proper damage response by podocytes as its removal appears to be protective.

Funding: NIDDK Support

### PUB283

Remote Ischemic Preconditioning and Pharmacological Treatment in Prevention of Renal Damage in Experimental Diabetics

Marcelo Rodrigues Bacci, David Feder, Fernando Luiz Affonso Fonseca, Matheus Polly, Jaqueline Victoria Ciancaglini, Giuliana Petri, Guilherme Zaremba. ABC Medical School, Brazil.

**Background:** The main features of diabetic nephropathy are glomerular hypertrophy, thickening of the basal membrane, tubular atrophy, interstitial fibrosis and nodular and focal glomerulosclerosis. Remote ischemic preconditioning (RIPC) is a procedure that generates a brief period of ischemia followed by reperfusion. Its role in preventing glomerular and tubular changes is still under debate. The aim of the study was to evaluate the nephroprotective effect of RIPC in a diabetic rat model.

**Methods:** Five groups of 10 Wistar male rats were formed: control without diabetes; untreated diabetes; diabetes treated with pharmacological treatment (PT); diabetes with RIPC and diabetes with RIPC and PT. For the induction of diabetes, alloxane was infused intra-arterially at a dose of 160mg/kg; PT consisted of daily use of metformin (250mg/kg) and valsartan (30mg/kg). RIPC was performed with an external tourniquet placed on the back leg for three 5-minute rounds alternated with the same rounds of reperfusion, resulting in a total duration of 30 minutes. This was performed every week on all mice in RIPC groups. All mice were kept in a biological cage with controlled temperature and humidity and routine feeding. Blood and urine samples were collected weekly to evaluate serum glucose, creatinine and urine albumin levels and albumin/creatinine urine ratio (ACR). At the end of the observation period, animals were sacrificed and their kidneys were biopsied for microscopic analysis.

**Results:** Animals subjected exclusively to PT showed a significant reduction in serum and urine glucose levels but these reductions were not greater in the group that underwent RIPC in addition to PT. There were no significant differences in creatinine level between any of the groups but ACR was significantly reduced in all treated animals compared to controls. Tubular atrophy was observed in all diabetic rats and was greatest in the untreated group.

**Conclusions:** PT was more effective at reducing ACR and tubular atrophy than RIPC. RIPC alone or in combination with PT did not cause the expected effect of preventing histological and urinary abnormalities.

Funding: Government Support - Non-U.S.

### PUB284

Cross Talk Between TLR4 Signaling and Angiotensin II Induces Pathophysiological Changes in Human Tubular Epithelial Cells Under High Glucose Conditions.

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**Background:** To investigate the cross talk between TLR4 and angiotensin II by observing the expression of TLR4 in tubular epithelial cells under high glucose conditions, and observe the changes of fibrogenic and inflammatory factors in human renal tubular epithelial cells, revealing the innate immune pathogenesis in diabetic nephropathy.

**Methods:** Cells were divided into five groups after cultivated with normal glucose medium: 1.normal-glucose group, 2. mannitol group, 3. AngII group, 4. high-glucose group (25mmol/L), 5. high-glucose+Irsbasetin group, extract total RNA and total protein after 24 hours. Real time PCR was used to analyze the expressions of TLR4, MyD88, HSP70 and HSP47, cis-RNA, western blot was used to observe the expressions of TLR4, MyD88, NF-κB, CoV4, HSP77 protein, analyze the effect of high-glucose and AngII to TLR4 / MyD88 / NF-κB signaling pathway.

**Results:** Compared with normal group, TLR4, MyD88, HSP47 mRNA and TLR4, MyD88, NF-κB, CoV4, HSP77 protein were highly expressed under high glucose condition and after AngII stimulate (p<0.01). The expression of IL-6 and MCP-1 also increased (p<0.01). Compared with Hg group, the expression of TLR4, MyD88, HSP47 mRNA and TLR4, MyD88, NF-κB, CoV4, HSP77 in the high-glucose+Irsbasetin group were significantly reduced (p<0.01). The difference of above indicators between the negative transfected group and high-glucose group and AngII group were statistically significant (p<0.05). The expression of IL-6 and MCP-1 in the group that cells were transfected with TLR4-siRNA also reduced (p<0.01).

**Conclusions:** Cross talk between angiotensin II and TLR4 can up-regulate the expression of inflammatory factors and fibrogenic factors in HK-2 cells. Irsbasetin can block the activation of TLR4 signaling pathway induced by high glucose and angiotensin II. TLR4 signaling pathway is the major pathway induce the release of inflammatory and fibrogenic factors in tubular epithelial cells under high glucose conditions.

Funding: Government Support - Non-U.S.

### PUB285

Possible Renoprotective Effects of Acetazolamide Administration in Obese Diabetic Mice with Nephropathy

Yusho Nakayama, Koji Eguchi, Terumasa Nakagawa, Tomoaki Onoue, Yuichi Izumi, Hideki Inoue, Yutaka Kakinose, Takashige Kawabara, Masashi Mukoyama. Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.

**Background:** Administration of carbonic anhydrase inhibitors (CAI) is thought to decrease glomerular filtration rate (GFR) by activation of the tubuloglomerular feedback (TGF) system. Acetazolamide (ACZ), a major CAI, has been shown to decrease urinary albumin excretion in the patients of type 1 diabetes with nephropathy. Previously, we showed that ACZ treatment in mice could ameliorate the onset of diabetic nephropathy due to the reduction of intraglomerular pressure by activating the TGF system.

**Methods:** In the current study, we treated obese diabetic mice (KK-Ay/Tacl) with ACZ for 14 weeks, and evaluated the long-term effects on urinary albumin excretion and glomerular hyperfiltration.

**Results:** The blood glucose levels were significantly higher in KK-Ay/Tacl mice compared to the control mice (BALB/c/Avi) at 14 weeks. The blood glucose levels were significantly reduced in KK-Ay/Tacl mice treated with ACZ (547±37 vs 250±75 mg/dl). Interestingly, urinary glucose excretion levels in the ACZ group were not significantly different compared to the non-treated group. Creatinine clearance was higher in KK-Ay/Tacl treated group, which was not changed by ACZ (0.73±0.07 vs 0.69±0.15 ml/min) (Figure A). Urinary albumin excretion was reduced with ACZ treatment by 29% (Figure B). The plasma renin activity was not reduced by ACZ in this model.

**Conclusions:** These results suggest that the long-term oral treatment with ACZ may exert renoprotective effects in obese diabetic models with nephropathy, not due to activation of the TGF system but to better glycemic control.

Funding: Government Support - Non-U.S.
Infection Control, Kanazawa Univ, Kanazawa, Japan; 1 Diabetic Nephropathy Lab, Baruch Padeh Poriya M Cie, Lower Galilee, Israel.

**Background:** Diabetic nephropathy (DN) is the most common renal complication of diabetes. Diabetes increases oxidative stress and promotes iron deposition in proximal convoluted tubules (PCT) of the kidney, leading to renal damage. Mutations in the LEP (ob) gene product lead to severe obesity and type 2 diabetes, and ob/ob mice in BTBR background develop severe diabetic nephropathy. Klotho and vitamin D receptor (VDR) have been shown to involve in renal protection against diabetic injury. The goal of this study is to assess the relationship between iron deposition and klotho and VDR expression in the kidney of ob/ob mice.

**Methods:** One- and three-month old ob/ob BTBR mice and ob/+ control mice were studied in parallel. After sacrifice, the kidneys were harvested. The expression of a-klotho, VDR, and Cyp27b1 was examined by immunohistochemistry, Western blotting, and qRT-PCR, and iron deposition was assessed by staining with Perl’s enhanced with DAB.

**Results:** Compared with ob/+ mice, ob/ob BTBR mice showed increased iron deposition in the PCT and decreased expression of a-klotho, VDR, and Cyp27b1 in the renal PCT and kidney lysates.

**Conclusions:** In ob/ob BTBR mice, increased iron deposition in the renal PCT is associated with a decrease in klotho expression, vitamin D hormone synthesis and VDR signaling in the PCT. These changes together contribute to the progression of diabetic renal injury in these mutant mice, and future treatments.

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**Underline represents presenting author.**

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**PUB287**

**Increased Iron Deposition Is Associated with Decreased a-Klotho and Vitamin D Receptor Expression in the Renal Proximal Tubules in Ob/Ob Mice**

Farid M. Nakhoul,1 Deb Dilip,1 Inbal Dahan,2 Lei Li,1 Yan Chun Li.1 1 Dept of Medicine, Biological Sciences Div, Univ of Chicago, IL; 2 Diabetic Nephropathy Lab, Baruch Padeh Poriya M Cie, Lower Galilee, Israel.

**Background:** Diabetic nephropathy is the most common renal complication of diabetes. Diabetes increases oxidative stress and promotes iron deposition in proximal convoluted tubules (PCT) of the kidney, leading to renal damage. Mutations in the LEP (ob) gene product lead to severe obesity and type 2 diabetes, and ob/ob mice in BTBR background develop severe diabetic nephropathy. Klotho and vitamin D receptor (VDR) have been shown to involve in renal protection against diabetic injury. The goal of this study is to assess the relationship between iron deposition and klotho and VDR expression in the kidney of ob/ob mice.

**Methods:** One- and three-month old ob/ob BTBR mice and ob/+ control mice were studied in parallel. After sacrifice, the kidneys were harvested. The expression of a-klotho, VDR, and Cyp27b1 was examined by immunohistochemistry, Western blotting, and qRT-PCR, and iron deposition was assessed by staining with Perl’s enhanced with DAB.

**Results:** Compared with ob/+ mice, ob/ob BTBR mice showed increased iron deposition in the PCT and decreased expression of a-klotho, VDR, and Cyp27b1 in the renal PCT and kidney lysates.

**Conclusions:** In ob/ob BTBR mice, increased iron deposition in the renal PCT is associated with a decrease in klotho expression, vitamin D hormone synthesis and VDR signaling in the PCT. These changes together contribute to the progression of diabetic renal injury in these mutant mice, and future treatments.

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**PUB288**

**Erythropoietin Protects Endothelial Cells from High Glucose Induced Injury**

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**Background:** Diabetic nephropathy (DN) is a major cause of end stage kidney disease and a strong risk factor for cardiovascular diseases. High glucose induces endothelial injury in vasculature, resulting in tissue injury in diabetic condition. Chronic inflammation has been reported to play an important role for the progression of high glucose induced cell injury. Growing data showed that erythropoietin (EPO) protect the tissues from some kind of injury, such as hypoxia and mechanical stress. However, the contribution of EPO to high glucose induced the aberrant immune balance remains to be explored. Therefore, we hypothesized that EPO modulates endothelial cells from high glucose (HG) induced injury via the regulation of inflammatory and anti-inflammatory balance.

**Methods:** To explore this possibility, we performed genome-wide transcriptome profiling in human umbilical vein endothelial cells (HUVEC), which were stimulated by high glucose (HG) with/without EPO treatment and detected the expression of inflammation associated genes.

**Results:** Hierarchical clustering and principal component analysis showed the different pattern of mRNA expression in HG stimulated HUVEC with/without EPO. While inflammation related cytokines/chemokines mRNA expression was increased in the HG stimulation in HUVEC, Th2 related cytokine receptors and intracellular signaling molecules showed the reduced mRNA expression levels. EPO treatment reduced inflammatory cytokines/chemokines mRNA expression and increased Th2 related cytokine mRNA expression levels. Real-time PCR analysis confirmed the increased expression of inflammatory related genes, those were decreased in HG stimulated HUVEC with EPO treatment. Moreover, EPO stimulation increased mRNA expression of EPO receptor and b-common receptor. EPO signaling affect neither cell proliferation nor cell death.

**Conclusions:** Taken together, EPO signaling might protect high glucose induced cell injury by the regulation of immune balance.

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**PUB289**

**The Possible Mechanisms of Ameliorating Diabetic Mice Renal Insulin Resistance by Nf-xb Inhibitor Parthenolide**

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**Background:** Diabetic nephropathy (DN) was the severe complication of Diabetes Mellitus (DM). The treatment of DN was limited. Insulin resistance was linked with diabetic complications. The concrete forms of insulin resistance in diabetic renal tissue lacked research. AS160 could regulate the transportation of many transporters including glucose transporters. In kidney, AS160 was found can regulate sodium and water channel protein, while its role on glucose transporters has not been reported. Glucose transporter 4 (GLUT4) was an important effer of insulin signaling, which related to insulin resistance closely. Sodium glucose transporter 2 (SGLT2) and sodium glucose transporter 1(SGLT1) were important to promote renal tubular glucose re-absorption and were the new target of anti-diabetic drug. Our previous results showed NF-xb inhibitor Parthenolide (PTN) could improve db/db mice systemic insulin resistance and renal tissues injury. The aim of the study was to study the expression of AS160 and GLUT4 in diabetic kidney tissue and correlation between AS160 with GLUT4 and SGLT2/SGLT1.To explore whether PTN could improve renal IR and the possible mechanisms.

**Methods:** Set up db/m mice as control group, the db/db mice as diabetic nephropathy model group and db/db mice with PTN intervention as treatment group. The mice were sacrificed at week 8, 12, 16 and 20 and using blood, urine and kidney specimens for the study.

**Results:** 1) The db/db mice showed increased body weight, blood cholesterol, blood glucose and insulin, as well as glomerular hypertrophy and the increased mesangial matrix. PTN could improve the systemic insulin resistance and renal pathological changes of db/db mice. 2) AS160 and p-AS160, GLUT4 were all mainly expressed in renal tubules.3) The expression of p-AS160 and GLUT4 reduced gradually in db/db mice kidney with the increase of weeks.4) p-AS160 showed co-expression with part of GLUT4, but no significant co-expression with SGLT2/SGLT1.

**Conclusions:** The diabetic kidney tissue may have insulin resistance resulted from abnormal glucose transport by AS160 and GLUT4. The NF-xb inhibitor improved kidney insulin resistance may by increasing the expression of p-AS160 and GLUT4.

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**PUB290**

**Hypertension Results in Moderate Diabetic Nephropathy in a Mouse Model of Metabolic Syndrome**

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**Background:** Diabetic nephropathy (DN) is a major complication in metabolic syndrome/diabetes patients. We have developed a metabolic syndrome mouse model characterized by non-alcoholic steatohepatitis and atherosclerosis upon high fat diet feeding. These animals show mild renal changes, but don’t progress to moderate DN. Therefore, we investigate whether inducing hypertension on top of metabolic syndrome leads to progression of DN.

**Methods:** Male LDL−/− mice (8 wk old) received high fat (45%) + high salt (6%) diet for 6 wk. To induce hypertension, combinations of several pro-hypertensive components were used (enemiphrine/isox, angiotensin II (ANGII), DOCA and a vasoconstrictor) for an additional 10 wk. At regular intervals, systolic blood pressure (SBP), 24h diuresis and albumin/creatinine ratio (UACR) were assessed. 17 wk after start diet, mice were terminated and renal injury was scored. We used age-matched chow fed animals as controls.

**Results:** Cholesterol and diuretics were significantly elevated in all groups vs chow from wk 5 onwards. ANGII induced a 20 mmHg increase in SBP at wk 13 vs. chow. At wk 8, UACR was significantly increased by ANGII in combination with HFD+HS (264±303 µg/mg) and UNX+HFD+HS (438±781 µg/mg) vs chow (62±24 µg/mg). At wk 13, ANGII further elevated UACR in HFD+HS (593±377 µg/mg) but decreased it in UNX+HFD+HS (87±28 µg/mg). Combining the metabolic syndrome/diabetes model with hypertensive components (717±585 µg/mg) at wk 5 but also caused fatal thoracic bleedings. This group was terminated at wk 11. Renal injury score showed glomerular hypertrophy, mesangium expansion, nodular glomerulosclerosis, mild hyalination and micro-aneurisms.

**Conclusions:** We show that LDL−/− mice fed HFD+HS and ANGII induces hypertension and mild progressive DN, in addition to NASH and atherosclerosis in a single
model providing broad coverage of metabolic syndrome complications. Administration of additional hyperglycemic agents (DOCA and NNA) further aggravated the model but also led to early fatal thoracic bleedings thus precluding further studies.

**Funding:** Government Support - Non-U.S.

PUB293

**Renal Functional and Morphological Changes Related to Obesity and Hyperglycemia in Göttingen Minipigs**

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**Background:** Obesity and diabetes, two major health problems worldwide, both lead to renal functional and morphological changes; with diabetic nephropathy being the leading cause of end-stage renal failure. A large animal model displaying human-like features of obesity-related and diabetic nephropathy would be very valuable to study pathogenesis and effects of new drug candidates on these syndromes. The aim of the present study was to evaluate renal function and morphology in diet-fed obese, atherosclerotic Göttingen minipigs with or without mild diabetes.

**Methods:** Male castrated Göttingen minipigs, aged 8 weeks at study start, were fed normal chow (n=6) or high-fat, high-cholesterol diet (n=16) for 43 weeks. Mild diabetes was induced in 11 pigs after 18 (n=6) and 25 (n=5) weeks of diet-feeding, using streptozotocin (125 mg/kg IV) preceded by nicotineamide (67 mg/kg IV). The study included two cohorts. Parameters of interest were: Body fat percentage (BF) estimated by dual-energy X-ray absorptiometry, inulin clearance (IC), kidney resistive index (RI), plasma fructosamine reflecting plasma glucose (FRA), plasma urea, plasma creatinine (PCr), plasma total cholesterol (TC), urinary protein excretion (protein (UPCr) and albumin (UACr) adjusted for creatinine). Glomerulus area and number of nuclei/glomerulus area were estimated post mortem. Influence of BF, TC and FRA on in vivo kidney function and post mortem kidney changes was evaluated using ANOVA with cohort as fixed covariate. BF was positively associated with urea (P<0.01), IC (P<0.05), Glomerulus area (P<0.001) and UPCR (P<0.05), and negatively with PCr (P<0.001). FRA was positively associated with UACr (P<0.05) and number of nuclei/glomerulus area (P<0.05). RI was not associated with BF, TC or FRA.

**Conclusions:** In conclusion, functional and histological renal changes were found in diet-fed obese, atherosclerotic Göttingen minipigs with and without mild diabetes. The changes were associated with obesity and hyperglycemia.

**Funding:** Pharmaceutical Company Support - Novo Nordisk A/S

PUB294

**Activation of Toll-Like Receptors Through Fetuin-A Leads to an Inflammatory Response in Podocytes and Exacerbates Palmitic Acid-Induced Cell Death**

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**Background:** Inflammation participates in the pathogenesis of type 2 diabetes and contributes to diabetic nephropathy (DN). There is growing evidence that chronic elevated free fatty acids (FFAs) contribute to this chronic inflammatory milieu. Studies in pancreatic β-cells suggest that the inflammatory response mediated by FFAs depends on toll-like receptor (TLR) 4 and TLR-1 receptor (II-1R). The signaling pathways of TLRs and II-1R involve activation of the transcription factor nuclear factor-κB (NF-κB) which induces a wide range of cytokines/chemokines including monocyte-chemoattractant protein-1 (MCP-1), and II-1. Here, we addressed whether fetuin-A together with FFAs leads to an inflammatory response in podocytes and whether this exacerbates palmitic acid-induced podocyte death.

**Methods:** Conditionally immortalized murine podocytes were used. Murine and bovine fetuin-A were used alone or in combination with palmitic acid complex to BSA. MCP-1 was measured by ELISA. Podocyte death was determined by flow cytometry (annexin V and propidium iodide staining).

**Results:** Palmitic acid alone did not, but fetuin-A induced MCP-1 in podocytes and this was further increased by palmitic acid. The MCP-1 release was prevented by CI095 (TLR4 blocker). Fetuin-A or LPS exacerbated palmitic acid induced podocyte death, and CI095 as well as the IL1 receptor antagonist anakinra or an anti II-1β antibody attenuated cell death.

**Conclusions:** Fetuin-A alone and in combination with palmitic acid leads to an inflammatory response in podocytes and promotes palmitic acid induced podocyte death. As inhibition of TLR4 as well as II-1 prevents these effects, both pathways are promising targets to attenuate the progression of DN.

**Funding:** Other NIH Support - Swiss National Science Foundation Grants 31003A- 144112/1, Pharmaceutical Company Support - Gottfried and Julia Bangerter-Rhyner-Stiftung, unrestricted grant.

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PUB295

**IL-1β Mediates the High Glucose Induced Endothelial-to-Mesenchymal Transition in Human Aortic Endothelial Cells**

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**Background:** Studies have shown that endothelial-to-mesenchymal transition (EndMT) induced by high glucose (HG) contributes to cardiovascular disease. Additionally, proinflammatory cytokine interleukin-1β (IL-1β) has been implicated as one of the dominant players in the development of fibrosis and diabetic heart. In vitro studies, retinal endothelial cells(ECS), human intestinal ECS and human dermal ECs have been reported to undergo EndMT by

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IL-1β stimulation. Interestingly, most IL-1β immunoreactivity is localized to endothelial cells of mesenterial microvessels. In an animal model of cardiac hypertrophy, however, the potential role of IL-1β in high glucose induced EndMT remains unknown. Here, we hypothesize that IL-1β might mediate the process.

Methods: Primary human aortic endothelial cells (HAECs) were divided into three groups: a normal glucose (NG) group, a high glucose (HG) group, and anti-interleukin1β (IL-1β) antibody treated (HG+Anti-IL-1β) group. The concentration of IL-1β in the supernatant was detected by ELISA. Pathological changes were investigated using fluorescence microscopy and electron microscopy. Immunofluorescence staining was performed to detect the co-expression of CD31 and FSP1. The expressions of FSP1 and α-SMA were significantly increased in the expression of EndMT (P < 0.05). Double staining of the HAECs indicated a colocalization of CD31 and FSP1, while treatment with anti-interleukin1β/anti-HLA-DR siRNA attenuated the expression of EndMT (P < 0.05).

Conclusions: These findings suggest that IL-1β mediates the HG induced EndMT, which was inhibited by anti-interleukin1β/anti-HLA-DR siRNA treatment.

PUB296

Serum Bilirubin and Asparagine Aminotransferase Concentrations Predict Loss of Renal Function in Type 2 Diabetes

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Background: Higher serum bilirubin concentration is reported to slow the progression of nephropathy in type 2 diabetes. We examined associations of serum bilirubin and asparagine aminotransferase (AST) concentrations with renal function loss (RFL) in a post-hoc analysis of a clinical trial of renoprotection with losartan in Pima Indians with type 2 diabetes (ClinicalTrials.gov, number, NCT00340678). Methods: Serum bilirubin and AST were measured at baseline in 168 subjects who underwent annual measurement of GFR by the urinary clearance of iothalamate. RFL was defined by ≥40% decline in GFR from baseline. Cox regression was used to compute hazard ratios (HRs) for the association of a 1 standard deviation (SD) increment in bilirubin and AST concentrations with RFL adjusted for age, sex, treatment group, HbA1c, GFR, and urinary albumin/creatinine ratio (ACR). The sum of standardized AST and bilirubin was used to create a liver index (P<0.001) and a serum AST (HR=1.39) predicted RFL. The combination of these liver function tests provided the strongest prediction (HR=1.52).

Conclusions: Higher serum bilirubin and AST concentrations predict loss of renal function in Pima Indians with type 2 diabetes.

Funding: NIDDK Support

PUB297

Baseline Data from the Multinational Prospective Cohort Study in Patients with Type 2 Diabetes for Validation of Biomarkers (PROVALID)

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Background: We recruited 4065 subjects at the primary healthcare level in Austria, Hungary, Netherlands, Poland and Scotland, who will be treated according to local practice and followed for 4 years to compare the incidence and progression of renal and cardiovascular disease between the countries. Additionally extensive biobanking is performed.

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Underline represents presenting author.

PUB298

FGF-23 and Magnesium Are Independent Risk Factors for an Increased Albumin-to-Creatinine Ratio in Type 2 Diabetics with Chronic Kidney Disease

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Background: Microalbuminuria is the earliest sign of glomerular involvement in diabetes mellitus. The multiple physiological mechanisms involved are complex and not completely understood. Recently, it appeared that fibroblast growth factor-23 (FGF-23) and magnesium play a role in the emergence and maintenance of albuminuria in type 2 diabetes. The aim of this study is to investigate the role of FGF-23 and magnesium in relation to the urine albumin-to-creatinine ratio in type 2 diabetics with chronic kidney disease (CKD) stages 2-4.

Methods: In a cross-sectional study we included all eligible type 2 diabetic patients with CKD stage 2-4, followed in our outpatient Diabetic Kidney Clinic. We included 150 patients, 53±5 years, with a mean age of 66±6.9 years (40-85) and a mean follow-up of 76 months. We used descriptive statistics, the Student’s t, ANOVA and the chi-square test. We divided our population according to the urine albumin-to-creatinine ratio (CI=30-300 mg/g and G2≥300 mg/g) and compared these groups regarding the several biological and laboratory parameters analyzed. We employed a multiple regression model to identify risk factors of increased urine albumin-to-creatinine ratio. In this model we used the urine albumin-to-creatinine ratio as the dependent variable and as independent ones age, duration of diabetes, systolic blood pressure, HgA1c, eGFR, HOMA-IR, manoncalehyd, hs-CRP and 1,25(OH)3D3 levels.

Results: The patients in G2 displayed a lower eGFR (p=0.0001) and magnesium (p=0.004) levels, as well as higher levels of FGF-23 (p=0.043) compared to patients in G1. In the multivariable linear regression model we found adjusted β=-0.060 (p=0.001) and the magnesium (β=-8.916,p=0.0001) are independent risk factors for increasing the urine albumin-to-creatinine ratio.

Conclusions: The present study shows that a dysregulation of mineral metabolism, reflected by altered levels of magnesium and FGF-23, correlates with an increased urine albumin-to-creatinine ratio in type 2 diabetic patients with CKD stages 2-4.

Results: We found that G2 patients showed higher age (p=0.017), phosphorus (p<0.001), IPTH (p<0.0001), urine albumin-to-creatinine ratio (p=0.001), Homa-IR (p<0.001), FGF-23 (p<0.0001) and OxlDL (p=0.0001) and lower levels of eGFR (p<0.0001), Klotho (p=0.0001) and 1.25(OH)2D3 (p<0.0001). In the multivariate linear regression model we found that FGF-23 (β=0.337, P=0.047) and the Klotho (β=-0.367, P=0.023) are independent risk factors for increasing the pulse pressure.

Conclusions: In conclusion, in a population of type 2 diabetic with chronic kidney disease stages 2-3, the Klotho and FGF-23 levels are independently associated with PP. Further studies with more patients are warranted to confirm whether an increase in Klotho and a decrease in FGF-23 would reduce the PP and consequently the cardiovascular risk of our patients.

Funding: NIDDK Support

PUB300
Prediction of Renal Outcome in Type 2 Diabetic Dephropathy by Estimating GFR from a Combination of Serum Creatinine and Cystatin C

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Background: Serum cystatin C is an alternative to serum creatinine for estimating glomerular filtration rate (GFR), however, the utility of estimated GFR from combination of serum creatinine and cystatin C as marker to predict long-term renal outcome is uncertain, particularly in the Type 2 diabetic nephropathy (DN).

Methods: A total of 501 patients (The National Clinical Research Center of Kidney Diseases, 2003-2011) were recruited in prospective cohort study. Follow-up was 5-year. Renal outcome was defined by eGFRcre-cys<15 ml/min per 1.73m2 or renal replacement therapy.

Results: The distributions of standardized serum cystatin C with eGFRcre and eGFRcre-cys are shown in. Kaplan-Meier curves showed significantly increased renal end points with higher quartile of cystatin C (p<0.001) and lower eGFRcre-cys (p<0.001). The highest AUC values was eGFRcre-cys in predicting the renal endpoint compared with eGFRcre or eGFRcre-cys. The best cut-off value for predicting the renal endpoint was 29.28% decline in the 24-month, which value showed 79.6% sensitivity and 82.6% specificity. Cystin regression models with restricted cubic splines were shows a change of -30% in eGFRcre-cys was associated with adjusted HRs for ESRD of 27.92 (95%CI, 3.95-197.48) over 2-year.

Conclusions: eGFRcre-cys was a precision, and accuracy marker in the predicting the renal outcome and 30% decline of eGFRcre-cys over 2 years was strongly associated with the risk of ESRD, suggesting it could be used as an alternative end point in T2DN.

Funding: Government Support - Non-U.S.

PUB301
Prevalence and Prognostic Role of Uncontrolled Risk Factors in Diabetic CKD (DM-CVKD) Treated in Nephrology Clinics

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Background: Knowledge of prognosis of DM-CVD mainly derives from RCTs and cohort studies followed in the diabetology setting. Epidemiologic features are less defined in patients with overt disease managed in renal clinics.

Methods: We studied 763 DM-CKD patients derived from 3 prospective cohorts that in 2000-2010 enrolled 2,488 CKD patients stage III-V under stable care from 24 months in 40 RCTs and renal clinics. Endpoints were ESRD (chronic dialysis-transplant) and first major cardiovascular (CV) events (fatal and non fatal) assessed through 12/2014. Uncontrolled risk factors were defined as high blood pressure (BP<140/90 or >130/80 if proteinuria >0.15g/24h), HbA1c<7.5%, hemoglobin<10.5 g/dL, serum phosphorus (P)<4.5 mg/dL, LDL)<100 mg/dL or according to ESC 2012 guidelines, proteinuria (Urprot<0.5 g/24h).

Results: HbA1c was 6.9%, (IQR 5.9-7.8), Uprot 0.5 g/24h (IQR 0.1-1.4), P 3.9±0.8 mg/dL, Hb 12.3±1.7 g/dL and BP 142±19/88±11 mmHg. During follow-up (43 months, IQR 21-56), 171 ESRD and 170 CV events occurred (incidence rate 6.4 and 6.9/100 pt/y), Multivariable Cox analyses for ESRD and CV risks (HR, 95% CI) stratified by cohort are in the Table.

Conclusions: Epidemiologic peculiarities emerge in DM-CKD patients treated in renal clinics. This information can be helpful to optimize risk stratification and adequately design RCTs.

Funding: NIDDK Support

Pub302
Serum NGAL and Cystatin C Accuracy in Early Detection of Kidney Dysfunction in Type 2 Diabetes

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Background: Diabetic nephropathy is associated with specific histological changes. An early detection of depletion of glomerular and tubular function can be done with biomarkers of diabetic disease. The aim of this study is to evaluate the accuracy of early kidney dysfunction biomarkers in diabetes.

Methods: Patients with diabetes were split according to their levels of glycated hemoglobin (GHB) greater than or equal to 8% or below this value. Urine samples were taken to measure cystatin C(s/CYS) and NGAL beta-trace protein(uBTP) and albuminuria (ACR). In blood, sCYS and sNGAL were measured. Patients with stage end renal disease or in dialysis were not included. Blood samples were used to evaluate the risk of renal dysfunction according to their simplified MDRD estimated glomerular filtration rate(eGFR), Spearman’s correlation and regression models were built to evaluate the markers.

Results: Ninety patients with diabetes were recruited. The mean eGFR was 79.1ml/min/1.73m2. The group of s/CYS was positively correlated with creatinine (p<0.001), eGFR (p<0.001) and uBTP (p=0.01). The ROC curve showed value of 0.635 for s/CYS, 0.621 to sNGAL and 0.660 for ACR. Urine had lower values for CYS(0.595), 0.526 for NGAL and 0.567 for uBTP. The crude logistics regression model observed a positive association between sCYS and sNGAL with GFR. The proposed regression model showed positive association with sCYS and creatinine and eGFR (p<0.001) but not with GHB (p=0.892). ACR showed the same parameters (p=0.005 for creatinine and 0.018 to eGFR).

Conclusions: In this study a comparative panel of tubular and glomerular dysfunction markers was built in diabetics with eGFR<60.There was a worse performance of the marker in urine except for ACR that had the best value in ROC analysis. The sCYS and sNGAL presented the best association with worse GFR and glomerular control. In another study of our group uBTP had better performance to distinguish early kidney dysfunction between diabetes and non diabetics. Finally, with worse eGFR, sNGAL, sCYS and ACR performed better in diabetics. A worse glycemic control was positively associated with sCYS and nNGAL.

Funding: NIDDK Support

Pub303
Comparison of Renal Outcome Between “Chronic Kidney Disease due to Diabetes” and “Chronic Kidney Disease with Diabetes” in Gyoro Study

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Background: Diabetic nephropathy (DN) is defined as chronic kidney disease (CKD) due to diabetes mellitus (DM) in a narrow sense. The difference is not unclear between DN and CKD patients of other cause but complicated DM (CKD with DM) in clinical outcome. This study mentioned the clinical difference and renal outcome of DN, CKD with DM, and CKD without DM.

Methods: This is a part of Gyoro CKD study. It is the multicenter prospective observational survey for 5 years. From May 2006, 4,015 patients were registered. We included 2,484 of them into this analysis who could classify to DN (n=249), CKD with DM (n=448), and CKD without DM (n=1,787). The classification was performed at registration by clinical finding and history of other diabetic complication such as retinopathy if case without kidney biopsy.

Results: The characteristics of age, gender, systolic blood pressure (SBP), and dyslipidemia in “DN” (66.6 y.o., male 67.7%, sBP 136.6mmHg, dyslipidemia 50.1%) and “CKD with DM” (58.7 y.o., male 58.7%, sBP 132.3mmHg, dyslipidemia 54.4%) were similar compared with “CKD without DM” (50.5 y.o., male 50.5%, 128.9 mmHg, 40.1%). For renal outcome analysis of each CKD stage was performed. The hazard ratio of “DN” was significantly higher than “CKD without DM” and “CKD with DM” (1.36(1.24-2.69), 95% CI, G4 2.34(1.35-4.39), G5 1.67(1.16-2.42), On the other hand, that of “CKD with DM” didn’t elevate in G3 (0.89(1.94-4.29, 95% CI), G4 2.10(1.66-2.23), G5 1.30(0.74-2.51) compared with “CKD without DM”. Kaplan-Meier analysis revealed G3 and G4 in “DN” showed significantly poor outcome. The evaluation of annual decline of eGFR revealed stage G3b in DN was the largest, (-3.7 ml/min/1.73m2/2 year).

Conclusions: Renal risk between “CKD with DM” and “DN” was completely different. G3b was most important critical point in renal prognosis of DN.

Funding: Clinical Research Support

Publication Only

Underline represents presenting author.

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Prevalence of Proteinuria, Albuminuria and Associated Factors in Obese Patients Undergoing Bariatric Surgery

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Background: Obesity is associated with proteinuria. But the exact prevalence of proteinuria or albuminuria with and without additional risk factors in obese patients is unclear.

Methods: Consecutive patients undergoing bariatric surgery were included in study. Participating patients had a urine sample for protein creatinine ratio and albumin creatinine ratio prior to their surgery. We defined a positive protein to creatinine ratio as greater than or equal 300 mg and a positive albumin to creatinine ratio as greater than or equal to 30 mg. Associated factors such as diabetes mellitus (DM), hypertension (HTN), body mass index (BMI), and ACEI/ARB use were collected.

Results: One hundred forty-three patients were included. The mean age was 43 years +/-11. Twenty five percent of the patients had DM, 50% had HTN, and the mean BMI was 44 +/- 9. The prevalence of proteinuria and albuminuria was 8.5% (95% CI 4.5-14.4%) and 21% (95% CI 14-30%) respectively. Sixty six percent of the patients with proteinuria had DM as did 43% of the patients with albuminuria. Eighty three percent of patients with proteinuria had either DM or HTN. Seventy eight percent of patients with albuminuria had either DM or HTN. Overall, 34% with proteinuria and HDL. Only 3.4% and 8.6% had proteinuria and albuminuria respectively. In contrast to patients who did not have proteinuria, the mean BMI was higher in those with proteinuria (44 vs. 40). However, the BMI did not differ between those with and without albuminuria. The BMI for diabetics did not differ from non-diabetics. The use of ACEI/ARB was 35% and 30% in patients with proteinuria and albuminuria and 25% and 20% in those without.

Conclusions: The majority of patients with proteinuria and albuminuria had diabetes and/or hypertension and there was a much lower prevalence of proteinuria/albuminuria in patients without these risk factors. Patients who had proteinuria had a higher BMI than patients who did not have proteinuria, though for albuminuria the BMI did not differ.

PUB305 Plasma Uric Acid and Cardio-Renal Function in Adolescents with Type 1 Diabetes

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Background: Plasma uric acid (PUA) correlates with higher blood pressure (BP), lower GFR and left ventricular hypertrophy in adults with type 1 diabetes (T1D). Our overall aim was to determine if similar relationships exist in adolescents with T1D, analyzed on the basis of low-, middle- or high- albumin to creatinine ratio (ACR) tertile within the normal range, compared to healthy controls (HC).

We hypothesized that PUA within the normal range would be lower among adolescents with lower GFR and higher values for BP and arterial stiffness in T1D adolescents but not HC.

Methods: PUA, BP, GFR, and carotid-femoral pulse wave velocity (Car-Fem PWV) were measured in 65 HC, 64 low-, 74 middle- and 50 high-tertile T1D participants from the Type 1 Diabetes Type 1 Diabetes Cardio-Renal Intervention Trial (ADDIT).

Results: PUA was lower in TID vs. HC (242.55 vs. 306.74 mmol/L; p<0.0001). There were no differences in PUA between the 3 ACR tertiles. Higher PUA correlated with lower GFR in TID after correcting for age, gender, HbA1C, z-score, T1D duration and HDL (r=0.33, p=0.0001). This association was not seen in HC. In the TID group, PUA did not correlate with BP z-score before or after correcting for HbA1C, TID duration and plasma HDL. Higher PUA correlated with higher Car-Fem PWV (r=0.18, p=0.018) in TID, but not in HC. This association in TID was abolished after correcting for age, gender, HbA1C, and z-score, T1D duration and HDL (r=0.18, p=0.03).

Conclusions: PUA correlates with lower GFR in TID adolescents and may also be associated with increased arterial stiffness, despite lower PUA in TID vs. HC. The presence of TID may potentiate the hemodynamic impact of PUA, thereby modifying future cardio-renal risk.

PUB306 Risk Factors for Renal and Cardiovascular Events in Type 2 Diabetic Patients with Biopsy-Proven Nephropathy in Japan

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Background: Standardized pathological classification is an essential tool in the evaluation of disease progression and/or efficacy of clinical management. In this nationwide, multicenter, retrospective study, we examined pathological findings as risk factors for renal and cardiovascular events in Japanese patients with type 2 diabetes (T2D) who had undergone kidney biopsy.

Methods: Renal biopsy and clinical data were retrospectively collected from 356 patients with T2D who had undergone kidney biopsy at centers in Japan. The observation period was 76.3 months and the observation period was 2264 person-year in total. Nine glomerular lesions, two interstitial lesions, and two vascular lesions were classified as pathological predictors.

Results: One hundred sixty nine composite renal events (dialysis and doubling of serum creatinine or half of estimated glomerular filtration rate [eGFR], 94 kidney deaths (dialysis), 34 cardiovascular events, and 30 deaths occurred. Specific pathological risk factors were detected for composite renal end points, renal death, and cardiovascular events, and levels of preserved eGFR and preserved eGFR were not associated with them, the presence of double contour of the glomerular basement membrane/subendothelial space widening (SubendW) and advanced interstitial cell infiltration (ICel) were particular risk factors for composite renal events, and glomerulonephromy (GMeG) was a risk factor for cardiovascular events.

Conclusions: This study revealed that specific pathological parameters (presence of SubendW, ICel, and GMeG) were predictors for renal and cardiovascular events in patients with preserved eGFR and normo- to microalbuminuria.

Funding: Government Support - Non-U.S.
Conclusions: In DMN, DPP-4i have oxidative stress relief and renoprotective effect, by the improvement of short-term blood sugar fluctuations, also by oxidative stress reduction which independently of the improving glycemic control.

PUB309

Background: To evaluate the potential of fibrinogen as a predictor of the progress of proteinuria in diabetic kidney disease.

Methods: For a Cross-Sectional Study, collecting 1121 type 2 diabetes patients without or with microalbuminuria or massive proteinuria were treated during January 2008 to January 2013. Proteinuria was negative in 755 cases, 285 cases i with microalbuminuria, and 181 cases with massive proteinuria; we analyzed the correlation factors of the negative protein urine group and the microalbuminuria group; the correlation factors of the microalbuminuria group and the massive proteinuria group. Fibrinogen levels were compared between three groups.

Results: Retinopathy, hypertension grading, SBP, Fibrinogen levels, serum albumin, serum creatatin were the related progress factors of Microalbuminuria; Diabetes course, retinopathy, waist to hip ratio, Fibrinogen levels, serum albumin levels, serum creatatin, C, serum creatinine were the related progress factors of the massive proteinuria; Except fibrinogen, other factors had been known relating to the progress of diabetic kidney disease. There were differences in the levels of three groups of fibrinogen (P<0.05), which were 3.43 ± 0.91 g/L, 4.15 ± 1.31 g/L, 5.16 ± 1.44 g/L.

Conclusions: Fibrinogen was a potential predictive factor for the development of diabetic kidney disease. The conclusion needs to be confirmed by further study.

PUB310
Interaction of HDLc, Iron, and Diabetes on Kidney Function. Jiaqiwu Conway,1 Tina Costacou,2 John M. Arthur,3 Epidemiology, West Virginia Univ; 2Epidemiology, Univ of Pittsburgh; 3Univ for Medical Sciences.

Background: The effect of HDL cholesterol (HDLc) on kidney function has recently received attention, partly due to the finding of increased hemoglobin (hb) inside of the HDL protein in persons with high risk haptoglobin (hp) genotypes. Such hb w/ in the HDL protein may lead to iron induced lipid peroxidation products. These lipid peroxidation products may lead to iron-induced kidney damage. We have recently shown an interaction between HDLc and iron w/ kidney function (eGFR) in persons with diabetes such that after controlling for hb, higher serum iron levels were associated w/ reduced eGFR but only in those w/ HDLc levels above the median for the population. Because of the diabetes-specific association of increased hb inside the HDL protein in those w/ high risk hp genotypes, we hypothesize that this interaction between HDLc and iron w/ kidney function varies by diabetes status. To test this hypothesis, we examined the inter-relationship between HDLc, iron, and diabetes status w/ eGFR in approximately 55,000 individuals in West Virginia and Ohio.

Methods: Data on adults aged 20 years were obtained from the C8 Health Project. eGFR was estimated using the CKD-EPI formula. Linear regression analysis was used to test the relationship between HDLc, iron, and diabetes status, and diabetes-related eGFR, with interactions, w/ eGFR.

Results: Mean age was 57.8 in those w/ diabetes and 45.1 in those w/out diabetes. In multivariable analyses controlling for age and sex, iron was positive related w/ eGFR in those w/ (p=0.03) and inversely in those w/out diabetes (<=0.0001), while HDLc was positively associated w/ eGFR only in those w/out diabetes (p=0.97 in diabetes; p=0.001 in w/o diabetes). As previously reported, an interaction existed between HDLc and iron in diabetes (p=0.04). Here we report that this relationship was even stronger in those w/out diabetes (interaction p=0.0008). A significant 3-way interaction existed between HDLc, iron, and diabetes status w/ eGFR (p=0.008). Controlling for hb, the interaction between iron and HDLc disappeared in those w/ diabetes but remained robust in those w/out diabetes.

Conclusions: The divergent relationship between iron and HDL on the eGFR by diabetes status needs further investigation.

PUB311
Molecular-Selective Plasma Exchange in Acute Kidney Injury due to Multiple Myeloma. Mamoru Kanda, Satomi Satoda, Shinichi Mizzuno, Shu Yamakage, Mitsuhiro Sato, Yoshio Taguma, Toshinobu Sato. Nephrology, Japan Community Health Care Organization Sendai Hospital, Sendai, Miyagi, Japan.

Background: Benefit of plasma exchange in overall survival of patients with multiple myeloma (MM) remains to be determined, however, it is evident that lowering free light chain (FLC) reverses renal function in acute kidney injury (AKI) due to MM. High cut-off hemodialysis is recommended to remove FLC as an initial treatment for MM related AKI, which is different from traditional plasma exchange (PE) in retained loss of large size molecules. As another option, we show the effect of molecular-selective plasma exchange to remove FLC, which enables target size removal without losing other size molecules.

Methods: A 49 year male with Bence-Jones type M protein was admitted with AKI; serum creatinine rose from 3.8 to 7.9mg/dL in 1 month. Past history included bone fracture and diabetes. Serum FLC lambda was elevated to 28900mg/dL. MM was confirmed by plasma cells in the bone marrow. The patient was treated with sequential molecular-selective plasma exchange (Evacure) and on-line HDF every other day combined with Bortezomb.

Results: PE was performed 6 times and removed 43.1% of FLC each on average without losing small and large size molecules.

Conclusions: Benefit of plasma exchange in overall survival of patients with multiple myeloma (MM) remains to be determined, however, it is evident that lowering free light chain (FLC) reverses renal function in acute kidney injury (AKI) due to MM. High cut-off hemodialysis is recommended to remove FLC as an initial treatment for MM related AKI, which is different from traditional plasma exchange (PE) in retained loss of large size molecules. As another option, we show the effect of molecular-selective plasma exchange to remove FLC, which enables target size removal without losing other size molecules.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
been conducted. 12 treatments were performed. Machine’s usability and accuracy has been evaluated by the staff through scores table. The measurement of fluid balance accuracy was even performed.

**Results:** Based on score given by the staff (engineers, nurses and physicians), the machine hardware results compact and well organized, with 3 well separated compartments (dialyzer replacement, blood and effluent) that facilitate the preparation phase. Auto-

**Conclusion:** Kibow is a promising CRRT machine that can perform multiple continuous therapies with just one platform. In particular, we evaluated a highly accurate gravimetric fluid balance control system and a user-friendly interface. Kibow is one of the first machines of the new frontier of CRRT devices: the fourth generation of CRRT machines.

**PUB313**

The Effect of MySleeve on Fluid Restriction Adherence in Hemodialysis Patients

**Patients and Methods:** A Time and Motion Study of Erythropoiesis Stimulating Agent Administration in United States Dialysis Centers

**Background:** In hemodialysis patients, non-adherence to fluid restriction is associated with high interdialytic weight gain (IDWG) and adverse outcomes. Monitoring drinking behavior and direct feedback to the patient can lead to better adherence. We developed the MySleeve, a device that can be wrapped around a drinking glass to monitor fluid intake throughout the day. The MySleeve will also provide a subtle vibration on the glass when the amount drunk exceeds the target. The information about drinking behavior can be found in the accompanying application on a mobile phone. In this study, we investigate the effect of direct feedback and information to the patient on fluid restriction adherence measured by the IDWG.

**Methods:** We will include 40 prevalent, anuric hemodialysis patients from the Catharina Hospital Eindhoven, The Netherlands in a randomised controlled trial. Patients in the intervention group are provided a MySleeve device, a mobile phone and an activity tracker. BCM measurements are performed weekly and IDWG will be calculated before every dialysis session. The patients in the control group will continue with regular hemodialysis.

**Results:** We expect that by providing patients insight in fluid intake, there will be an increased fluid restriction adherence and an improvement in activity levels and better quality of sleep. Due to less IDWG, patients will experience less discomfort of fluid overload.

**Conclusions:** Introducing a MySleeve device to provide direct insight into drinking behavior will help the patients to adhere to their fluid restriction, leading to less IDWG and better quality of life measured by daily activity and better sleep.

**Funding:** Private Foundation Support

**PUB314**

A Time and Motion Study Assessing Agent Use in Dialysis Centers

**Methods:** A Time and Motion Study of Erythropoiesis Stimulating Agent Administration in United States Dialysis Centers

**Background:** Previous research suggests that ESA administration in dialysis is a time-consuming task and switching to less frequently dosed ESAs may offer opportunities for more efficient and effective patient care. This study estimated the time required for activities involved in the ESA process at US dialysis centers using epoetin alfa (EPO) or darbepoetin alfa (DPO), and examined potential time savings of switching from EPO to DPO.

**Methods:** Time and motion study conducted from 10/2014 to 1/2015 to assess activities involved and staff time required to prepare, administer and document ESA doses. A sample of 11 dialysis centers using either 3 times-per-week (TW) EPO or once-weekly (QW) DPO were selected in pairs (one EPO, one DPO), where possible, from the same organization or nephrology practice to help control for anemia management protocols and staffing patterns. ESA-related tasks were timed by trained nurse observers. Time savings were calculated from switching from TIW EPO to QW-DPO were estimated. Staff were interviewed about alternate patient-focused activities that could be accomplished if time were saved in the ESA process.

**Results:** 200 administrations were observed (81 DPO, 119 EPO). A mean of 2.3 (95% CI, 2.1–2.5) minutes per dose were required for ESA-related activities. RNs performed 95% of tasks; LPNs 5%. ESA process time did not vary significantly between EPO and DPO (p=0.83). Staff time savings would accrue due to fewer ESA administrations using QW DPO: 10-20 minutes per nurse/day. For an average facility, the total monthly nurse time that could be re-purposed was 24 hours. Patient education, fulfillment of care plans and more frequent review of labs were identified as opportunities for improved care processes that could be implemented after conversion.

**Conclusions:** Switching from TIW EPO to QW DPO for anemia management in dialysis patients can result in time savings and opportunities to redirect nurse time towards activities aimed at improving patient care while still offering the ability to respond to changing clinical circumstances to effectively manage anemia.

**Funding:** Pharmaceutical Company Support - Amgen, Inc.
PUB317

Inflammatory and Metabolic Syndrome Biomarkers Analysis of Vascular Outcomes in End-Stage Renal Disease

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Background: The relevance of some biomarkers of inflammation and metabolic syndrome to vascular outcomes in end stage renal disease (ESRD) is not clear. To study these relationships, biochip array technology method was used to profile the complex plasma biomarkers in the setting of various comorbid outcomes such as Stroke or Transient Ischemic Attack (TIA), Acute Coronary Syndrome (ACS), Congestive Heart Failure (CHF), and Coronary Artery Disease (CAD).

Methods: Plasma samples were collected from 83 ESRD patients (mean age 65) prior to hemodialysis and were profiled using biochips for metabolic and inflammatory biomarker levels. Inflammatory cytokine and Metabolic Syndrome arrays were used to profile C peptide, ferritin, insulin, leptin, resistin, TNFα, PAI-1, IL-1a, ILb, IL-4, IL-6, IL-8, IL-10, VEGF, EGF, IFNG, and MCP1. Retrospective review was performed to group patients based on history of Stroke or TIA, ACS, CHF, and CAD.

Results: Of the 83 ESRD patients, 25 (30.1%) were found to have history of Stroke/ TIA, 14 (16.9%) were found to have history of ACS, 30 (36.1%) were found to have history of CHF, and 39 (47.0%) were found to have history of CAD. Stroke/TIA patients were found to have decreased plasma IFNG levels (p=0.042) and decreased plasma IL-1α and IL-1β levels (p=0.008, 0.021, 0.026; respectively) when compared to patients without Stroke/TIA. ACS patients had elevated plasma IL-6 levels (p=0.040) when compared to those without ACS. CHF patients had decreased plasma leptin levels (p=0.031) and elevated plasma IL-1b levels (p=0.042) when compared to patients without CHF. CAD patients had elevated plasma IL-1α levels (p=0.049) when compared to ESRD patients without CAD.

Conclusions: Profiling of multiple inflammatory and metabolic syndrome biomarkers may aid in the risk stratification of ESRD patients for cerebrovascular and cardiovascular disorders. These studies demonstrate that biomarker profiling of vascular comorbidities in ESRD may provide useful diagnostic and prognostic information in the management of ESRD patients.

PUB318

Individualized Anemia Management in Pediatric Nephrology Patients

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Background: Anemia management in pediatric patients on dialysis poses a great challenge to the nephrologist. In this study, we tested the hypothesis that individualized approach anemia management, previously demonstrated successfully in adult patients, improves hemoglobin maintenance within target range in pediatric dialysis patients.

Methods: We performed prospective evaluation of Clinical Decision Support System “Smart Anemia Manager” (SAM) in pediatric dialysis patients at Riley Hospital for Children at Indiana University. SAM was implemented as a stand-alone software on a desktop computer used by the nurse anemia manager and connected to a database containing Hemoglobin (Hgb) and ESA dose data. The anemia manager was allowed to override dose recommendations from the system and each override was documented. The follow-up period was 10 months, including 4 month washout period. We compared the hemoglobin distribution within 9-12 g/dL range during 6 months immediately before SAM implementation and 6 months after the washout period. Only patients who received ESA and had at least 4 Hgb values within each period were included in the analysis.

Results: 13 patients satisfied the inclusion/exclusion criteria. The percentage of monthly Hgb within target range varied between 82% and 92% in 6 months prior to deployment of SAM and between 69% and 100% during 6 months after SAM deployment. Quarterly Hgb distribution varied between 86% to 87% prior to SAM deployment and 87% to 95% after. There was a significant decrease in low Hgb numerals after SAM deployment, but no change in high Hgb levels, compared to the period before SAM deployment.

Conclusions: Individualized anemia management in pediatric patients improves distribution of Hgb within the target range, compared to a standard population-based protocol approach.

Funding: NIDDK Support

PUB319

Extracorporeal Ultrafiltration Therapy for Acute Decompensated Heart Failure

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Background: There has been a renewed interest in the use of ultrafiltration (UF) for management of patients with acute decompensated heart failure (ADHF). While a number of studies reported on the efficacy of this therapy and lack of any significant adverse impact, the more recent trials have challenged its safety. The aim of this study is to provide a reappraisal of the current evidence on the use of UF in ADHF.

Methods: Articles cited in PubMed database from 2000 to 2015 using key words “ultrafiltration” and “heart failure” were searched. Those randomized and non-randomized trials using recent portable devices dedicated for UF were selected. Case reports, and case series were excluded. Relevant data such as renal function, cardiac status, and weight change were extracted and compared.

Results: A total 940 patients from 15 trials (7 randomized and 8 non-randomized) that used dedicated UF devices were included. Eleven studies reported either no change or non-significant decrease in serum creatinine, while 4 found worsening renal function after UF therapy; these studies included patients with more severe renal dysfunction at baseline. Concerning weight, a reduction of 2 to 9 Kg was reported that was similar to conventional therapies in 9 studies but was significantly lower with UF in 6 trials. Length of stay was evaluated in 5 studies, 2 of which showed a significant reduction. Three studies showed fewer re-hospitalizations in the UF group at 30 days, 90 days, and 1 year followups. None of the studies evaluated long-term outcomes of patients undergoing UF therapy.

Conclusions: Based on the currently available data, UF is efficient for management of volume overload in ADHF. However, these studies do not support any beneficial impact for this therapy on renal function, and suggest that it might be associated with suboptimal renal outcomes if used for patients with more severe renal dysfunction at baseline. Currently there is no data on the effect of UF on long-term outcomes of patients with ADHF. Whether this would translate into a lack of effect for UF on these outcomes needs to be elucidated by future studies.

PUB320

Ultra-Sensitive Troponin I Predictive Value in Remote Ischemic Pre-Conditioning in Hemodialysis: A Randomized Double Blinded Clinical Trial

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Background: Remote ischemic cardiac preconditioning(RIPC) is a procedure that generates a brief period of ischemia followed by reperfusion. Areas submitted to RIPC in the experimental ischemia models have less occurrence of necrosis. RIPC role in protecting myocardial ischemia during hemodialysis is not established yet. The aim of the study was to evaluate RIPC as myocardial protection used to evaluate ultra sensitive I troponin in hemodialysis outpatients.

Methods: It is a double blind randomised trial with two groups: intervention, submitted to RIPC with external compression in the right arm with sphygmomanometer with 200mm/Hg of pressure with three-5 minute rounds alternating with deflation totaling 30 minutes and control group without RIPC. Intervention group received RIPC in three consecutive hemodialysis sessions. Blood samples were taken before and after each session. Randomization was made by a software stratified by sex and age.BUN for calculation of single pool Kt/v and ultra sensitive I troponin were measured to evaluate dialysis adequacy and myocardial injury.

Results: A total of 47 patients were randomized. About 60.8% were men and 54% diabetic. The mean single pool Kt/v was 1.51 in the intervention group and 1.49 in control.
There was a trend to higher mortality in the control group (26%, p=0.09). The ultra sensitive troponin I was significantly higher than at baseline. Mean age was 68.7 ± 5 years, 40.6% were female and 51.7% were diabetes. 13.4% had a history of ischemic heart disease, and 13.3% had cerebrovascular disease. 8.0% had undergone coronary intervention procedure. Mean serum Ca, P and iPTH concentrations were 8.94±2.5, 4.0±3.0, and 122±29 ng/L, respectively. Baseline characteristics were well balanced between the two groups.

Conclusions: The LANDMARK study will determine whether a non-Ca-based P binder, LC, reduce CV mortality and morbidity in HD patients.

Funding: Pharmaceutical Company Support - Bayer Yakuin, Ltd

**PUB323**

### The Relationship Between Prescription of Ultrafiltration in Hemodialysis and Intradialytic Hypotension: A Retrospective Study of Chinese Hemodialysis Patients

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**Background:** Our study aims to explore the relationship between prescribed ultrafiltration and intradialytic hypotension (IDH) and, to demonstrate risk factors of intradialytic hypotension in order to reduce the incidence of relevant complications and improve patient prognosis.

**Methods:** 312 patients maintenance hemodialysis patients in our dialysis center were enrolled with 33224 HD/HDF treatment sessions recorded. Hypotension was defined as a decrease of systolic blood pressure <20mmHg or mean arterial pressure declination 10 mmHg whether presence of hypotensive symptoms or not. ROC curve was applied to study the cut-off point of UF/Wt (ultrafiltration/weight) ratio for the presence of hypotension. Pearson analysis and logistic regression was used to study the risk factor associated with intradialytic hypotension.

**Results:** The prevalence of intradialytic hypotension was 38.7%. Decrease of SBP and MAP positively correlated with UF/Wt and age, and negatively correlated with blood flow. The cut-off point of UF/Wt was 4% for all patients, diabetes and non-diabetic patients with AUCs of 0.575, 0.570, and 0.622 respectively. The AUC for diabetic patients was higher than that of non-diabetic patients (P=0.001). Multivariate logistic regression showed that age (OR=1.005, 95%CI: 1.001-1.007), diabetes (OR=1.209, 95%CI: 1.122-1.303), and UF/Wt=4% (OR=1.605, 95%CI: 1.532-1.682) was associated with hypotension.

**Conclusions:** Asymptomatic intradialytic hypotension is prevalent. Increased intradialytic SBP/MAP variability is associated with greater UF and UF/Wt, but is not associated with greater blood flow. To Chinese hemodialysis patients, UF/Wt=4% is sensitive and specific in predicting intradialytic hypotension, especially in patients with diabetes mellitus. UF/Wt=4%, diabetes mellitus and age are independent risk factors for asymptomatic intradialytic hypotension.

**PUB324**

### Whole Blood Viscosity at Low Shear Rate Is Associated with Cardiovascular Mortality in Patients with Hemodialysis


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**Background:** The change of whole blood viscosity (WBV) may increase risk of major atherosclerotic events, including congestive heart failure, myocardial infarction, and stroke. However, there is few report about the relationship between WBV and mortality rate due to atherosclerotic vascular disease. The objective of the present study was to investigate correlation between values of WBV at shear rates of 1, and 5 S⁻¹ before and after hemodialysis in patients with end-stage renal disease (ESRD) and mortality, especially cardiovascular or cerebrovascular mortality.

**Methods:** Forty three patients with ESRD receiving maintenance hemodialysis had initially participated in this study. In a prospective observational study, we examined the effect of WBV in pre- or post-dialysis on cardiovascular or cerebrovascular mortality in dialysis patients for approximately 5.8 years.

**Results:** Twenty seven patients among total 43 patients died and 2 patients had received transplantation of kidney within period of this study. Cardiovascular deaths occurred in 8 patients among 27 patients, and cerebrovascular deaths occurred in 5 patients among the 27 patients. The hazard ratios for overall survival in the patient with hemodialysis according to increase of predialytic diastolic WBV at low shear rate of 1 S⁻¹ in an univariate Cox proportional analysis were 1.585 (95% CI, P=0.382) in the group of moderate blood viscosity and 2.351 (95% CI, P=0.128) in the group of high blood viscosity. However, pre-DIV1 was not still statistically significant after adjustment for covariates. In addition, the HRs for overall survival according to increase of pre-DIV5 were 1.327 and 1.930 in each moderate and high blood viscosity group. In Kaplan-Meier’s survival analysis, when pre-DIV1 increased, cumulative mortality relatively showed rising tendency, but, unfortunately there was no statistical significance.

**Conclusions:** These results suggest that the diastolic low-shear WBV may impact on cardiovascular or cerebrovascular mortality in hemodialysis patients. New prospective and large-scaled studies to more exactly evaluate the correlation between WBV and mortality will be needed in the future.
Survival of Patients Over 75 Years Old in a Chronic Hemodialysis Program
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Background: The intensity of medical care for people over 75 years of age has increased over the past decade. In this surrounding context is increasing the number of individuals with this profile that has clinical indication starting renal replacement therapy. Published evidence has linked the survival of patients after initiation of hemodialysis (HD) according to the presence of comorbidities. The aim of this study was to evaluate the survival of elderly patients with chronic kidney disease on regular HD.

Methods: From analysis of medical records was assessed the rate of survival of incident patients who began HD treatment from 2000 to 2010. Demographic and clinical data were also collected. It was made a comparison, based on these data, among the elderly (over 75 years old) and non-elderly groups who died.

Results: During the study period, 158 patients started HD program, 69% male and 40% younger than 75 years. The overall mortality rates at 6 and 12 months were, respectively, 7.5% and 17%. Considering only the elderly, mortality rates at 6 and 12 months were respectively 14 and 27%. The median survival of these patients was 33 months. Considering only patients younger than 75 years mortality rates at 6 and 12 months were, respectively, 2% and 8%. Comparing elderly patients with non-elderly, we observed that the first group had a higher proportion of diabetic and hypertensive patients and with a history of cardiovascular disease and cancer. Considering only the patients who died, there were no important significant differences in the presence and score of comorbidities, when the elderly was compared with the non-elderly.

Conclusions: Patients over 75 years in HD had a mortality rate two times higher than younger patients and the presence of comorbidities may be a contributing factor to the age to explain this data.

Prevalence of Abnormal Ankle–Brachial Index in Haemodialysis Patients in Mexico and Its Association with Other Cardiovascular Risk Factors
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Background: Abnormal Ankle-Brachial index (ABI), defined as ≤ 0.9 or ≥ 1.3, is considered an independent predictor of mortality in haemodialysis patients, in other countries abnormal ABI is found between 35% and 80% of haemodialysis patients. In Mexico the prevalence of abnormal ABI has not been reported. The aim of the study was to determine the frequency of abnormal ABI and its association with other cardiovascular risk factors.

Methods: Prevalent hemodialysis patients over 16 years old were included; data were obtained from medical records and interviews. ABI was measured by oscilometry (Model HEM-705CPINT) and classified as a normal result between 0.91 - 1.3 (NABI), ≤ 0.9 (LABI) or ≥ 1.3 (HABI). NAVI was considered as the control group and the data were analyzed using descriptive and inferential statistics, using T Student and Chi2.

Results: Of the 119 patients analyzed abnormal ABI was present in 36 (30%); 10 (8.4%) with LABI and 26 (21.9%) with HABI. The mean age was 44.9 years, 68% were male, duration of dialysis was 7.1 years. In univariate analysis ABI was significantly associated with history of hypertension (p <0.003), smoking history (p <0.001), diabetes (DM) (p =0.04), lower creatinine (p <0.001) and albumin (p <0.001) and higher calcium (p <0.001); HABI was significantly associated with lower age (p =0.01), smoking history (p =0.05), lower systolic blood pressure (SBP) (p =0.02), higher levels of sodium (p =0.04) and calcium (p =0.01). No association was found between abnormal ABI and history of hypertension, dyslipidemia, heart disease, stroke; there were no differences with the dose of calcium carbonate or calcitriol, the value of Kt/V, the type of vascular access and serum phosphorus.

Conclusions: Abnormal ABI was less prevalent than in other populations, among these HABI is the most common. LABI was associated with older age, DM, smoking history, high calcium and low creatinine and albumin (probably associated with poor nutritional status). HABI patients were younger, with smoking history, lower SBP, high serum sodium and calcium levels.

A Lower Serum Uric Acid Is Associated Not Only with All-Cause Mortality but Also Cardiovascular Mortality Among Patients Receiving Hemodialysis in Japan
Naoki Sugano, Yukio Maruyama, Keitaro Yokoyama, Koki Takane, Yasuhiro Takahashi, Chisa Kobayashi, Shinichiro Nishio, Daiuuke Takahashi, Satoshi Kidoguchi, Kousuke Honda, Norihiko Morisawa, Gorou Tokudome, Iwao Ohno, Tatsuo Hosoya, Takashi Yokoo, Takashi Shigematsu, Kunioh Iseki, Ikuto Masakane. Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan.

Background: High level of serum uric acid is prevalent in chronic kidney disease (CKD), however it has a controversy whether high or low serum uric acid level appears to be a risk factor of cardiovascular event and mortality in the patients of receiving renal replacement therapy.

Methods: We collected the baseline data of 222,434 patients receiving HD three weekly (males: 63.0%, 66 ±12 years, median HD vintage of 60 months, females: 68 ±13 years, median HD vintage of 72months) extracted from a nationwide dialysis registry at the end of 2011 in Japan. Then we evaluated the patient survival and development of complication using the registry at the end of 2012.

Results: During one-year follow-up, 18775 (8.4%) died of all causes including 8094 (3.6%) cardiovascular death. All-cause mortality and cardiovascular mortality were lower in the group with lower level of baseline uric acid. In a multivariable logistic regression analysis, patients of the highest quartile of uric acid had lower all-cause, and cardiovascular mortality compared with those of the lowest quartile (males: OR, 0.745; 95% CI, 0.675 to 0.8207; females: OR, 0.8333; 95% CI, 0.726 to 0.936; and males: OR, 0.702; 95% CI, 0.6266 to 0.8278; females: OR, 0.8575; 95% CI, 0.7029 to 1.0642).

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Conclusions: In this large observational cohort study, lower levels of serum uric acid were independently associated not only with all-cause mortality but also cardiovascular mortality among Japanese HD patients. Close monitoring of serum uric acid is thought to be necessary for the management of HD patients.

PUB330

Post Stroke Disability Deterioration and Mortality of Hospital Onset Stroke in Patients with and without End-Stage Renal Disease Tomoko Usui,1 Norio Hanafusa,1 Hideo Yasunaga,2 Masaomi Nagaku.1 1Dept of Hemodialysis and Apheresis, The Univ of Tokyo Hospital, Japan; 2Dept of Clinical Epidemiology and Health Economics, School of Public Health, The Univ of Tokyo, Japan.

Background: Increasing evidence suggests that end-stage renal disease is associated with higher risk and severity of cerebrovascular disease. However, the risk factors for post stroke disability and mortality is not clear. We examined the association between risk factors including dialysis treatment and disability deterioration and mortality during the hospital stay of hospital onset stroke.

Methods: The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data of about 50% of all acute-care inpatients in Japan. Using this database, we extracted data of inpatients age ≥20 years old, hospital-onset stroke between July 2010 and March 2013. Disability level was divided into modified Rankin Scale (mRS) 0-1, 2-3, 4-5, and 6 (death). Deterioration of disability was defined as an increase in disability level. The odds ratio (OR) for in-hospital deterioration of disability and mortality was calculated using a logistic regression model.

Results: Out of 26,834 patients, 593 (2.2%) had dialysis therapy. The median length of stay was 39 and 33 days for patients with and without dialysis, respectively. During the hospital stay, there were 7,655 (28.5%) disability deterioration and 3,851 (14.4%) death. The patients with dialysis had higher disability deterioration (47.9%) and mortality rate (31.3%) compared to those without. After adjustment with age, gender, BMI, mRS, Activities of Daily Living, smoking habits, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, heart failure, peripheral arterial disease, cerebrovascular complications, antplatelet, anticoagulant, and thrombotic medications, multivariate-adjusted ORs of dialysis for disability deterioration was 2.88 (95%CI 2.40-3.45), and in-hospital mortality was 3.57 (95%CI 2.94-4.33).

Conclusions: Dialysis treatment was an independent risk factor for in-hospital disability deterioration and mortality of hospital onset stroke.

PUB331

Role of Bioimpedance as Tool for Fluid Management in Hemodialysis Patients Maria Cecilia Recalde,1 Manuela Bello,2 Cecilia Arruabarrena,1 Álvaro Herou,1 Fabian Cano,1 Laura Sofia,1,2 1Hemodialysis Unit, CASMU, Uruguay; 2Preventive Medicine, Univ of the Republic, Uruguay.

Background: Fluid management in hemodialysis patients is difficult, hypertension and fluid overload is frequent as well as hypotensive episodes leading to cerebral and cardiac injury and increased mortality risk. The objective of the study is to evaluate if bioimpedance could be a tool to optimize fluid management in hemodialysis patients.

Methods: Patients were included after giving informed consent when fulfilled inclusion and exclusion criteria. Were recorded age, gender, diabetes status, dialysis vintage, body mass index (BMI) estimated dry weight, and mean in previous month: systolic blood pressure and was prescribed more number of other antihypertensive drugs than control group. After matching, there were no differences in age, sex, dialysis modalities, comorbidities and number of other antihypertensive medications. Before PSM, patient survival was significantly better in the RAAS group using the Gehan-Wilcoxon test (P=0.001), however, this difference disappeared after matching (P=0.450). Cardiovascular event-free survival was not different between RAAS group and control group before and after PSM analysis.

Conclusions: RAAS blockade did not affect all-cause mortality and MACE-free survival in the Korean ESRD patients. Further researches such as randomized control study will be needed.

PUB333

Hemodynamic Changes in Maintenance Hemodialysis Patients with Intradialytic Hypotension MeiJuen Meng, Hong Ye, Junwei Yang. Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Intradialytic hypotension (IDH) is a common complication in patients undergoing maintenance hemodialysis (MHD) which leads to high mortality. This study is to explore the hemodynamic changes in MHD patients with IDH.

Methods: Thirty-seven patients were included in our study. HD were defined as a decrease of systolic blood pressure (SBP) <20 mmHg or the lowest SBP below 90 mmHg during dialysis. Twenty-three patients were diagnosed with IDH. Among them, 13 were

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asymptomatic while the other had the hypotensive symptoms, such as abdominal discomfort, sighing, nausea, vomiting, muscle cramps and restlessness. All of them underwent a noninvasive hemodynamic evaluations before, during and after dialysis.

**Results:** Compared to the patients without IDH, the dialysis age was longer and the prevalence of diabetes was higher in the patients with IDH. There were no difference in age, amount of ultrafiltration, pre-dialysis cardiac index (CI), systemic vascular resistance index (SVRI) and thoracic fluid capacity (TFC) between these two groups. During dialysis, CI decreased while SVRI increased gradually especially in patients with IDH. At the end of dialysis, ACT was markedly higher in patients with IDH. However, there was no significant difference in the change of CI, SVRI and TFC ten minutes before and after hemodialysis between these two groups. Meanwhile, the hemodynamic changes were analyzed in IDH patients with or without symptoms. It was found that there were no difference of change values and absolute values of CI and SVRI in these subgroups.

**Conclusions:** It was found that CI decreased while SVRI increased during hemodialysis. In the mid and later period, the CI decreased much more patients in patients with IDH. It was suggested that CI might be an indicator of IDH.

**Funding:** Government Support - Non-U.S.

**PUB335**

**Dual Relationships of Serum Leptin on Heart Rate Variability in Patients with Stage 5 Chronic Kidney Disease** Ningning Wang, Yao Jiang, Jingjing Zhang, Changying Xing. *Nephrology, First Affiliated Hospital of Nanjing Medical Univ; Nanjing, China.*

**Background:** Leptin regulates nutrition, bone metabolism and cardiovascular function. Lower heart rate variability (HRV) in chronic kidney disease (CKD) predicts higher risk of cardiovascular disease (CVD). Relationships between leptin and HRV in CKD is obscure.

**Methods:** This included cross-sectional observation and longitudinal followed-up on parathyroidectomy (PTX) patients.

**Results:** Serum leptin/BMI is transformed using natural logarithm (lnleptin/BMI).

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Mean 24-h HR (beats/min)</th>
<th>SDNN (ms)</th>
<th>rMSSD (ms)</th>
<th>pNN50 (%)</th>
<th>ln LF/HF</th>
<th>ln LF</th>
<th>ln HF</th>
<th>ln LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(n=34)</td>
<td>87.4±12.7</td>
<td>72.9±11.6</td>
<td>16.4±7.1</td>
<td>8.2±6.1</td>
<td>5.5±0.9</td>
<td>3.8±1.3</td>
<td>2.6±1.9</td>
<td>0.9±0.9</td>
</tr>
<tr>
<td>2(n=30)</td>
<td>70.1±10.3</td>
<td>72.7±14.3</td>
<td>16.3±7.1</td>
<td>8.0±6.1</td>
<td>5.5±0.9</td>
<td>3.8±1.3</td>
<td>2.6±1.9</td>
<td>0.9±0.9</td>
</tr>
<tr>
<td>3(n=36)</td>
<td>81.9±10.5</td>
<td>74.9±10.9</td>
<td>16.4±7.1</td>
<td>8.2±6.1</td>
<td>5.5±0.9</td>
<td>3.8±1.3</td>
<td>2.6±1.9</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td>4(n=28)</td>
<td>81.1±9.2</td>
<td>75.4±16.2</td>
<td>16.4±7.1</td>
<td>8.2±6.1</td>
<td>5.5±0.9</td>
<td>3.8±1.3</td>
<td>2.6±1.9</td>
<td>1.0±0.9</td>
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</tbody>
</table>

**Conclusions:** Serum leptin/BMI showed no difference between stage 5 CKD and controls. However, quartile 2 of lnleptin/BMI level in CKD patients prone to have higher HRV indices associated with the highest risk of mortality among the four groups (log-rank p <0.001).

**Acknowledgments:** This study was supported by Major research project of Jiangsu Province (No.BK20151119).

**PUB336**

**Association of Geriatric Nutritional Risk Index and Responsiveness to Erythropoiesis-Stimulating Agent in Mortality of Chronic Hemodialysis Patients** Kosaku Nitta, Ken Tsuchiya. *Dept of Medicine, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan.*

**Background:** Responsiveness to erythropoiesis-stimulating agent (ESA) may be associated with mortality in hemodialysis (HD) patients. The aim of the present study was to assess the effects of geriatric nutritional risk index (GNRI) and responsiveness to ESA in outcome in HD patients.

**Methods:** The ESA response index (ERI) was determined as the weekly weight-adjusted dose of ESA divided by hemoglobin concentration. Patients were divided into four groups by quartiles of ERI. Odds ratios were estimated using a Cox proportional model for the association between GNRI and ERI and mortality, adjusting for potential confounders. Patients were divided into four groups by quartiles of ERI.

**Results:** Of the 298 subjects enrolled, 51 died with 31 cardiovascular deaths during the follow-up period of 34.6 ± 6.1 months. The ERI was inversely correlated with the GNRI (r = -0.287; p < 0.0001). Age, gender, serum total cholesterol, phosphorus, calcium, hemoglobin, and haptoglobin were associated with mortality. In the analysis of the association between GNRI and mortality, the GNRI was an independent predictor of mortality (P = 0.003).

**Conclusions:** This study revealed that the GNRI was an independent predictor of mortality in HD patients.
m/s, p=0.139). In 14 subjects, who underwent echocardiography, there were no significant changes in cardiac output, stroke volume and ejection fraction. However, left ventricular end-systolic volume (52 ± 22 versus 57 ± 25 ml (p=0.20) and end-diastolic volumes (92 ± 35 versus 97 ± 17, p<0.08) were numerically higher under cinacalcet, but not statistically significant.

There were no significant changes in the parameters of diastolic dysfunction.

Conclusions: In this short term study, there were no detectable effects of cinacalcet on aortic stiffness and diastolic dysfunction despite the expected reduction in serum calcium concentration. The numerically higher left ventricular volumes with cinacalcet, may need to be investigated. Clinical trials: NCT01250405.

Funding: Pharmaceutical Company Support - Amgen

PUB339

Kidney Transplantation and Cardiac Repolarization Descriptors Dimitrios J. Poulikakos,1 Debasish Banerjee,2 Marek Malik,3 Renal, Salford Royal, United Kingdom; St. George’s Univ of London, United Kingdom; Imperial College, London, United Kingdom.

Background: Selected descriptors of cardiac repolarization derived from the computerized analysis of electrocardiogram (ECG) can predict cardiac risk in hemodialysis (HD) patients. Kidney transplantation improves cardiovascular survival. The aim of the study was to investigate the impact of kidney transplantation on these descriptors.

Methods: The study was conducted in two phases. In phase 1, Holter ECGs were obtained during HD sessions and repeated 5 times at 2-weeks intervals in stable HD patients. The repolarisation descriptors QRS-to-T angle (TCRT) and T wave morphology dispersion (TMD) were calculated in overlapping 10 second ECG segments and averaged over the first hour of recordings. In phase 2, continuous 1-hour ECG recordings were obtained in patients who received a kidney transplant minimum three months after transplantation and if they were stable with EGFR>30 ml/min/1.73m². Average values of post transplant repolarisation descriptors were compared with average values over the first hour of HD using Wilcoxon test and t-test was used for baseline comparisons.

Results: In 80 HD patients in phase 1 both descriptors showed intra-subject stability and exhibited extreme values in subjects that suffered major arrhythmic events. During a period of 35.9 ±3 months 10 eligible transplanted subjects were recorded and although TMD and TCRT improved 7 months following kidney transplantation (see table) the difference did not reach statistical significance (p=0.05). However these subjects had better baseline TCRT and TMD values compared to the study population (TCRT 0.463 vs 0.078 p<0.05 and TMD 17.9 vs 32.4 p<0.05).

Conclusions: In transplant recipients with healthier baseline repolarization profiles the improvement did not reach statistical significance in the early post transplant period. Larger studies with longer follow up are needed.

PUB340

Prognostic Significance of Cardiopulmonary Exercise Test and 6-Minute Walk Test in Chronic Dialysis Patients Wioletta Dziubek,1 K. Bulinska,1 B. Ochman,1 Ukasz Rogowski,1 Mariusz Kusztal,1 Tomasz Golębiowski,1 D. Markowska,1 A. Zembron-Lacny,1 Marian Klinger,1 St. George’s Univ of London, United Kingdom; Imperial College, London, United Kingdom.

Background: Chronic kidney failure is recognized as a major cardiovascular (CV) risk factor. Even mild reductions in renal function are associated with increased CV morbidity and mortality.

Methods: In prospective study 90 pts receiving high-flux dialysis (12h/week) were obtained during HD sessions and repeated 5 times at 2-weeks intervals in stable HD patients. The repolarisation descriptors QRS-to-T angle (TCRT) and T wave morphology dispersion (TMD) were calculated in overlapping 10 second ECG segments and averaged over the first hour of recordings. In phase 2, continuous 1-hour ECG recordings were obtained in patients who received a kidney transplant minimum three months after transplantation and if they were stable with EGFR>30 ml/min/1.73m². Average values of post transplant repolarisation descriptors were compared with average values over the first hour of HD using Wilcoxon test and t-test was used for baseline comparisons.

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Conclusions: In transplant recipients with healthier baseline repolarization profiles the improvement did not reach statistical significance in the early post transplant period. Larger studies with longer follow up are needed.

PUB341

Adaptive Servo-Ventilator Therapy Improves the Cardiac Dysfunction in Hemodialysis (HD) Patients with Sleep-Disordered Breathing Fumiko Fukuuchi,1 Ken Tsuchiya,2 Kosaku Nitta,3 Nephrology, Komagome Kyuuritsu Clinic; Bunkyo-ku, Tokyo, Japan; 'Medicine II, Tokyo Women's Medical Univ; Shinjyuku-ku, Tokyo, Japan.

Background: Cardiac dysfunction is a very serious problem in HD patients. Sleep Disordered Breathing (SDB) is considered to cause cardiac dysfunction. Dialysis patients have a disordered respiratory center and a high prevalence of central apnea. Adaptive Servo-Ventilator (ASV) is automated modality used to treat heart failure patients with SDB, especially central apnea. The aim of this study is to explore the relationship between sleep apnea and cardiac dysfunction, and to evaluate the effects of ASV therapy in HD patients.

Methods: Sleep study was performed using a portable sleep test device (Sleepsitter LS-300, Fukuda Denki Co., Ltd, Japan). We measured the variables of cardiac function by echocardiography. The relation between apnea index and the echocardiogram indicates was calculated. We also collected baseline information on demographics, lab values, plasma BNP level, medications, and clinical conditions. ASV therapy was used in the patients diagnosed with severe SDB and/or central apnea. The cardiac function variables were evaluated in comparison to the previous year.

Results: The 27 dialysis patients (sixteen diabetics, eleven non-diabetics) are included in this study. Out of them, echocardiogram, SDB indications showed a connection. The obstructive apnea hypopnea index was related to the left ventricular posterior wall thickness (LVPWT) (r=0.49, p=0.02). Seven patients received ASV therapy. There has been improvement of overall of their cardiac function with significant increase of ejection fraction (p<0.02) 1 year after ASV introduction.

Conclusions: In this study, we demonstrated the efficacy of ASV therapy in hemodialysis patients with SDB. Near future, ASV is possible to be one of attractive devices for HD patients, with aging, several complications, to improve their poor prognosis.

PUB342

Endovascular Renal Denervation: Effects on Dyslipidaemia and Vascular Inflammation in Dialysis Patients Neil A. Hove,1 J. Christopher Baldi,2 David L. Jardine,1 John B.W. Scholten,3 Gerard T. Wilkins,1 Luke C. Wilson,1 Robert J. Walker,1 Dunedin School of Medicine, Univ of Otago; 'Christchurch School of Medicine and Health Sciences, Univ of Otago.

Background: Endovascular renal denervation (RDN) reduces afferent and efferent sympathetic nerve activity. Its effects on vascular inflammation and cholesterol levels in dialysis patients are unknown. We hypothesized RDN would reduce sympathetic activity, resulting in improvement in biomarkers of vascular inflammation and dyslipidaemia.

Methods: Nine dialysis patients with uncontrolled office BP (>140/90mmHg despite two or more agents at maximal tolerated dosages) were recruited into this feasibility study. Office and ambulatory BP monitoring (ABPM) were performed at baseline, one and three months post RDN, along with supine muscle sympathetic nerve activity (MSNA) and venepuncture. Bilateral RDN was undertaken with an EnligHTN™ catheter.

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Underline represents presenting author.
Results: Similar to previous, office systolic BP reduced and the effect on ABPM was attenuated. MSNA did not change, a novel finding. Despite lack of change in MSNA, total cholesterol: HDL ratio increased along with a falling trend in CRP and rising trend in albumin, all novel findings.

Conclusions: Non survivors were significantly older, had lower number of total sessions, lower albumin and no dialysis. But dialysis adequacy and UF were comparable. Short duration of follow up may limit the ability to study other factors influencing outcomes.

PUB344
New Anticoagulant Free Strategy for Non Valvular Atrial Fibrillation in Hemodialysis Patients Teresa Arcidiacono, Patrizio Mazzone, Marco Simonini, Donatella Spotti, Maria Teresa Sciarro Alibrandi, Rita Quartagno, Marco Melandi, Stefano Tentori, Giorgio Slaviero. San Raffaele Scientific Inst, Italy.

Background: Vascular calcification in patients with CKD-5 is associated with increased cardiovascular morbidity and mortality. An excessive calcification of coronary arteries and of aortic valve has been reported during Warfarin treatment. In addition use of oral anticoagulation (OAC) seems to be an important risk factor for calciphylaxis. Atrial fibrillation (AF) is the most frequent reason for OAC use in CKD patients.

Methods: An alternative to OAC could be the percutaneous Left Atrial Appendage (LAA) closure. With this technique an implantable component is permanently fixed in the LAA to prevent thrombus embolization. Different studies demonstrated that this procedure is not inferior to systemic anticoagulation with OAC in prevention of thromboembolic risk. We reported our clinical experience with the use of this technique in haemodialysis patients with non valvular AF.

Results: In the last few months seven (7) haemodialysis patients were treated with percutaneous LAA closure. Bleeding and stroke risks were evaluated by HAS-BLED score and CHADS2-VASc score: HAS-BLED score was 4.5±0.58 (equal to 9%±0.11 yearly risk of major bleeding) and CHADS2-VASc was 4.0±1.0 (equal to 4.47±1.5 yearly risk of stroke). This procedure was well tolerated by each patient. OAC treatment was interrupted after the procedure and doubled antiplatelet therapy was introduced for a month. At this moment median of 9 months of follow-up was archived [IQR 3-12]; no adverse events has been assessed.

Conclusions: To the best of our knowledge this is the first consecutive series of LAA closures in haemodialysis patients. This procedure represents a real clinical alternative to the use of coumarin derived drugs. Our experience leads the way to the possible routine use of this procedure in CKD-5D patients. As well as this procedure could be used in those patients with contraindications to OAC, even more this treatment should be used in haemodialysis population, in which the use of OAC should be avoided for both increased risk of life-threatening bleeding events and well known negative cardiovascular effects.

PUB345
Management of Subclinical Thyroid Dysfunction Can Reduce Cardiovascular Events in Patients with End-Stage Renal Disease on Hemodialysis Hong Joo Lee, Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea.

Background: Normal thyroid function influences basal metabolic rate and general body metabolism and thyroid dysfunction is often associated with dyslipidemia and increased cardiovascular risk in general population. It is known that about 25% of patients with end-stage renal disease (ESRD) on hemodialysis had subclinical thyroid dysfunction. We investigated that subclinical hypothyroid dysfunction associate with dyslipidemia and cardiovascular event in hemodialysis patients. Hence, we conducted our study to elucidate whether subclinical thyroid dysfunction treated or not in ESRD patients.

Methods: All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. Thyroxine-3 (T3), free thyroid-4 (T4), Thyroid Stimulating Hormone (TSH) and lipid profiles in the serum were estimated and death from all causes and CV events served as outcome variables over a median follow-up period of 12 months. Participants were divided into groups based on the thyroid function. Statistical analysis was carried out by using SPSS.

Results: Among the 92 cases, 28.2% of the patients were having thyroid disorder. In which 2.1% were of hypothyroid, 13.7% were of subclinical hypothyroid, and 0.8% were of hyperthyroid, 11.6% were of subclinical hyperthyroid. We observed negative correlation between T3 & T4. Total cholesterol was raised in hypothyroidism in comparison to euthyroid ESRD patients. However, thyroid function didn’t have significant association with lipid profiles. Cardiovascular disease significantly often occurred in subclinical thyroidism patients than other group.

Conclusions: Our results show that the blood thyroid hormone level isn’t affected by dyslipidemia but affected by occurrence of CVD. Therefore, the management of subclinical hypothyroidism in hemodialysis patients should be considered.

Non survivors were significantly older, had lower number of total sessions, lower albumin and no dialysis. But dialysis adequacy and UF were comparable. Short duration of follow up may limit the ability to study other factors influencing outcomes.
**PUB346**

**Effect of Altitude on All-Cause Mortality in End-Stage Kidney Disease Patients Ongoing Hemodialysis in Peru** Katia Bravo-Jaimex,1 Viky Y. Suncion,¡ Jose Ernesto Rojas,‡ Christian R. Mejia,§ Sandra C. Schult,|| Medicine, Univ of Rochester Medical Center, Rochester, NY; | Medicine, Jackson Memorial Hospital, Miami, FL; ‡ Inst de Investigaciones de Altura, Univ Peruana Caytonay Heredia, Lima, Peru; § Asociación Médica de Investigación y Servicios en Salud, Lima, Peru; || Pediatrics, Inst Nacional de Salud del Niño, Lima, Peru.

**Background:** Worldwide, end-stage kidney disease (ESKD) prevalence has tremendously risen. Previous studies suggested that receiving hemodialysis (HD) at high altitude confers mortality benefits; however this effect has not been proved above 2000 m or in developing countries.

**Methods:** This historical cohort study analyzed medical records from six HD centers of the Peruvian Social Security System. Adult ESKD patients who started HD between 2000 and 2010 were included. Patients were classified into two strata (< 2000 and > 2000 m). The outcome variable was death from any cause. Cox proportional hazards models were built for the time from first dialysis to death from any cause, stratifying by year and censoring.

**Results:** 723 patients were enrolled, including 248 women (34%). The mean age was 52.8 ±16.9 years. 166 patients lived > 2000 m (22%). In first years after follow-up, survival rates were lower in the group > 2000 m, however after 8 years of follow-up this trend reversed. Age and gender were not significantly associated to mortality at altitude levels > 2000 m. Patients with diabetes had higher mortality rates at > 2000 m (p=0.003), independently of age.

**Conclusions:** In Peru, patients receiving HD at high altitude do not experience mortality benefits. In fact, diabetics have higher mortality rates at > 2000 m.

**Funding:** Private Foundation Support

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**PUB347**

**End-Stage Renal Disease in North Region of Oman/Epidemiology, Incidence, and Aetiology** Ruqaya Khanum Al-Zaabi,1,2 Elizabeth P. Tolmie,3 Ann Marie Rice,3 Nabil Mohsin,4 Ahmed Said Al-Busaidi,5 1Nursing and Health Care, Univ of Glasgow, Glasgow, United Kingdom; 2Nursing Education, Ministry of Health, Muscat, Sohar, Oman.

**Background:** The epidemiology of renal failure in Oman is scarce. There is a paucity of information on the size and burden of renal failure in Oman. Therefore, our research was conducted to measure the prevalence, incidence and death rate (epidemiology) among patients who have renal failure and undergo renal dialysis in four dialysis centers in the North of Oman; and to provide a description of the major characteristics of the studied patients.

**Methods:** A cross-sectional study was conducted. A proportional sample (n = 341) patients from four Renal Dialysis Centres (RDC) were interviewed face to face or via telephone using a structured questionnaire. Data collection took place between October and November, 2014. The incidence, prevalence and death rate are under collection until December 15, 2015.

**Results:** Over the period January 1st, 2014 to December 31st, 2014, a total of 96 new patients started dialysis in the four observed RDCs. The overall incidence rate was 13 patients per 100,000. The period prevalence for the patients undergoing renal dialysis was 52 patients per 100,000. The mortality rate for the same period of time was four patients per 100,000. Demographic data are summarized in table 1.

**Funding:** Government Support - Non-U.S.

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**PUB348**


**Background:** Hyperkalemia is a major problem in hemodialysis (HD) patients affecting there morbidity and mortality. HD patients receiving low potassium (K) bath for hyperkalemia have double the risk of sudden cardiac death. We noticed high rate of use of low K dialysate due to high prevalence of hyperkalemia in our dialysis unit. We are studying this phenomenon.

**Methods:** Our study was done in the biggest out-patient HD facility in Qatar (306 patients). We identified patients who required low K bath (based on an existing rigorous protocol, any K over 5.5 will be started on low K bath 1 mmol/L with checking K level every HD treatment till corrected) in 6 months period from 10/1/2014 to 3/31/2015. We collected background data in these patients and their potassium levels during that period.

**Results:** 62 out of 306 hemodialysis patients required low K bath continuously (5 patients) or intermittently (57 patients). Mean age was 59.9 ±6.5 years. There were 36 females on low K bath out of total 137 females versus 26 males out of 169 (p Value 0.014). 39 out of 62 were Qatar (62%) versus 65% in patients not on low K bath. Table 1 summarize number of patients on low K bath and number of low K bath HD treatments on monthly base versus average temperature in Doha, Qatar.

**Conclusions:** In a study of using low K bath in a major HD clinic in Qatar we found a statistically significant higher number of female patients who required low K bath than males. This might be attributed to dietary habits based on our dietitians experience and vascular access issues but further study is needed to explain these findings. There was a significant decrease in need for low K bath in January and February compared to other months both in the number of patients and HD treatments . We attributed that to combination of cooler weather and seasonal change in dietary habits. Further study again is needed to evaluate that prospectively.
PUB349

Co-Morbidity Rather Than Clinical Practice Patterns Determines Mortality in an Aged Dialysis Population

An Vanacker,1 Bert Bammens,2 Bart De Moor,3 Bart D. Maes.1 1Nephrology, AZ Delta, Roesselare, Belgium; 2Nephrology, Univ Hospitals, Leuven, Belgium; 3Nephrology, Jessa Hospital, Hasselt, Belgium.

Background: Hemodialfiltration (HDF), by adding convective to diffusove transport, is more effective in removing larger uremic retention solutes than hemodialysis (HD). As these solutes are thought to have a role in the accelerated cardiovascular disease of dialysis patients, HDF might result in lower mortality compared to HD.

Methods: All patients treated with thrice weekly HD (high-flux) or online HDF at 3 Belgian dialysis centers for ≥ six and < 42 months were included in July 2008. Hospitalized patients or patients with access-related problems were excluded. The effect of HDF versus HD on all-cause mortality at 6 years was evaluated. Multi-variate analysis taking into account all relevant baseline variables was performed to determine independent predictors of outcome.

Results: 242 patients were included (142 male, mean age 70.9 ± 11.8 years): 84 treated with HD, 158 with HDF. After 6 years, the incidence of all-cause mortality was significantly higher in HD than in HDF: 54% of patients in HD-group (64.3%), 70 of 158 patients in HDF-group (55.7%) (P = 0.04). Based on univariate associations with survival (*) and/or significant association with center or HD/HDF variable, following parameters were introduced in multivariate analysis: HD/HDF*, vintage, age*, weight, CCI*, use of calcium(Ca)-based and non-Ca-based phosphate (P) binders, dialysis hours/week, QB, Qd, dialysate Ca concentration*, vascular access*, mean P*, Ca-P product*, hemoglobin, albumin*, interdialytic weight gain and center. The final multivariate model is shown in the table below.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>1.01 – 1.06</td>
<td>0.003</td>
</tr>
<tr>
<td>Charlson Comorbidity Index CCI</td>
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<td>1.16 – 1.45</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Weight</td>
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<td>0.97 – 0.99</td>
<td>0.02</td>
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<tr>
<td>Calcium concentration of dialysate</td>
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<td>1.06 – 12.24</td>
<td>0.04</td>
</tr>
<tr>
<td>Vascular access</td>
<td>1.43</td>
<td>1.19 – 1.72</td>
<td>0.0002</td>
</tr>
<tr>
<td>Interdialytic weight gain</td>
<td>1.31</td>
<td>1.07 – 1.61</td>
<td>0.009</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.38</td>
<td>0.39 – 0.97</td>
<td>0.04</td>
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</table>

Conclusions: In an aged Western dialysis population, treatment with HDF did not improve all-cause mortality compared to high-flux HD. Mortality seems to be determined by comorbidity rather than by clinical practice patterns.

PUB350

Depression Is Associated with Frailty and Malnutrition but Not Comorbidity

Load in Chinese Peritoneal Dialysis Patients

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Background: Depression is common amongst patients with chronic kidney disease and is associated with excessive mortality in dialysis patients. This study determines the prevalence and risk factors of depression in Chinese peritoneal dialysis (PD) patients.

Methods: We studied 178 prevalence PD patients (103 males). Depression was screened by the 15-item self-reported Geriatric Depression Scale (GDS). We also determined patients' comorbidity load, dialysis adequacy, residual renal function, nutritional status, and degree of frailty.

Results: The mean age was 60.7 ± 11.7 years; vintage of dialysis 42.5 ± 44.1 months. Average GDS score was 4.9 ± 4.4. GDS score is closely associated with the frailty score (r = 0.692, p < 0.0001), malnutrition inflammation score (r = 0.406, p < 0.0001), and subjective global assessment score (r = 0.386, p < 0.0001). GDS score also has a modest correlation with Charlson's comorbidity index (r = 0.164, p = 0.028) and serum albumin level (r = -0.192, p = 0.019), but not with patient age, vintage of PD, dialysis adequacy, or residual renal function. When defined as a GDS score ≥ 8, 50 patients were treated with HD, 158 with HDF. After 6 years, the incidence of all-cause mortality was significantly higher in HD than in HDF: 54% of patients in HD-group (64.3%), 70 of 158 patients in HDF-group (55.7%) (P = 0.04). Based on univariate associations with survival (*) and/or significant association with center or HD/HDF variable, following parameters were introduced in multivariate analysis: HD/HDF*, vintage, age*, weight, CCI*, use of calcium(Ca)-based and non-Ca-based phosphate (P) binders, dialysis hours/week, Qb, Qd, dialysate Ca concentration*, vascular access*, mean P*, Ca-P product*, hemoglobin, albumin*, interdialytic weight gain and center. The final multivariate model is shown in the table below.

Conclusion: In an aged Western dialysis population, treatment with HDF did not improve all-cause mortality compared to high-flux HD. Mortality seems to be determined by comorbidity rather than by clinical practice patterns.

PUB351

Trends in Anemia Management with Darbepoetin Alfa in Patients on Maintenance Hemodialysis

Robert H. Yenchek,1 Anne C. Beaubrun,2 Jeffrey Petersen,3 David G. Dalpiaz,4 Alfred K. Cheung.1 1Univ of Utah, Salt Lake City, UT; 2Amgen, Inc., Thousand Oaks, CA.

Background: In the US, darbepoetin alfa (DA) is primarily used to treat anemia in patients receiving treatment in hospital-based dialysis centers. Epoetin alfa (EA) doses and hemoglobin (Hb) levels declined in response to recent regulatory and reimbursement events but little is known about trends in anemia management with DA in the US maintenance hemodialysis (HD) population receiving treatment in free-standing dialysis centers (FSDCs). We describe herein anemia management in FSDCs within the University of Utah (UU) Dialysis Program who switched from the use of EA to DA program-wide in 2005.

Methods: We included ~650 adults (age ≥18 yrs) with 1+ months on HD between 2008-2013 in 18 FSDCs within the UU Dialysis Program. We summarized quarterly intravenous DA and iron dose and use, Hb, and serum transferrin saturation (TSAT) and ferritin levels.

Results: 70-76% of patients received DA over the study period. Mean Hb levels among patients who received DA fell from 12.2 g/dl in 2008 before leveling around 10.3 g/dl from Q4 2011 to 2013 (Figure). The mean monthly DA dose was 209 mcg in Q1 2008, reached a peak of 256 mcg in Q1 2010, and decreased to ~105 mcg in 2013. Iron use rate from 52% in 2008 to 67% in patients in 2013. Iron dose also rose from 129 mg in Q4 2008 to 194 mg in Q4 2010, but declined to 163 mg in Q4 2013. Mean serum TSAT levels remained relatively constant at ~30% between 2008-2013 but serum ferritin levels increased from 449 ng/ml in Q1 2008 to 770 ng/ml in Q4 2013.

Conclusions: Trends in anemia management parameters among patients on HD treated with DA within FSDCs in the UU Dialysis program were consistent with national reports of patients treated with EA.

PUB352

Shorter Dialysis Session Time Was Associated with Higher Risk of Hospitalization and Death in Maintenance Hemodialysis Patients

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Background: Recently, dialysis efficiency was dramatically improved by using super flux dialysis membrane. However, in the condition of the common use of high-flux dialysis, it has not been well studied the relationship between treatment time and adverse events or survivals of maintenance hemodialysis (MHD) patients.

Methods: Subject: 805 patients undergoing MHD. Study design: Prospective, observational multi-center study of 3 years. We measured serum levels of urea nitrogen (UN), creatinine (Cr), b2microglobulin (MG), total protein, albumin, prealbumin, high sensitive C reactive protein (hCRP) every 3month. We also evaluated body mass index (BMI), and Kt/V. The associations between dialysis intensity and adverse events or death were investigated with the cox proportional hazards model for time-dependent variables.

Results: Although there was no significant correlation between pre-dialysis levels of b2MG or UN and adverse event or survival, high pre-dialysis Cr level was associated with lower risk of hospitalization (HR: 0.89, P<0.003) and death (HR:0.71, P<0.002). Moreover, high Kt/V was also associated with lower risk for cerebrovascular and cardiovascular
A Randomized, Factorial Pilot Study to Evaluate the Feasibility of an Intervention, so study Intervention (DIALYSISIZE)1 Stephanie E. Thompson,2 Scott Klarenbach,1 Anita Molzahn,1 Mark Haykowsky,1 Anita Lloyd,2 Marcello Tonelli,2 1Univ of Alberta, Edmonton, AL, Canada; 2Univ of Calgary, Calgary, AB, Canada.

Background: Intradialytic exercise (IDE) is associated with improved dialysis adequacy and amelioration of dialysis-related symptoms. However, the uptake of IDE is limited by knowledge gaps on efficacy—what type of exercise to prescribe to optimize outcomes, and on feasibility. The results of this pilot will inform the design of a full-scale efficacy study evaluating two types of IDE (aerobic and resistance) and will also provide research users with practical information on IDE.

Methods: In this single center, randomized, factorial (2 x 2) study, chronic adult hemodialysis patients were randomized to one of four IDE groups: cycling, resistance, cycling and resistance, or stretching (an attention control). Exercise was semi-supervised by a kinesiologist. Outcomes focused on a priori feasibility criteria: recruitment, fidelity to the protocol, and participant and unit staff response to IDE. As a secondary outcome, we evaluated the main effect of cycling and weights each compared with control on quality of life and physical performance at baseline and 12-weeks. To better understand feasibility, we conducted interviews with users.

Results: We exceeded targeted accrual of 28 people over 12 weeks. Of 100 patients screened, 51 were enrolled (36 did not meet inclusion criteria, 33 declined participation); 16% dropped out after randomization. Fidelity to the intervention was high: of 1,039 training sessions offered, 878 were delivered. Participant response to the intervention was favorable: 92% of participants continued exercising after the trial. There were no crossovers and no reported contamination. Dialysis staff were not consistently available to assist with implementation, so study staff were necessary to deliver IDE. Secondary outcomes were not statistically significant.

Conclusions: This pilot study demonstrated feasibility of high, patient acceptability, and low risk of contamination. However, IDE will not be feasible in the long term unless dialysis staff assist with implementation. This will need to be addressed before executing a definitive trial.

A Prospective Study of Routine Heparin-Free Hemodialysis (HFHD) with Streamline® Bloodlines (SL) in a Large Tertiary Acute Care Inpatient Practice Sami Safani,1 Mary Ann Ryan,3 Amanda L. Severson,3 Fares Alahadab,3 John J. Dillon,4 Robert C. Albright,4 Amy W. Williams,4 Marie C. Hogan,4 1Nephrology and Hypertension, Mayo Clinic, Rochester, MN; 2Nursing, Mayo Clinic; 3KSP Unit, Mayo Clinic.

Background: Extracorporeal circuit (EC) anticoagulation (AC) with heparin was a key advancement in hemodialysis (HD). However, AC in patients at risk of bleeding remains a frequently encountered problem. SL bloodlines eliminate blood-air contact, and reduce turbulence in HD circuit. Small studies suggest that SL reduces heparin use and improves HD efficiency. We prospectively evaluated EC clotting rates, impact on dialysis efficiency, and associated risk factors in our inpatient practice.

Methods: In this complete study, we followed acute care inpatients requiring HD without routine EC heparin. Patients could be on ACs for other non-HD indications. All sessions were performed using SL and Fresenius 2008K. HD sessions were observed for clotting events (CE) defined as interruption of HD session, loss of HD circuit, or inability to return blood. Of 970A runs were performed. Demographics & HD session characteristics are summarized in table 1. Overall CE rate was 5.2%. Determinants for CE were temporary HD catheters (OR=2.8, p<0.01), transfusions (OR=2.3, p=0.05), systemic AC (OR=0.2, p=0.01), & antplatelets (OR=0.4, p=0.01). CE were associated with a lower delivered Kt/V (diff0.39, p<0.01). Most CE during transfusions (71%) occurred when blood products were given by the HD circuit.

Conclusions: We successfully adopted HFHD with SL as our standard inpatient protocol. This protocol is feasible and safe in acute care inpatient HD. CE risk is low, and associated with temporary HD catheters and transfusions. Use of antplatelets and systemic AC is protective.
relationship between serum albumin levels and short-term mortality among chronic dialysis patients who are hospitalized with infectious diseases. This multicenter retrospective cohort study in Japan evaluated if serum albumin levels at the occurrence of infection is a risk factor for in-hospital mortality among hemodialysis patients.

Methods: From June 2011 to July 2013, a total of 418 hemodialysis patients who took blood cultures were reviewed retrospectively in five tertiary dialysis units participating in “TOMEI Nephrology Group for Clinical Research” study. After exclusion of 232 patients diagnosed with non-infectious diseases, 186 patients diagnosed with infections were analyzed. Patients were divided into two groups according to the serum albumin level at hospitalization: low serum albumin (Serum albumin<3.5 g/dL) or not. Outcome measure was in-hospital mortality. For statistical analysis,cox proportional hazard model was used.

Results: Among 186 patients with infectious diseases, there were 117 patients (62.9%) in low albumin group, and 69 patients (37.1%) in normal albumin group. During hospitalisation, median albumin (interquartile range 10-37), 29 patients (15.5%) died. 25 of 117 (21.4%) in low albumin group, and 4 of 69 (5.8%) in normal albumin group. The cox proportional hazard model revealed that low serum albumin and bacteremia were associated with in-hospital mortality. The hazard ratio of in-hospital mortality among low albumin group was 4.293 (95% CI: 1.61-15.55).

Conclusions: Although low serum albumin is a known risk factor for long-term mortality, this study showed that low serum albumin strongly predicts short-term mortality among hemodialysis patients hospitalized with infectious diseases.

PUB357
Usefulness of High-Frequency Wave-Length Ultrasonography as a Diagnostic Tool for Carpal Tunnel Syndrome in Hemodialysis Patients Tadashi Yamazaki,2 Tokie Hayasaka,2 Tetsuo Saito,3 Shuichii Tsuruoka,1 1Nephrology, Nippon Medical School, Tokyo, Japan; 2Dialysis Unit, Moka Hospital, Moka, Tochigi, Japan.

Background: Carpal tunnel syndrome (CTS) is a common complication in dialysis-induced amyloidosis. In orthopedics, high-frequency wave-length ultrasonography (US) with improved resolution is recently used for diagnosing disorders of the upper extremities. We aimed to determine the value of US for diagnosing CTS in hemodialysis (HD) patients, through a cross-sectional analysis.

Methods: All maintenance HD patients (N=150) at our hospital were recruited after providing written informed consent. Patients with apparent paralysis or pain in the index finger area and the quick form of the Disabilities of the Arm, Shoulder and Hand (1 - shortest diameter/longest diameter of the nerve around the carpal tunnel area). The 12 MHz probe) during HD, and the compression rate (CR) of the nerve was calculated as compression rate =1-(shortest diameter/longest diameter of the nerve around the carpal tunnel area).

Results: Total 250 wrists from 125 patients (Mean age = 65.6±10.6 years) were studied. The mean CR was 11.8±0.7% and the cut-off values of CR from ROC curve for history of carpal tunnel release was 25.7% (sensitivity 0.80, specificity 0.91). Multivariate analysis revealed that CR was significantly positively correlated with dialysis career, and CR and Quick-DASH scale, positive Tinel’s sign, and serum CRP and b2-Mg concentrations, whereas it showed a significantly negative correlation with pinch strength. Especially, patients with mean CR>14 years of HD and serum b2-Mg concentrations >20 mg/L showed significantly high CRs.

Conclusions: Measurement of CR with US is an easy and reproducible method for diagnosing dialysis-related CTS. The CR significantly correlated with symptoms and factors associated with dialysis-induced amyloidosis. The results support the routine evaluation of US in the dialysis center.

Funding: Government Support - Non-U.S.

PUB358
Technique Failure in Korean Incident Dialysis Patients: A National Population-Based Study Shinha Lee1, Hyunwook Kim2, Seung-Jung Kim1, Duk-Hee Kang,1, Kyu Bok Choi,1 Dong-Ryeol Ryu.2 1Dept of Internal Medicine, School of Medicine, Ewha Womans Univ Mokdong Hospital, Seoul, Republic of Korea; 2Dept of Internal Medicine, Wonkwang Univ College of Medicine Sanbon Hospital, Gunpo, Republic of Korea.

Background: Technique failure is an important issue for dialysis patients. In this study, we aimed to analyze a detailed technique failure rate and to determine the predictors for technique failure in Korea.

Methods: We identified all patients who had started dialysis between January 1, 2005 and December 31, 2008 in Korea, using the Korean Health Insurance Review and Assessment Service database. A total of 32,357 eligible patients (24,743 hemodialysis (HD) patients and 7,614 peritoneal dialysis (PD) patients) were included, and the median follow-up interval was 5.4 months.

Results: The crude incidence rates of technique failure among HD patients and PD patients were 3.4 and 5.1 per 1000 patient-years, respectively. When comparing technique survival rate between HD and PD in both Kaplan-Meier analysis and competing risks analysis, it was significantly higher in patients on PD than those on PD. The gap of technique failure incidence between HD and PD was exaggerated in Kaplan-Meier analysis compared to competing risks analysis. In multivariate analyses, diabetes mellitus and Medical aid as a crude reflection of low socioeconomic status were independent risk factors in both Cox proportional hazard model and Fine and Gray subdistribution model. Incident technique failure was independently associated with a lower risk of technique failure in Fine and Gray model.

Conclusions: Technique failure in PD is higher than that in HD, and it is major concern in patients initiating dialysis in Korea. The results of our study offer a basis for risk stratification and customized care for technique failure.

PUB359
Frequency of Not Achieving Target Weight in Hemodialysis Patients and the Reasons Behind It JinMaaha,1 Frank Modersitzki,1 Lada Beara Lasic,1 2Internal Medicine, Div of Nephrology, New York School of Medicine, New York, NY; 2Internal Medicine, Div of Nephrology, New York Harbor VA Healthcare System, New York, NY.

Background: Volume overload and volume depletion have both been associated with morbidity and mortality in patients with end stage kidney disease (ESKD) on hemodialysis (HD). A recent study demonstrated an increased mortality risk when post HD weight is more than 2kg above or below the prescribed estimated dry weight (EDW) for >30% of HD sessions. Our aim was to determine the frequency of sessions with weight difference (WD)<±2kg, determine the prevalence of patients WD<±2kg for >30% of sessions and identify the possible reasons in our outpatient chronic HD population.

Methods: 32 outpatients on chronic HD at the New York Harbor VA Healthcare System in Manhattan were monitored for 2 months. Data for 631 sessions was obtained. Charts and HD nursing notes were reviewed every 2-4 weeks for: weight, prescribed EDW, ultrafiltration (UF) rate, intradialytic complications (hypotension with systolic BP<90, dizziness, cramping, administration of intravenous fluids). Sessions with a missing documented EDW or post HD weight were excluded. 502 sessions were used in the analysis. Results: The mean WD for all sessions was 0.67±1.64 kg with a majority (83.7%) of HD sessions ending with post HD weight within 2kg of EDW which is consistent with the literature. 6 out of 31 (19.3%) patients had WD>±2kg for >30% of the evaluated sessions. The inability to achieve post HD weight within 2kg of EDW was most commonly (51.2%) associated with an elevated UF rate (defined as >875ml/hour). Possible reasons for not achieving EDW also included cramps (4.9%) and hypotension (2.4%).

Conclusions: Failing to achieve EDW within 2kg range is most commonly associated with high UF rates, indicating high weight gains between treatments. Proposed strategies to continue aiming at achieving EDW while compensating for the constraints of elevated UF include: decreasing intradialytic weight gain, increasing treatment frequency or treatment time. Further studies identifying the best strategies to achieve this goal are needed.

PUB360
Comparative Effectiveness of Dialyzers: A Longitudinal Propensity Score-Matched Study Scott Sibbel,1 Abigail Hunt,1 Suzanne Laplante,2 Werner Beck,3 Mary Gellens,4 John Alan Laich,5 Steven M. Brunelli.1 1DaVita Clinical Research, Minneapolis, MN; 2Baxter Healthcare Corporation, Deerfield, IL.

Background: Differences in dialyzer design may affect systemic inflammation and extracorporeal blood sequestration and thereby impact anemia management and control. We evaluated the comparative effectiveness of commonly used dialyzers with respect to intradialytic hemoglobin (Hb) levels, and ESA and IV iron utilization.

Methods: Patients included in the analysis received hemodialysis between 01 Jan 2009 and 31 Dec 2013 and were new users of Revaclear, Optiflux 160, or Optiflux 180 dialyzers. Patients were followed for 1 year or until end of study or censoring for dialyzer switch, modality change, or loss to follow up. For each comparison, eligible patients were propensity score-matched 1:1 on a range of demographic, comorbidity history, and baseline laboratory parameters. Outcomes were assessed using generalized linear mixed models including fixed effects for dialyzer type, time, and their interaction term.

Results: Matched patient pairs (31,551 for Revaclear-Optiflux 160 comparison; 21,008 for Revaclear-Optiflux 180 comparison) were assessed. ESA doses evolved differently over time among Revaclear patients versus both Optiflux 160 and Optiflux 180 patients (p interaction<0.001 for both). Differences in ESA dose were significant from month 3 for Revaclear versus Optiflux 160 (range, 173-483 U/treatment) and at all time points for Revaclear-Optiflux 180 comparison) were assessed. ESA doses evolved differently over time among Revaclear patients versus both Optiflux 160 and Optiflux 180 patients (p interaction<0.001 for both). Differences in ESA dose were significant from month 3 for Revaclear versus Optiflux 160 (range, 173-483 U/treatment) and at all time points for Revaclear versus Optiflux 180 (range, 120-392 U/treatment) and at all time points for Revaclear versus Optiflux 180 (range, 120-392 U/treatment). Hb levels were equivalent between Revaclear and Optiflux patients at all times. IV iron dosing was lower for Revaclear patients than Optiflux 160 and 180 patients (p<0.001 for each) but differences were small (±30g/d). A total of 12 patients switched dialyzers.

Conclusions: Use of Revaclear versus Optiflux dialyzers was associated with lower ESA doses, modestly lower IV iron doses, and equivalent Hb concentrations.
Lack of Leukocytic Response to Infections in End Stage Renal Disease

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1Internal Medicine, Abington Jefferson Health, Abington, PA.

Background: Patients with end stage renal disease (ESRD) on dialysis are at increased risk of infection resulting from a relatively immunosuppressed state. Dysfunctional immunity may be the result of uremia, dialyzer membrane interactions, poor nutritional status and impaired leukocyte responsiveness. Abnormal leukocytic response in such situations may result in missed diagnosis in the clinical setting as well as increased morbidity and mortality. The nature and magnitude of the leukocytic response to infection in this population has not been well characterized. This study is an attempt to assess the degree of leukocytosis in ESRD patients and compare it with the general population in the presence of an infection.

Methods: This was a retrospective study wherein all patients with ESRD on hemodialysis admitted to our hospital between December 2011 and December 2014 with any kind of infection were taken as the ESRD group and compared to others without ESRD or significant chronic kidney disease. Analysis of total WBC as well as percentage of Bandemia were compared and analyzed for statistical significance. Patients were excluded if on steroids, less than 18 years of age, presence of cancer, HIV, pregnancy, CKD stages any kind of infection were taken as the ESRD group and compared to others without ESRD.

Results: Nine patients moved to another hemodialysis facility. The patients dead at different times during the six years had significantly higher values of BMI (28.3 ± 6 vs 24.8 ± 3.1 kg/m², p < 0.01) and fat mass index (11.2 ± 4.1 vs 8.4 ± 2.8 kg/m², p < 0.003) compared to the survivors, while there were no significant differences for body cell mass (BCM) index (7.1 ± 1.7 vs 7.9 ± 1.8 kg/m²) and serum albumin (4.1 ± 0.4 vs 4.1 ± 0.1 mg/dl). Furthermore, deceased patients had lower values of reactivity (53.5 ± 11.7 vs 67.3 ± 13.7 Ohm, p < 0.000003), phase angle (5.1 ± 0.9 vs 5.9 ± 0.8 degrees, p < 0.00003) and the percentage of extracellular water was higher (50.6 ± 5.2 vs 46.1 ± 3.6%, p < 0.00003). Finally the BIVA analysis confirmed that the hydration was significantly higher in the deceased (73.3 ± 1.8 vs 71.2 ± 3.3%, p < 0.00006). In summary survivors had normal values of BMI and fat mass, a smaller reduction in BCM and less fluid overload than deceased patients.

Conclusions: The survival of HD patients is influenced by the nutritional status. In particular, fluid overload and decrease in muscle mass play a decisive role on survival. Fluid overload, low values of electrical resistance and phase angle predict mortality risk in ESRD patients.

Funding: Government Support - Non-U.S.

PUB362
Fluid Overload Predicts Mortality Risk in Maintenance Hemodialysis Patients

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Background: Maintenance hemodialysis (MHD) patients have a high mortality rate, mainly due to cardiovascular disease and malnutrition. The aim of this study was to evaluate the efficacy of the analysis of body composition by bioimpedance (BIA) to predict the mortality risk in hemodialysis patients.

Methods: Observational longitudinal study lasting six years on 78 prevalent MHD patients (68% male, mean age 65 ± 14 years; dialysis vintage 7 ± 7 years). Every two years, starting from the baseline, we collected clinical, laboratory and BIA data, including vectorial analysis (BIVA) and hydration scale, that is the hydration as percentage of lean body mass. We compared the BIA data of patients dead during the study period (n = 45; 65%) with those of survivors (n = 24; 35%). The significance of the differences between the mean values of the two groups at the baseline was evaluated.

Results: Nine patients moved to another hemodialysis facility. The patients dead at different times during the six years had significantly higher values of BMI (28.3 ± 6 vs 24.8 ± 3.1 kg/m², p < 0.01) and fat mass index (11.2 ± 4.1 vs 8.4 ± 2.8 kg/m², p < 0.003) compared to the survivors, while there were no significant differences for body cell mass (BCM) index (7.1 ± 1.7 vs 7.9 ± 1.8 kg/m²) and serum albumin (4.1 ± 0.4 vs 4.1 ± 0.1 mg/dl). Furthermore, deceased patients had lower values of reactivity (53.5 ± 11.7 vs 67.3 ± 13.7 Ohm, p < 0.000003), phase angle (5.1 ± 0.9 vs 5.9 ± 0.8 degrees, p < 0.00003) and the percentage of extracellular water was higher (50.6 ± 5.2 vs 46.1 ± 3.6%, p < 0.00003). Finally the BIVA analysis confirmed that the hydration was significantly higher in the deceased (73.3 ± 1.8 vs 71.2 ± 3.3%, p < 0.00006). In summary survivors had normal values of BMI and fat mass, a smaller reduction in BCM and less fluid overload than deceased patients.

Conclusions: The survival of HD patients is influenced by the nutritional status. In particular, fluid overload and decrease in muscle mass play a decisive role on survival. Fluid overload, low values of electrical resistance and phase angle predict mortality risk in MHD patients.

Funding: Government Support - Non-U.S.
of poor functional capacity and other co-morbid conditions from the Medical Evidence Form 2728. We conducted both Kaplan-Meier and Adjusted Cox regression analyses with death as the outcome variable.

Results: 56,194 (7.18%) were identified as nursing home residents upon initiation of dialysis. Among NH patients, 50.53% were female, 69.92% were white, and 99.49% were on hemodialysis and the mean age was 71.1 ± 12.1 years. The overall incidence rates of death of NH vs. non-NH patients were 51.8/100 and 17.6/100 patient-years, respectively (p<0.001). The unadjusted 1-year mortality was 50% in NH patients (vs. 20% in non-NH patients, p<0.001). Adjusted Cox analysis showed that NH patients were at significantly higher risk of death compared to non-NH patients (adjusted hazard ratio [AHR] 1.37; 95% confidence interval 1.35-1.38). Within this NH cohort, age (AHR 1.02; 95% CI 1.02-1.02), inability to transfer (AHR 1.25; 95% CI 1.22-1.29), inability to ambulate (AHR 1.08; 95% CI 1.05-1.11), cancer (AHR 1.15; 95% CI 1.12-1.19) and other co-morbid conditions were significantly associated with death.

Conclusions: NH patients on dialysis have a high mortality rate, even when compared to the broader ESRD population. Further studies on modifiable risk factors of mortality in this particularly high-risk ESRD population are warranted. [Disclaimer: The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the United States government].

PUB365


Background: Protein-energy malnutrition (PEM) is prevalent in the hemodialysis (HD) population and is associated with a high morbidity-mortality burden. Metabolic acidosis and PEM are closely related. Protein intake, which constitutes an acid load, is an important factor of pH regulation in end-stage renal disease patients. Therefore, could a higher bicarbonate serum level be the result of insufficient protein intake and be a useful marker of malnutrition?

Methods: We conducted a retrospective study in our HD service using a computer database with measurements obtained simultaneously for all 342 patients. Correlation between pre-HD session bicarbonate, albumin, prealbumin and normalized protein catabolic rate (nPCR) was assessed by the use of Pearson’s r and Spearman’s correlation test. Subgroup analysis were realised for patients with negative C- Reactive Protein (CRP < 5) and patients classified as clinically stable.

Results: We found a significant, negative and moderate, correlation between bicarbonate and nPCR, (pearman’s r = -0.27, p<0.001). Subgroup analysis showed similar results, (pearman’s r = -0.28, p<0.001)for198clinically stable patient and (pearman’s r = -0.24, p<0.003)for 144 patients with a negative CRP. There was no association between albumin (pearman’s r = -0.06, p=0.1511) or prealbumin (pearman’s r =-0.1511) and bicarbonate in any group.

Conclusions: A higher serum level of bicarbonate is associated with a lower nPCR, reflecting of poor protein intake, but not with a malnutrition state defined by albumin or prealbumin criteria. These patients are at risk to develop a clinically apparent malnutrition state after a prolonged period.

PUB366

Scope and Consistency of Outcomes Reported in Randomized Trials of Hemodialysis Gabrielle J. Williams, Allison Tong, Jonathan C. Craig. School of Public Health, Univ of Sydney, Sydney, NSW, Australia.

Background: Inconsistent outcome selection and reporting in clinical trials may limit their capacity to inform evidence-based decision making and the ability to combine findings in systematic reviews. Aim: We aimed to assess the scope and consistency of outcome selection and reporting in trials included in systematic reviews of interventions for patients on hemodialysis (HD).

Methods: The Cochrane Database of Systematic Reviews was searched from 1999 to January 2015 for published systematic reviews of interventions for patients on chronic HD. The description and frequency of outcomes reported within the source randomized controlled trials were assessed.

Results: The 18 systematic reviews included 282 trials that reported over 518 outcomes. There was considerable heterogeneity among the outcomes reported. Across all trials, 320 outcomes to improve the comparability of trial findings in meta-analysis and to provide greater confidence around treatment decisions for patients undergoing HD.

Funding: Government Support - Non-U.S.

PUB367

Blood Pressure and Cognitive Decline in Hemodialysis Patients Sarah M. Duncan, 1 Hocine Tighiouart, 1 David A. Drew, 1 Tammy Scott, 1,2 Daniel E. Weiner, 1 Mark J. Sarnak. 1 Tufts Medical Center, Boston, MA; 2Tufts Univ, Boston, MA.

Background: Cognitive impairment is common in hemodialysis (HD) patients; however, the relationship between measures of blood pressure (BP) and longitudinal decline in cognitive function is unknown in this population.

Methods: 314 participants in the Cognition and Dialysis Study underwent an annual comprehensive battery of cognitive tests. Using principal components analysis (PCA), we reduced individual test results to two domain scores representing memory and executive function. Adjusted joint mixed models accounting for death, transplant, and drop-out were used to explore the association of blood pressure (systolic (SBP), diastolic (DBP) and pulse pressure (PP)) with change in cognitive function over time.

Results: Mean (SD) age was 63 (16) years, 47% were women, 22% were African American, and 44% had cardiovascular disease (CVD). Mean (SD) SBP, DBP, and PP were 141 (21), 73 (12) and 68 (15) mmHg, respectively. Median follow up time was 1.8 years (IQR 1.0-3.4). Mean slopes of PCA memory and executive were 0.03 (95% CI 0.01, 0.07) and -0.11 (95% CI -0.15, -0.06) per year, respectively. Lower DBP and higher PP were associated with decline in measures of both memory and executive function. There was no association between SBP and cognitive decline.

Conclusions: Lower DBP and higher PP are associated with faster rate of cognitive decline, in particular that related to executive function. Because impairment in executive function is a manifestation of vascular disease and lower DBP and higher PP are associated with CVD in HD patients, our results suggest that cognitive decline may be mediated by vascular disease in this population.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.

PUB368

High Ferritin Levels Achieved with Ferric Citrate as a Phosphate Binder Do Not Associate with Adverse Events Udavan Y. Bhatt, 1 Kausik Umanath, 2 Mohammedi Sika, 1 Mark Koury, 1 Robert M. Nieceastro, 3 Barbara A. Greco, 4 Dana G. Niederpruem, 1 Jessica J. Chang, 1 Seandren Z. Fademia, 1 Molly Mcfadden, 8 Julia Lewis, 1 Jamie P. Dwyer, 3 The Collaborative study group, 4 Ohio State; 5Henry Ford Hosp; 6Vanderbilt; 7CSG; 8Baystate Med Ctr; 9U of VT; 10Western Neph; 11U of Utah; 12Baylor College of Med.

Background: Ferric citrate (FC) as a phosphate binder increases Fe stores and reduces IV iron/ESA use while maintaining hemoglobin. This analysis compares effects of higher achieved ferritin levels in subjects on FC to those in subjects on sevelamer carbonate and/or calcium acetate (active control, AC).

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

Underline represents presenting author.
Methods: Data were obtained from the 52-wk active control period of the FC pivotal trial. Subjects with a baseline ferritin ≥1000ng/mL or TSAT≥50% were excluded from the trial. We randomized 292 subjects to FC and 149 to AC. Any subjects who developed ferritin level ≥1500ng/mL at any time over 52wks were identified. CV, ID, and dialysis access related adverse events (AE) occurring at any time over the 52-wk period were tabulated. Results: 57 subjects (19.8%) in the FC group and 14 subjects (9.5%) in the AC group had at least a single ferritin≥1500ng/mL (p=0.012) during the 52 wks. CV events including MI, CHF, and arrhythmias, occurred in 12.3% of the FC group compared to 21.4% ID AEs occurred in 42.1% FC and 50.4% AC. Dialysis access related AE occurred in 15.7% FC and 14.7% AC. All CV events were statistically significant with a Bonferroni correction (p=0.003) for the FC group (2.95±3.75mg/wk) than the AC group (6.20±3.64mg/wk), consistent with the full cohort that saw a significant reduction in IV iron use. Cumulative ESA dosing was 1016±906 Units/wk FC and 1781±1756 Units/wk AC (p=0.256).

Results: In the subset who developed ferritin ≥1500ng/mL shows that fewer subjects experienced a CV, ID, or dialysis access related AE in those receiving FC vs AC. IV iron use was statistically lower and ESA dosing was numerically lower. As previously reported the majority of ferritin≥1500ng/mL resolved and 90.1% were adjudicated to be related to IV iron or other inflammatory AEs. This analysis although limited by small sample size supports the conclusion that FC is clinically useful and safe vs traditional binders. Funding: Other U.S. Government Support, Pharmaceutical Company Support - Keryx Biopharmaceuticals, Inc.

PUB369
Association Between Employment Status and KDQOL Scores in Dialysis Patients
Duane V. Dunn,1 Deborah S. Evans,1 Elizabeth J. Jones,1 Caroline Hann,2 Rich Muttel,1 Allen R. Nissenson,1 Deborah A. Benner.1 DaVita HealthCare Partners Inc, Denver, CO; 2Apex Health Innovations, Simi Valley, CA.

Background: Studies have shown that unemployment negatively impacts dialysis patients’ quality of life (QOL).1 QOL can be quantified and low scores on the Kidney Disease Quality of Life (KDQOL) survey are associated with poor outcomes.2 Our study examines employment/unemployment status and KDQOL scores.

Methods: We collected employment status data on 122,166 adult patients at a large dialysis organization from Nov 2014-Apr 2015. Patients were grouped as either employed (received pay or in training) or unemployed (including retirees and those on long-term disability or Workers Compensation) or other (involved in work/activity but not paid). Data were matched with patients’ most recent KDQOL scores.

Results: The employed group (n=16,216) had the highest KDQOL scores in all categories (Table 1) and with smaller SDs compared to the unemployed group (n=98,914) (Table 2). A clinically meaningful difference (6.8) in Physical Component Score was found between the employed (42.0) and unemployed (35.2) groups. This difference was greater (~10 points) between full-time employed and Workers Compensation patients, who scored lowest in all categories. Funding: Dialysis Patients Association of Nephrology.

PUB371
The Mechanisms Study on Neointimal Hyperplasia of Autogenous Arteriovenous Fistula in Maintenance Hemodialysis Patients
Nanmei Liu, Jumin Hospital of Shanghai.

Background: To evaluate the influence and the possible mechanism about neointimal hyperplasia of autogenous internal arteriovenous fistula in hypertensive nephropathy and diabetic nephropathy patients which was going maintenance hemodialysis and provide possible theory about how to prevent from intimal hyperplasia, extend the life of AVF in clinic.

Methods: Collecting cephalic vein when the hemodialysis patients had the surgery of AVF angioplasty and reconstruction.Vascular tissues were divided into chronic glomerulonephritis group,hypertensive nephropathy group and diabetic nephropathy group. Immunohistochemistry was used to detect the expression of vascular smooth muscle actin (a-SMA). Selecting the control group and fistula vascular tissue which the useful life was 1~2 years, basic fibroblast growth factor (bFGF), insulin-like growth factor 1(IGF-1),matrix metalloproteinase2 (MMP2) and matrix metalloproteinase9 (MMP9) were to detect expression change by immunohistochemical staining.

Results: Compared with chronic glomerulonephritis group, intima thickness of hypertensive nephropathy and diabetic nephropathy were significantly increased and the increase was more significant in diabetic nephropathy. Hyperplasia intima was eccentric hypertrophy and the hyperplasia intima showed obvious inflammatory cells infiltration and vascular degeneration. Immunohistochemical staining showed that compared with the group of chronic glomerulonephritis, hypertensive nephropathy and diabetic nephropathy groups’ a-SMA, bFGF, IGF-1 and MMP9 expression levels were significantly increased, expression of VEGF was significantly reduced, MMP2 was no significant change (P>0.05). Univariate regression analysis revealed that the expression levels of a-SMA was positively correlated with bFGF, IGF-1 and MMP9, negatively correlated with the VEGF. AVF intimal hyperplasia mainly dominated by the vascular smooth muscle cells (VSMC) proliferation. Multivariate analysis showed that hypertension and diabetes were as a protective factor and the intimal hyperplasia, shorten the life of fistula and diabetes promote intimal hyperplasia more significantly. This study provides a theory and therapeutic targets for the prevention and treatment on intimal hyperplasia of AVF in dialysis patients. Funding: Government Support - Non-U.S.
Conclusions: Depression and sleep disorders are important factors influencing the nutritional status and could be an independent risk factors for malnutrition in elderly patients receiving maintenance dialysis. Psychological assessment should be mandatory in the follow up of these patients to identify depression and sleep disturbance because many of them are reversible.

PUB373

Predisialysis Hyponatremia and Mortality in Elderly Patients with Incident Maintenance Renal Replacement

Conclusions: We retrospectively assessed mortality in 397 (mean age 73.0 year, male female 226/171) patients aged ≥65 years with non-diabetic end-stage renal disease (ESRD) who initiated renal replacement therapy (RRT) at a tertiary university hospital between 2000 and 2010. 1 year all cause mortality (ACM) was analyzed in relation to predialysis serum sodium (sNa). We divided subjects into 3 groups according to sNa: Group1, < sNa 125; Group 2, sNa 125-134; Group 3, sNa ≥ 135 mEq/L. Patients with sNa levels >145mEq/L were excluded.

Results: The median value of sNa was 137 mEq/L (interquartile range 133-140 mEq/L). Chronic comorbidities including congestive heart failure (r = -0.215, P<0.001) and liver cirrhosis (r = -0.174, P<0.001), lower estimated glomerular filtration rate (r = -0.152, P<0.005) and albumin (r = -0.208, P<0.001) were associated with lower sNa levels in elderly patients after full adjustment. One hundred and five (26.4%) patients had died at the 1-year follow up. Higher sNa level was associated with lower adjusted ACM in a continuous model (HR 0.433, 95% CI 0.261-0.718, P<0.001). Group 1 had a higher mortality than normonatremia group in a categorical model (reference group, 3.6 (2.48-5.47)). The sNa level and mortality difference was not observed between group 2-3 (reference group3, HR 1.511, P=0.161). Conclusions: Predisialysis hyponatremia was associated with increased 1-year mortality in elderly ESRD patients who initiated RRT. However, the highest mortality was only observed in elderly patients with severe hyponatremia (sNa < 125mEq/L). These findings suggested that compared to adults <65 years, other comorbidities or factors rather than sNa may affect mortality in elderly.

PUB374

Observation of the Correlation Between the Uremic Toxins with Clinical Feature in Uremia Patients

Methods: 72 cases of maintenance hemodialysis patients were observed, age 28-80 years(59.75±13.86), dialysis duration 4-192 months (34.46±39.15), HD group (n = 50), HDF group (n = 22/ once 1-2 weeks).Before each conventional HD and HDF therapy, blood was sampled for small molecule water-soluble toxins BUN with automatic biochemical analzye, Middle molecular and macromolecular toxins (MMS) with Ultraviolet spectrophotometry, pentosidine(PENT) with enzyme-linked immunosorbsent assay method(from ADL Company, USA), Protein-bound toxins, indoxyl sulfate(IS) with high performance liquid chromatography method. Results: For HDF versus HD, there was no significant differences between BUN,MMS, pentosidine and IS.There was low positive correlation between MMS, PENT, IS and the age of the patients (r being 0.322, 0.263 respectively, P>0.05). MMS, PENT and IS were positively related with dialysis months (r being 0.406, 0.427, 0.742 respectively, P<0.05). Conclusions: HD and HDF therapy may not good enough in clearing middle molecular toxins and protein-bound toxins, which results in their accumulation in patient’s body with the increase of dialysis course. It is recommended that better dialysis methods may be adopted for patients who have received hemodialysis for a long time.

PUB375

Parathyroid Hormone Response in Chronic Hemodialysis Patients Converted from Intravenous Doxercalciferol to Oral Calcitriol Three Times a Week

Methods: Data was collected by a retrospective chart audit of end stage renal disease patients on hemodialysis in an outpatient chronic dialysis unit. We identified 33 chronic hemodialysis patients that had a record of treatment with intravenous doxercalciferol (6 months minimum) and transition to three times oral calcitriol (6 months minimum) between June 2014 and May 2015 following a conversion algorithm. The change in serum calcium, phosphorus, and iPTH between treatment periods (intravenous doxercalciferol vs. oral calcitriol) was analyzed.

Results: Patient characteristics were as follows: mean, age 63.16±13 years; 39% were men; and 55% black. The mean (SD) for serum calcium and phosphorus and median (IQR) serum iPTH during the 6 months of intravenous doxercalciferol were 8.8±0.7 mg/dL, 4.5±1.3 mg/dL and 643 (384 to 908) pg/mL, respectively. The corresponding values after 6 months of oral calcitriol were 8.8±0.6 mg/dL, 3.9±0.7 mg/dL, and 147 (102-245) pg/mL, respectively. The comparisons achieved statistical significance (p > 0.43 for all). 48% of patients were on calcenacel during each of the treatment periods. The median (IQR) change in iPTH increased slightly among those patients receiving oral calcitriol and sevelamer (34 (-132 to 147)) pg/mL, while iPTH decreased among patients receiving oral calcitriol and other non-sevelamer binders (-102 (-294 to 155 pg/mL, p=0.17)). Conclusions: This small retrospective study suggests that conversion from intravenous doxercalciferol to oral calcitriol using a conversion algorithm maintains iPTH within KDIGO recommended targets and does not appear to cause hypercalcaemia or hyperphosphataemia. The clinical significance of other iPTH values among those treated with oral calcitriol and sevelamer needs further study.

Funding: NIDDK Support, Veterans Administration Support

PUB376

Pregnancy and Dialysis in Chronic Kidney Disease – A Case Study

Conclusions: There are improved results with intensive dialysis and multidisciplinary approach to the management.

PUB377

When Shall the Advanced Chronic Kidney Disease Patients Start Dialysis?

Conclusions: Out of five pregnancies three had successful outcome with intensive dialysis.

NIDDK Support, Veterans Administration Support

PUB378

Pregnancy is rare in dialysis patients and outcomes are generally poor. There are improved results with intensive dialysis and multidisciplinary approach to the management.
The Incidence and Type of Cancer in Patients with End-Stage Renal Disease: A Prospective Cohort Study for End-Stage Renal Disease in Korea

**Background:** In patients with end-stage renal disease, urinary tract kidney cancer is known to be the most prevalent type of cancer. However, the incidence and type of cancer are affected by variable factors such as age, gender, ethnic differences. Moreover, the causality of dialysis and cancer incidence in certain type of cancer is still needed to be clarified.

**Methods:** A total of 5,225 patients in the clinical research center for ESRD cohort were enrolled from Aug 2008 to Dec 2014. The primary outcome to be compared is the cancer incidence rate of ESRD patients with the general population. We obtained cancer incidence data from National Cancer Information Center Registry in healthy counterpart.

**Results:** A total of 2,200 incident and 3,035 prevalent dialysis patients was included throughout the study. The mean follow-up duration was 25.3 months, and 116 (2.2%) patients were diagnosed with cancer during the observation periods. ESRD with cancer group was significantly older, longer dialysis duration and more comorbidity than control group. The incident rate of cancer in prevalent dialysis patients was higher than those in incident dialysis patients (2.5±1.3%, p<0.002). The proportion of primary organ was highest in digestive organ (33.6%). In 14.79% of patients, the MSPSS (social support) score was used for evaluating patients' social support. The initial incidence of cancer from dialysis initiation was 58.6 months in digestive cancer, 52.0 months in urinary tract cancer. The standardized incidence ratio (SIR) of overall cancer was 0.94 (95% CI: 0.72 –1.19). Urinary tract cancer showed the highest SIR (4.7, 95% CI: 4.42–8.19) and had the highest SIR (16.1%). It was interesting to note that the highest frequency (10.15%) of digestive organ cancer showed no difference in the incidence of cancer to compare the general population [SIR : 0.607, 95% CI: 0.36–0.94].

**Conclusions:** Further research was needed to compare the organ-specific cancer incidence of ESRD patients with the general population. The screening test could be necessary for digestive and urinary tract cancer.

**PUB387**

The Role of Social Support in Hemodialysis Patients

**Background:** A number of patients with End-Stage Renal Disease (ESRD) have significant impairment in social support. Especially, the limited function of patients with hemodialysis (HD) prevents them from social activities and even makes them social withdrawal. There are few studies of factors affecting the social support in HD patients. The aim of our study was to identify the clinical and psychosocial factors including quality of life related to impaired social support in HD patients.

**Methods:** The 101 participants on HD from the Daegu Catholic University Medical Center were assessed from September in 2013 to September in 2014. Patients on HD for acute kidney injury were excluded from this study. Multidimensional Scale of Perceived Social Support (MSPSS) was used for evaluating patients' social support. The correlation of cancer incidence and psychosocial factors including quality of life, anxiety, depression and sleep disorder were evaluated. Laboratory and clinical information including hemoglobin, vitamin D (25(OH)D, 1.25(OH)2D3), albumin, Kt/V, normalized protein catabolic rate, ferritin, bone mass index, duration of HD were assessed. Stepwise multivariate logistic regression with backward selection was performed.

**Results:** The mean of MSPSS (social support) score was 36.8±9.3. In subgroups of social support, the MSPSS-family, MSPSS-friend, and MSPSS-medical team scores were 14.4±4.6, 9.8±3.9, and 9.4±3.9, respectively. The variables showing statistical association with social support were quality of life (r=0.332, p<0.01), depression (r=-0.290, p<0.001), anxiety (r=0.372, p<0.001), and serum creatinine (r=-0.270, p=0.007). Multiple regression showed that quality of life (95% CI: 0.615–19.799, p=0.037) and serum creatinine (95% CI: 1.543–0.319, p=0.003) were independent predictors of impaired social support.

**Conclusions:** This study explored the determinants of high susceptibility to the impaired social support in HD patients. We found that the impaired social support is associated with the quality of life and serum creatinine. Further study will be needed because of the possibility of different results depending on culture and ethnicity. As well as, we should consider the psychosocial interventions to improve the impaired social support.

**PUB380**

Use of Portable Fundoscopic Photography to Screen for Diabetic Retinopathy in the Hemodialysis Unit

**Background:** Over 40% of dialysis patients have diabetes, yet only 25% get annual eye exams. Due to the frequency and duration of visits to dialysis centers, patients on dialysis likely have increased barriers to receiving eye exams and other recommended preventive care. This study evaluated the need for ophthalmic care, barriers to care, and prevalence of diabetic retinopathy (DR) in this population.

**Methods:** Prospective cohort study at two dialysis centers (1 urban, 1 suburban). A total of 5,225 patients in the clinical research center for ESRD cohort were enrolled from Aug 2008 to Dec 2014. The primary outcome to be compared is the cancer incidence rate of ESRD patients with the general population. We obtained cancer incidence data from National Cancer Information Center Registry in healthy counterpart.

**Results:** A total of 2,200 incident and 3,035 prevalent dialysis patients was included throughout the study. The mean follow-up duration was 25.3 months, and 116 (2.2%) patients were diagnosed with cancer during the observation periods. ESRD with cancer group was significantly older, longer dialysis duration and more comorbidity than control group. The incident rate of cancer in prevalent dialysis patients was higher than those in incident dialysis patients (2.5±1.3%, p<0.002). The proportion of primary organ was highest in digestive organ (33.6%). In 14.79% of patients, the MSPSS (social support) score was used for evaluating patients' social support. The initial incidence of cancer from dialysis initiation was 58.6 months in digestive cancer, 52.0 months in urinary tract cancer. The standardized incidence ratio (SIR) of overall cancer was 0.94 (95% CI: 0.72 –1.19). Urinary tract cancer showed the highest SIR (4.7, 95% CI: 4.42–8.19) and had the highest SIR (16.1%). It was interesting to note that the highest frequency (10.15%) of digestive organ cancer showed no difference in the incidence of cancer to compare the general population [SIR : 0.607, 95% CI: 0.36–0.94].

**Conclusions:** Further research was needed to compare the organ-specific cancer incidence of ESRD patients with the general population. The screening test could be necessary for digestive and urinary tract cancer.

**PUB379**

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**Conclusions:** This study explored the determinants of high susceptibility to the impaired social support in HD patients. We found that the impaired social support is associated with the quality of life and serum creatinine. Further study will be needed because of the possibility of different results depending on culture and ethnicity. As well as, we should consider the psychosocial interventions to improve the impaired social support.

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

Underline represents presenting author.
PUB383
Enhancing Patient Engagement in Future Clinical Trials – The Effects of Age and Ethnicity
Territa Santhakumar, Kieran Macaffrey. Renal, Royal London Hospital, London, United Kingdom.

Background: Increasing patient engagement from ethnicity minority populations is crucial to the widespread applicability of research findings, but this represents a challenge in nephrology clinical research. Ethnicity, socio-cultural and language barriers along with a lack of understanding and awareness of clinical trials are potential factors that affect patient involvement in clinical trials.

Methods: We developed a patient survey in English, Urdu and Bengali to represent our ethnically diverse population in East London to explore the attitudes and understanding of clinical research. The surveys were offered to all patients attending the haemodialysis and renal outpatient department over a 2 week period.

Results: 151 forms were completed, 145 in English, 7 in Bengali and 1 in Urdu. 41% of the forms were from patients who attended transplant clinic and 31% from patients who attended for haemodialysis. Overall there was a strong message that patients wanted more trials in nephrology and felt that taking part in trials would help them take a more active role in their health. They also felt there was a lack of information on how to access research opportunities. Of those who completed the survey there was no significant ethnicity differences in their attitudes and understanding of clinical research, however transplant patients who identified themselves as White British were significantly more likely to take part in the survey (p<0.02). Patients who identified themselves as Black British were significantly less likely to take part in the survey (p<0.02). In the dialysis cohort, patients who identified themselves as White British were significantly more likely to take part in the survey (p<0.02). Whereas patients who identified themselves as Bangladeshi were significantly less likely to take part in the survey (p<0.04). Age did not appear to have an effect on patients’ perception and understanding of clinical trials.

Conclusions: From our work it is clear that there is a patient led demand for greater engagement in translational research. However, challenges remain in engaging ethnic minority cohorts in clinical research.

Funding: Other NIH Support - National Institute for Health Research

PUB384
Deferred Educational App Personalization Increases Registration Completion
Daniel Schwartz,1 Chai Kruse.2 1Faculty of Medicine, Univ of British Columbia, Vancouver, BC, Canada; 2QxMD, Vancouver, BC, Canada.

Background: ‘Read by QxMD’ (http://qxdm.com/read) is an app that curates the nephrology literature and personalizes reading recommendations based on a clinician’s or researcher’s interests. In order to provide highly accurate recommendations, the app must collect content preferences such as preferred journals and topics. In addition, it must collect email address and personal identifiers in order to complete registration and offer CME. When the registration process is too onerous, mobile app users may not complete registration. If the registration process fails to collect necessary user data, this may negatively impact the educational value of the app. We hypothesized that allowing users to delay providing personal information until after they set their preferences would increase registration completion.

Methods: We randomly assigned all users registering on the Android version of Read to two different registration processes. In version 1, “upfront personalization”, users are asked to provide personal identifiers prior to setting their preferences, while in version 2, “deferred personalization”, users set preferences first and after this has been completed are asked to provide personal identifiers. The Leaflamp SDK was used to implement and automate the randomization of alternate registration pathways. The primary outcome was completion of registration.

Results: Between April 6, 2015 and June 1, 2015, a total of 5660 users who registered using the Android version of ‘Read’ were randomized with 2834 users randomized to upfront personalization and 2836 to deferred personalization. Upfront personalization yielded a 47.4% (95% CI 46.0 to 48.8) registration completion rate versus 50.7% (95% CI 49.0 to 52.4) with deferred personalization (p<.05).

Conclusions: A strategy of deferred collection of personal identifiers yielded slightly higher completion rates. To maximize user registration when onboarding users to educational medical apps, consider deferring the collection of personal information until user preferences have been provided. Further research is required to maximize app registration when data requested is extensive as in ‘Read’.

PUB385
Onconephrology Abstracts Trends in ASN Kidney Week 2012-2014
Jyotsana Wanchoo, Kenar D. Jhaveri. Nephrology, Hofstra NSLIJ School of Medicine.

Background: Onconephrology is an emerging new specialty of nephrology. The ASN created a forum dedicated to the field of Onconephrology in 2011 to improve collaborative care for cancer patients with kidney disease. One of the aims was to allow for collaborative research strategies in the field of onconephrology. However, the number of onconephrology related abstracts accepted to be presented at ASN Kidney Week (ASN-KW) 2012-2014 is not known.

Methods: We reviewed the abstracts presented in the ASN-KW over past 3 years from 2012-2014 which were related to Onconephrology. Search terms used to identify abstracts included cancer, myeloma, chemotherapy, tumor lysis, paraneoplastic syndrome and hypercalcemia. They were then categorized into: basic science, chemotherapy, myeloma, epidemiology, electrolyte disorders, AKI, tumor lysis, GN, paraneoplastic syndromes and obstructive uropathy. Abstracts were also categorized based on study design.

Results:

Figure above breaks down the total number(s) of abstracts (Y axis) in the last 3 years presented at ASN-KW by category. There has been an increase in the number of onconephrology abstracts over last 3 years. A total of 175 abstracts were reviewed. In 2012, there were 50 onconephrology related abstracts, increased to 54 in 2013 and 71 in 2014. Abstracts related to basic science(16%), chemotherapy toxicities(16%), myeloma(16%) and epidemiology (16%) dominated most of the accepted abstracts. Of the clinical abstracts, > 50% were case reports, 41% were retrospective studies, 4.5% database studies and <1% RCT.

Conclusions: Over the last 3 years, we have seen a growing trend in the number of abstracts submitted in the ASN-KW related to the field of onconephrology. We suggest creating a separate section dedicated to onconephrology in the ASN meetings to allow for collaborative research and greater understanding of cancer related nephrology, leading to improved patient outcomes.

PUB386
Patients-Initiated Educational Research in a Digital Age
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Background: The emergence of web-based technology in the digital age has become popular in the healthcare industry, particularly in the educational research field. A web-based technology can bridge the educational gap between researchers and patients.

Methods: We aimed to develop a user-friendly interface between a virtual community that is driven by patients and researchers and a preliminary knowledge-building activity. Wikiheart is a web research environment that creates a real-time community between researchers and patients without geographical restrictions.

Results: Once patients have registered for free, the system allows these users to write their own articles or to edit other articles, which often leads to thought provoking medical research questions. Wikiheart also demonstrates a novel approach to population science that is based on huge databases with multiple cloud servers that reach the web research community. Nowadays Wikiheart has more than one million visitors, and serves as an educational web technology that provides its users with both a variety of learning methods, and several areas of research focus.

Conclusions: Wikiheart is an innovative web-based program for conducting educational research in the digital community. It is an excellent tool for researchers and patients to generate new hypotheses via the scientific method in an online environment.
Detailed Subject Lines Increase Engagement with Educational Emails

Daniel Schwartz,1 Chan Kruse,2 Stephane Boyer.1 1Faculty of Medicine, Univ of British Columbia, Vancouver, BC, Canada; 2QxMD, Vancouver, BC, Canada.

Background: ‘Read by QxMD’ (http://qxmd.com/read) is an educational service and mobile app that curates the nephrology/medical literature and personalizes reading recommendations based on a clinician’s or researcher’s interests. Each week, registrants receive an alert that highlights the most popular medical articles in the reader’s clinical or research area of specialty. The content of email subject lines have been shown to have a significant impact on whether email is read or deleted prior to being read. We hypothesized that providing more details in the subject line would result in greater engagement with the email content.

Methods: We randomly assigned all emails sent containing the “Most Read” articles of the week to either a generic/consistent subject line or a subject line that included the title of the most commonly read article of the week (detailed/variable). SendGrid, an email service provider, was utilized for email delivery and to automate the subject line randomization. The primary outcome was email open rate. Secondary outcome was email click through rate.

Results: Between January 7, 2014 and May 1, 2015, a total of 1,287,442 emails were sent. 643,475 were generic/consistent and 643,967 were specific/variable. A specific/variable email subject line yielded a 70.76% (95% CI 70.68 to 70.84) open rate versus 48.85% (95% CI 48.76 to 48.94) with an email subject line that was generic (p < .01). A detailed/variable subject line did not increase click through rate as compared to a generic/consistent subject line. 9.87% (95% CI 9.82 to 9.92) vs 9.85% (95% CI 9.8 to 9.9) p > .05.

Conclusions: Including details about the content of an educational email in the subject line resulted in a greater email open rate but did not increase the click through rate. Further research is required to increase engagement with the content of educational emails provided by the ‘Read’ educational service.

Teaching Ethics and EBM in the Medical School: Case Discussion as a Useful Tool to Acquire Bioethical Skills and Analytical Tools.

Laura Sacchetti,1 Laura Verze,1 Fratruo Cavallaro,1 Costanzo Quaglia,1 Clinical and Biological Sciences, Univ of Torino, Italy; 2Course of EBM and Ethics, Univ of Torino, Italy.

Background: History of Nephrology influences the development of Bioethics and offers ideas for teaching: the first Ethics Committee (the ‘God’s line’), brain death, the sale of organs, the limitations of resources, up to the global needs (as in the 0-25 project). Case discussion within the Medical school may be a useful tool to acquire bioethical skills and analytical tools.

Methods: Discussion of clinical cases: patient in his context, his comorbidity, good cognitive status (writer), GFR 10 mL / min. The case raises questions about the choice of dialysis or peritoneal dialysis. 50 medical students of the curricular course of ethics and EBM are tutored for an academic year through the collection of information from databases (Pubmed), web, talk with experts, tutors and teachers. The analysis is performed according to the 4 main ethical principles (beneficium, non maleficum, justice, autonomy) to a narrative approach.

Results: The students produces a text, here summarized: from a clinical standpoint, nephrology and ethics complement each other, making this case an interesting example. The patient had a history of polycystic kidney disease, end-stage renal disease, requiring a kidney transplant. The end-stage renal disease, his health status, and his desire for autonomy were important factors in this case. Considering the chronicity of the disease, treatment options, and the patient's cognitive status (writer), GFR 10 mL / min. The case raises questions about the choice of dialysis or peritoneal dialysis. The students were able to identify ethical principles (beneficium, non-maleficium) and the possibility of using EBM to support their discussion. The students also discussed the importance of considering the patient's autonomy in decision-making.

Conclusions: Nephrology offers suggestions for bioethical discussion. Conversely, bioethics offers analytical tools for the analysis of complex decisions such as dialysis in the “very old”.

SLIT2 Is Upregulated in Proximal Tubules and Urine following Folic Acid Induced Kidney Injury

Jonathan Street, Ana C. Souza, Xuzhen Hu, Yuning George Huang, Peter S.T. Yuen, Robert A. Star. NIDDK, Bethesda, MD.

Background: SLIT2, signaling via ROBO receptors, was originally described for its role in neuronal guidance, and has since been linked with leucocyte chemotaxis and angiogenesis. As both processes might be involved in kidney injury and repair, we tested whether SLIT2 signaling is involved in folic acid induced kidney injury.

Methods: Eight-week-old male CD-1 mice were injected i.p. with 250 mg/kg folic acid. Groups were euthanized 0-7, or 14 days later. Expression levels were determined by RT-qPCR and western blot of whole kidney lysates. Localization was determined by immunohistochemistry. In a second experiment mice received folic acid and then 70 µg/kg i.p. recombinant human SLIT2 or vehicle on days 2, 4, and 6. On day 14 GFR was measured in conscious mice by transcutaneous fluorescence monitoring of FITC-Sinistrin elimination.

Results: Following folic acid injection, whole kidney SLIT2 mRNA and protein levels were increased on day 3, whereas SLIT2 were given folic acid, then recombinant human SLIT2 i.p. on days 2, 4, and 6. Kidney function measured directly as GFR or indirectly via BUN 14 days after injection was not significantly improved by SLIT2 treatment.

Conclusions: Folic acid induced injury increased expression of SLIT2 in proximal tubules, followed by detection of SLIT2 in the urine, which points to SLIT2 as a candidate urine biomarker for tubular injury. Amelioration of injury with systemic SLIT2 treatment was not observed, suggesting better utility as a marker than a mediator.

Funding: NIDDK Support

Urinary Trefoil Factor 3 Is Significantly Associated with Renal Tissue Fibrosis in Patients with Tubulointerstitial Nephritis


Background: Trefoil factor 3 (TFF3) is a small peptide involved in mucosal protection. TFF3 is widely expressed in multiple tissues including kidney. Previous studies have suggested that serum and urinary TFF3 significantly increases in patients with chronic kidney disease and that urinary TFF3 level decreases in rats with acute kidney injury. However, it is unclear whether serum or urinary TFF3 is associated with human renal tissue injury. The aim of this study is to elucidate the relationship between serum and urinary TFF3 levels and the degree of renal tubulointerstitial injury.

Methods: The total study population included 52 patients (tubulointerstitial nephritis: 31, minor glomerular abnormalities and thin basement membrane disease as controls; 21) who underwent renal biopsy. The serum and urinary TFF3 concentrations were determined by a specific ELISA. The degrees of tubulointerstitial cell infiltration and fibrosis were semiquantitatively graded in biopsy specimens and defined by the inflammation score and the fibrosis score, respectively. An immunohistochemical analysis was performed to reveal the localization of the TFF3 protein.

Results: The median serum and urinary TFF3 levels of the disease group were significantly higher than those of the controls (p<0.002 and p<0.008, respectively). A statistically significant positive correlation was observed between the urinary TFF3 levels and the fibrosis score in the disease group. However, there was no correlation between the serum or urinary TFF3 level and the renal inflammation score in disease group. TFF3-positive cells were observed in the renal tubular epithelium.

Conclusions: The data indicate that serum and urinary TFF3 levels are significantly increased and, in particular, that urinary TFF3 could reflect renal tissue fibrosis in patients with tubulointerstitial nephritis. Further studies are required to elucidate the precise distribution of renal TFF3 protein and mRNA, and the mechanism underlying the contribution of TFF3 to renal fibrosis.

Induction of Epithelial-to-Mesenchymal Transition and Fibrosis Signals via AKT and Peroxisome Proliporator-Activated Receptor Pathway in Renal Tubular Cells Induced by a Plasticizer Di(2-ethylhexyl) Phthalate

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Background: Di(2-ethylhexyl)phthalate (DEHP) is a plasticizer and a probable endocrine disruptor. More than two million tons of DEHP were used each year worldwide. Recent studies have suggested that DEHP has potential adverse effects on the liver, kidney, and reproductive system. It could also cause carcinogenicity and developmental toxicity. DEHP exposure might exacerbate kidney progression. Tubular epithelial-to-mesenchymal transition (EMT) is recognized to play pivotal role in the process of renal fibrosis. However, the mechanisms of nephrotoxicity induced by DEHP remain unclear. Here, we investigated whether DEHP could induce renal fibrosis via EMT process.

Methods: A rat renal proximal tubular cell model (NRK-52E cells) was used to evaluate EMT and fibrosis signaling. Cell morphology was observed by microscope. Cell viability evaluated by MTT assay. The molecular signals of EMT and fibrosis were analyzed by flow cytometry, confocal laser scanning microscopy, immunocytochemistry, and Western blotting. Treatment with DEHP (5-25 µM) for 72h caused the change in renal tubular cell morphology shifting to spindle-like shape. DEHP did not induce cell apoptosis, but significantly induced G2/M cell cycle arrest. Moreover, the expressions of vimentin, α-SMA, and CTGF, which are the markers of the mesenchymal phenotype, were significantly increased. The expressions of E-cadherin, a maker of epithelial cells, was significantly decreased by DEHP. DEHP could also inhibit the expression of peroxisome proliferator-activated receptor (PPARα) and α. The phosphorylation of Akt and Smad 2/3 was also significantly increased by DEHP. Notably, treatment with MK2206 (an Akt inhibitor) significantly inhibited DEHP-induced phosphorylation of Akt and EMT. Further investigation revealed that MK2206 suppressed the expression of Akt downstream proteins (NF-kB and GSK3).

Conclusions: These findings suggest that DEHP is capable of inducing the EMT process through AKT and PPAR signaling pathway, which may lead to renal fibrosis.

Funding: Government Support - Non-U.S.
Case Report: A 61-year-old man was admitted for orthostatic hypotension with syncopal episodes and proteinuria. He was well until six months prior to admission, when he began experiencing frequent unexplained dizziness. His past medical history included hypertension, hypercholesterolemia, and obesity. On initial evaluation, his blood pressure was 90/60 mmHg while lying supine and 70/40 mmHg when standing. Cardiac and neurological examinations were unremarkable.

Methods: This case report highlights the need for further research in the field of orthostatic hypotension and showcases the importance of early diagnosis and management.

Results: Our findings emphasize the importance of a multidisciplinary approach to the management of orthostatic hypotension, including the use of pharmacological and non-pharmacological interventions.

Discussion: The case presented here underscores the need for increased awareness and education among healthcare providers to improve patient outcomes.

Conclusion: Early recognition and appropriate treatment of orthostatic hypotension can significantly improve quality of life and prevent morbidity in affected individuals.
Discussion: The B Thalassemia is a hereditary disorder of hemoglobin synthesis in the B-globin gene that present clinically with microcytic hypochromic anemia, erythropoiesis ineffective, normal reticulocyte counts or slightly elevated and high levels of A2 hemoglobin. In the kidneys can cause tubular injury and GFR decline. Developing glomerulosclerosis and fibrosis. We can not rule out that CKD is secondary to B-thalassemia, a genetic study would be necessary. It is an uncommon diagnosis in Latin America, but should be considered in patients with CKD and microcytic hypochromic anemia refractory to convecional treatment.

PUB397


Introduction: Intestinal obstruction, even without perforation or ischemia, predisposes patients on peritoneal dialysis (PD) to peritonitis by gut commensals including fungi. Fungal peritonitis (FP), with (Secondary) or without (Primary) prior antibiotic use, is associated with increased mortality and technique failure. This raises the question of empirical antifungal use in PD patients with bowel obstruction. We present our experience with such a patient.

Case Description: A 74 year old male who had been on Continuous Cycling Peritoneal Dialysis for the past four years with his prescription being 5 exchanges of 2 liters of 1.5% and 2.5% dianeal with a last fill of 2 liters of icodextrin, presented with worsening abdominal pain. His dialysate was clear and had just 3 leucocytes. His CT abdomen showed small bowel obstruction (SBO) with conservative management pursued. Over the next few days, the SBO resolved and dialysate cell counts remained unremarkable. On day 5, he became hypotensive. Examination was notable for increased abdominal tenderness and a cloudy dialysate. Repeat dialysate studies were sent and intraperitoneal vancomycin and cefepime were started. Imaging suggested SBO. He responded appropriately to the antibiotics over the next three days with no growth on any cultures thus far. However, the dialysate grew yeast the next day. Fluconazole was started, later being switched to micafungin with the next three days with no growth on any cultures thus far. However, the dialysate grew Candida glabrata on day 1.2. His Tenckhoff catheter was removed and hemodialysis (HD) was initiated. He completed 4 weeks of micafungin and opted to continue on HD.

Discussion: Evidence on antifungal prophylaxis while treating PD related bacterial peritonitis has been mixed, with the decision being individualized on a per-center basis. Additionally, no clear role has been defined for prophylactic antimicrobials in PD patients with bowel obstruction. With a high risk for both primary and secondary FP, these patients may also develop IgA antibodies against specific HIV antigens. Renal lesions may result from HIV antigen-specific immune complexes that are derived from the circulation and from in-situ complex formation.

Case Description: We present a case of a patient with HIV/AIDS, on highly active antiretroviral therapy (HAART), who was evaluated for microscopic hematuria and worsening renal function. The patient’s only complaint was early morning peri-orbital edema. On examination, BP was 103/72 mm Hg with a BMI 23 kg/m². Labs showed normal electrolytes, serum creatinine 1.7 mg/dL (baseline 0.7 mg/dL), urine protein/creatinine ratio of 2.5 grams/dL. Other serologies were negative. HIV VL was undetectable, and CD4 count was 183. Renal US showed bilateral enlarged, echogenic kidneys. Renal biopsy revealed sclerosing glomerulopathy with IgA immune type deposits on immunofluorescence. The patient was initiated on an ACE inhibitor and a low salt and protein diet, with resolution of his proteinuria to 0.7 Grams/dl. His renal function stabilized, with a creatinine of 1.6 mg/dL.

Discussion: In conclusion, IgA glomerular disease arising in HIV positive patients has clinical and pathologic aspects similar to idiopathic IgA nephropathy. IgA nephropathy should be suspected in patients with HIV presenting with unexplained hematuria, and renal biopsy should be performed as soon as possible for early diagnosis and therapy. Current management recommendations are similar to those with idiopathic IgA, including ACE inhibitors orARB for control of proteinuria (>1 g / day) or hypertension.

PUB398


Introduction: Leukocytosis and peripheral blood eosinophilia were well described in acute rejection of transplanted livers and pancreas rejection This laboratory abnormality was not well evaluated in kidney allograft rejection. In this case report, we explore leukocytosis and peripheral blood eosinophilia as possible laboratory abnormalities preceding ACR.

Case Description: We are presenting a 65 years old woman with a history of ESRD due to ADPKD, who had a DDKT in 2012. Her medications included Prednisone, Tacrolimus, and Mycophenolate Mofetil. She maintained a stable allograft function, with a creatinine of 1.2. She was found to have leukocytosis and peripheral blood eosinophilia. Evaluation for infections and malignancy was negative. 6 weeks later she was noted to have AKI. She complained of mild lower extremities swelling. Physical examination was unremarkable. Labs evaluation revealed a creatinine of 2 mg/dL, WBCs count of 15.9 k/µL, and eosinophilia. Renal biopsy however, showed ACR (figure1). There were abundant infiltrates with neutrophils and eosinophils. She was treated for ACR with return of creatinine to baseline.

Discussion: Several reports have evaluated the predictive value of peripheral blood eosinophilia as a simple noninvasive diagnostic marker for ACR of transplanted livers and of acute pancreatic rejection. However, peripheral blood eosinophilia was not evaluated as a possible test predicting renal ACR. In a case report, Baradhin et al, described the etiology of AKI following treatment with armodafinil for narcolepsy. They indicated that both (AIN and ACR) has similar biopsy characteristics. However, our patient had no clinical features to suggest AIN, including no new medications. We conclude that leukocytosis and peripheral blood eosinophilia could represent signs of impending acute cellular rejection of transplanted kidneys.

PUB399

A Case of IgA Nephropathy in an HIV-Positive Patient Hermes Garcia-Sanchez, Vandana Niyyar, Thomas E. Rogers. Nephrology, Emory Univ, Atlanta, GA.

Introduction: IgA nephropathy has been described in patients infected with HIV. Though IgA levels are commonly elevated in HIV, these patients may also develop IgA antibodies against specific HIV antigens. Renal lesions may result from HIV antigen-specific immune complexes that are derived from the circulation and from in-situ complex formation.

Case Description: We present a case of a patient with HIV/AIDS, on highly active antiretroviral therapy (HAART), who was evaluated for microscopic hematuria and worsening renal function. The patient’s only complaint was early morning peri-orbital edema. On examination, BP was 103/72 mm Hg with a BMI 23 kg/m². Labs showed normal electrolytes, serum creatinine 1.7 mg/dL (baseline 0.7 mg/dL), urine protein/creatinine ratio of 2.5 grams/dL. Other serologies were negative. HIV VL was undetectable, and CD4 count was 183. Renal US showed bilateral enlarged, echogenic kidneys. Renal biopsy revealed sclerosing glomerulopathy with IgA immune type deposits on immunofluorescence. The patient was initiated on an ACE inhibitor and a low salt and protein diet, with resolution of his proteinuria to 0.7 Grams/dl. His renal function stabilized, with a creatinine of 1.6 mg/dL.

Discussion: In conclusion, IgA glomerular disease arising in HIV positive patients has clinical and pathologic aspects similar to idiopathic IgA nephropathy. IgA nephropathy should be suspected in patients with HIV presenting with unexplained hematuria, and renal biopsy should be performed as soon as possible for early diagnosis and therapy. Current management recommendations are similar to those with idiopathic IgA, including ACE inhibitors or ARB for control of proteinuria (>1 g / day) or hypertension.

PUB400


Introduction: Calcium channel blocker overdose is rare but carries a high mortality due to cardiovascular complications. Generally the management is supportive with use of vasopressors, IV fluids, cardiac pacing, and insulin therapy. There are reports of CVVHDF, hemodialysis or hemofiltration alone and charcoal hemoperfusion for the treatment of CCBB overdose. Effective management strategies are needed to improve outcomes.

Case Description: Here we describe a patient who presented to the ER after a suicide attempt with ingestion of Norvasc. On arrival to the ER he was awake but later he was intubated. The patient developed acute kidney injury and became anuric. Patient was started on CVVHDF that lasted 48 hours. Unfortunately after two days the patient continued to decompensate and expired.

Discussion: Amlodipine is a CCB of the dihydropyridine group acting primarily on vessel walls whereas the non-dihydropyridines act more on cardiac muscle and pacer cells. In our case it was clear Norvasc selectively took its effect on the vasculature with profound hypotension with preserved systolic function and no arrhythmia. The case was complicated with ARDS related to diffuse pulmonary edema, a well known complication with CCB overdose. In our case renal failure was likely related to severe hypoperfusion leading to ischemia. There was development combined respiratory and metabolic acidosis. The metabolic acidosis was attributed to renal failure but it is possible that CCB induced inhibition of insulin secretion leading to ketoacidosis may also have contributed. In terms of management of CCB overdose, if recent ingestion then GI decontamination is reasonable with activated charcoal or whole bowel irrigation. The use of high dose insulin therapy has been tried and its role may include increasing ionized calcium levels, improvement of hyperglycemic acidosis, and improved myocardial function. Most case reports, though
few, have shown little benefit from hemofiltration or hemodialysis therapy due to high protein catabolism, increases in protein catabolism and rapid metabolism of the drug. One case report did show some promise when multiple therapies were used including IV lipid emulsion, CVVHDF and charcoal hemoperfusion.

Introduction: Heavy chain disease (HCCD) is rare, especially without light chain deposition and when causing non-amyloid tissue deposits.

Case Description: A 75-year-old male with chronic kidney disease (CKD) stage 3 (baseline creatinine 2.3mg/dL) and right single lung transplant for idiopathic pulmonary fibrosis. In 2008 presented with extremity edema and decreased urine output. He has no history of diabetes or uncontrolled hypertension. Admission labs showed BUN 77 mg/dL, creatinine 4.37 mg/dL, and subtherapeutic tacrolimus levels at 3.9 mg/mL. Urine protein/creatinine ratio was 6.6. A 24-hr urine protein collection revealed 5822 mg/24hr. Serum protein electrophoresis showed hyperalbuminemia, but no monoclonal proteins were identified. Urine protein electrophoresis was negative for Bence Jones proteins or monoclonal proteins. Urine protein concentration was 713 mg/dL, consisting of 57.8% albumin and 42.2% globulins. C3 and C4 complement levels were low at 46.5 mg/mL and 8.92 mg/mL respectively. Antinuclear antibodies (ANA), anti-streptolysin O (ASO), anti-neutrophil cytoplasmic antibodies (C-ANCA and P-ANCA), and cryoglobulins were negative. Renal ultrasound showed multiple renal cysts without hydropsynthesis. Renal biopsy revealed nodular sclerosing glomerulonephritis with crescents involving 10% of glomeruli and interstitial fibrosis and microscopic dysmorphic RBCs. Skin biopsy showed thrombotic vasculopathy with no plasma cell dyscrasia. To our knowledge, no cases have been described with no plasma cell dyscrasia. To our knowledge, no cases have been described with no plasma cell dyscrasia. To our knowledge, no cases have been described with no plasma cell dyscrasia.

Discussion: With more than 2 million Americans using cocaine, diagnoses of cocaine-induced vasculitis are being made with increasing frequency. A case report described in this study is crucial in providing insight into the clinical presentation and treatment of such a rare disease. It is estimated that about 70% of the cocaine used here in the US is contaminated with levamisole – a substance used as a biocide in animal feed and agriculture. This contamination can increase Levamisole exposure should be included in guidelines for treatment make HCDD challenging to treat. We describe a rare case of IgG1 HCDD with no plasma cell dyscrasia. To our knowledge, no cases have been described using oral prednisone and therapeutic plasmapheresis to treat HCCD renal dysfunction.

Introduction: An increasing number of cases of cocaine-induced vasculitis are being found among cocaine users in the United States which is due to the use of Levamisole laced cocaine. It is estimated that about 70% of the cocaine used here in the US is contaminated with Levamisole.

Case Description: We describe a 65 year old male, with a 20 year history of cocaine abuse, who presented with a 1 month history of a progressively worsening, non-healing and painful rash on his trunk and extremities. He denied fever, weight loss and myalgias but admitted to itchiness. Examination revealed multiple tender, erythematous and indurated plaques with central necrosis on the trunk and extremities. These plaques were found to be in different stages of healing with their size ranging from 1cm-7 cms. Lab investigations revealed an elevated creatinine of 2.9 mg/dL, an elevated ESR, an elevated WBC, neutrophilic granulocytosis, and a negative ANA. Renal ultrasound showed multiple renal cysts without hydropsynthesis. Renal biopsy revealed nodular sclerosing glomerulonephritis with crescents involving 10% of glomeruli and interstitial fibrosis and microscopic dysmorphic RBCs. Skin biopsy showed thrombotic vasculopathy with no plasma cell dyscrasia. To our knowledge, no cases have been described using oral prednisone and therapeutic plasmapheresis to treat HCCD renal dysfunction.

Discussion: The Emergency room visits and hospital admissions are more in emergent dialysis patients with the complication of uremic ascites. The serum albumin, a marker for volume status especially in vascular-occlusive events and death is lower in these patients. We conclude that uremic ascites increase the morbidity and mortality in emergent dialysis population with ESRD. The modalities such as Continuous ambulatory peritoneal dialysis, scheduled outpatient dialysis and kidney transplant may prove beneficial.

Case Description: A 12-year-old boy was referred to our hospital for treatment of nephritic syndrome with massive proteinuria and generalized edema. He was treated with the standard corticosteroid regimen stipulated by the International Study of Kidney Disease in Children (ISKDC). Although he achieved complete remission, he suffered two relapses of nephrotic syndrome during administration of prednisolone in alternative days. In the second relapse, the disease became resistant to the steroid therapy, and therefore he received two courses of steroid pulse therapy followed by steroid tapering concomitant with cyclosporine administration. Two months after the diagnosis of steroid-resistant nephrotic syndrome, the patient underwent renal biopsy. Magnetic resonance imaging demonstrated compression fractures from the sixth thoracic vertebra to the first lumbar vertebra. Therefore, the steroid dosage was rapidly reduced and then withdrawn because he was able to maintain remission under cyclosporine therapy.

Discussion: It is necessary to evaluate the state of bone particularly the bone mineral density of the lumbar spine, at an early stage of treatment for nephrotic syndrome in children, even though the incidence of glucocorticoid-related vertebral fracture is low in this patient population.

Introduction: Dialysis related amyloidosis (DRA) is a debilitating complication of long-term hemodialysis characterized by excess accumulation of Beta 2-microglobulin, which deposits as amyloid fibrils in the bones, joints, and organs of affected patients. The Lixelle Beta 2-microglobulin apheresis column (Lixelle Column) in the United States Vesh Srivastava1, Anjali Masand, Jeffrey I. Silberzweig. 2Dept of Nephrology and Hypertension, NYP. Weill Cornell Medical Center, New York, NY; 2Dept of Nephrology, The Rogosin Inst, New York, NY.

Introduction: Lixelle Beta 2-Microglobulin Apheresis Column (Lixelle Column) for Dialysis Related Amyloidosis in the United States

Discussion: The patient is a 65 year-old man diagnosed with end-stage renal disease of unknown etiology in 1968. A deceased donor renal transplant in 1969 failed within 6 months, and a second transplant in 1970 functioned for 3 years. He has been diagnosed after excluding liver, cardiac, infectious and malignant causes. The incidence of uremic ascites in standard dialysis population was described as 0.7-20%. We believe that emergent dialysis patients with uremic ascites have higher morbidity and mortality.

Case Description: Total of 463 emergent dialysis patients, who were initiated on dialysis between July 2010 and April 2015 were analyzed. Among 36 patients with Ascites or of any cause, 12 patients were included in the study group of uremic ascites. A cohort of 36 patients without ascites was randomly selected for comparison. Two groups were compared based on demographics and morbidity indicators.

The mean age was 50 years with predominance of Hispanic male in both groups. The serum albumin in the uremic ascites group and the cohort group was 2.6±0.4 and 3.29±0.2 respectively. Volume overload and abdomen pain were the major reasons for admissions in the study group. They underwent paracentesis and frequent dialysis during the hospital course.

Introduction: Light chain deposition disease (HCDD) is rare, especially without light chain deposition and when causing non-amyloid tissue deposits. To our knowledge, no cases have been described using oral prednisone and therapeutic plasmapheresis to treat HCCD renal dysfunction.

Introduction: Glucocorticoid therapy has a number of adverse effects, among which osteoporosis and bone fracture are major complications. However, there are few reports of this condition in pediatric patients. Here we describe a pediatric case of multiple vertebral compression fractures due to glucocorticoid-induced osteoporosis in a Pediatric Patient with Nephrotic Syndrome Akihiko Shirasu,1 Akira Ashida,2 Yuko Fuji,3 Hideki Matsumura,4 Hiroyo Nakamura,5 Motoshi Hattori,2 Hiroshi Tamai,1,2 Dept of Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan; 1Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.

Introduction: Glucocorticoid-induced osteoporosis (GIO) is one of the adverse effects of glucocorticoid therapy, especially in children and young adults. GIO is diagnosed after excluding liver, cardiac, infectious and malignant causes. The incidence of uremic ascites in standard dialysis population was described as 0.7-20%. We believe that emergent dialysis patients with uremic ascites have higher morbidity and mortality.

Case Description: Total of 463 emergent dialysis patients, who were initiated on dialysis between July 2010 and April 2015 were analyzed. Among 36 patients with Ascites or of any cause, 12 patients were included in the study group of uremic ascites. A cohort of 36 patients without ascites was randomly selected for comparison. Two groups were compared based on demographics and morbidity indicators.

The mean age was 50 years with predominance of Hispanic male in both groups. The serum albumin in the uremic ascites group and the cohort group was 2.6±0.4 and 3.29±0.2 respectively. Volume overload and abdomen pain were the major reasons for admissions in the study group. They underwent paracentesis and frequent dialysis during the hospital course.
An Unusual Case of Anticoagulant-Like Nephropathy in a Non-Anticoagulated Patient

Elvah Safar, Apurv Khanna.

**Introduction:** Anticoagulant-related nephropathy is a well-known cause for Acute Kidney Injury (AKI), which was first described in Coumadin anti-coagulated patients, usually with excessive anticoagulation (INR >4). It was also reported to be associated with other Anticoagulants such as direct thrombin inhibitor Dabigatran. We report a case of Anticoagulant-related Like Nephropathy in a Non-anticoagulated patient.

**Case Description:** A 71-year-old male was admitted to the VA medical center for shortness of breath and hemoptysis. Past medical history was significant for Non Small cell Lung Cancer, Cryptogenic Liver cirrhosis and COPD. CT chest, showed no pulmonary emboli. He was treated with Vancomycin and Zosyn for Pneumonia. The patient reported gross hematuria initially, which resolved spontaneously. His admission creatinine was 1.1 mg/dl, (baseline 0.6 mg/dl), and went up to 2.4 mg/dl. The patient had another episode of gross hematuria and his creatinine went up to 3.5 mg/dl. The patient remained non-oliguric throughout the course of his AKI. Kidney biopsy showed Tubular epithelial cells injury with red cell casts, but no inflammatory changes and no Immune complexes by Immunofluorescence. The histopathologic pattern shown by the kidney biopsy was consistent with Anticoagulant-related nephropathy. However, the patient was not anticoagulated with Coumadin, Heparin, or any other anticoagulants. His Prothrombin time (PT) was 13.1 seconds (normal 9-12 seconds) and INR 1.2. His PTT was 20.1 seconds (normal 25-34 seconds). He had a low platelets count between 55-100K/mm3, due to liver cirrhosis.

The findings in this case, suggest a role for Thrombocytopenia in liver cirrhosis, in causing anticoagulant like intra-glomerular hemorrhage, which may result in an AKI.

**Discussion:** Thrombocytopenia and likely Platelets dysfunction in Liver cirrhosis can cause intra-glomerular Hemorrhage and results in Anticoagulant-like Nephropathy, even in the absence of excessive coagulopathy as evidenced by a normal PTT & near normal INR. To our knowledge, there has not been a reported case of Anticoagulant-like Nephropathy in Non-Anticoagulated patients.

**Smoking Related Idiopathic Nodular Glomerulosclerosis with Crescents**

Tahir Zaman,1 Frederic Clayton,2 Josephine Abraham.1 1 Nephrology, Univ of Utah, Salt Lake City, UT; 2 Pathology, Univ of Utah, Salt Lake City, UT.

**Introduction:** Idiopathic nodular glomerulosclerosis (ING) is a rare but important cause of nephrotic syndrome. There have been case series reported in the literature regarding the association of ING and smoking.

**Case Description:** A 37-year-old female with a history of rheumatoid arthritis (RA) presented to the hospital with cough and hemoptysis. Her RA treatment consisted of leflunomide, prednisone and folic acid. Her social history is pertinent for a history of smoking (20 pack-years). Urine analysis was with dysmorphic hematuria and proteinuria associated with ING.

**Discussion:** Smoking cessation was encouraged. Over time, it has progressed to involve his shoulders bilaterally, his hips, knees, wrists and most recently his colon. He has undergone bilateral total hip replacements and carpal tunnel release procedures. Given his extensive disease burden as a result of DRA despite adequate dialysis, we intend to enroll him in a post-approval study using the Lixelle column. Measures of disease burden will include pre- and post-treatment Beta 2-microglobulin levels, presence of bone cysts, and quality of life (QOL) scores.

**Discussion:** The Lixelle Beta 2-microglobulin apheresis column appears to increase the Beta 2-microglobulin reduction rate in a single dialysis session, and therefore may be an effective treatment option to improve symptoms and quality of life for patients with dialysis related amyloidosis.

An Unusual Case of Anticoagulant-Like Nephropathy in a Non-Anticoagulated Patient

**PUB406**

Thrombotic Microangiopathy Secondary to Hepatocellular Carcinoma

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**Introduction:** Thrombotic microangiopathy (TMA) is a microvascular occlusive disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia and end organ damage. We report a case of malignancy associated TMA.

**Case Description:** 65-year-old female presented with diarrhea and was noted to be in acute renal failure with microangiopathic hemolytic anemia and thrombocytopenia. Therapeutic plasma exchange was discontinued after ADAMST 13 activity was normal. Patient underwent colonoscopy and EGD with evidence of microthrombi in bowel wall concerning for TMA.

**Discussion:** TMA occurring in older patients who fail to respond to TPE should increase suspicion of malignancy-associated TMA. 1 HCC is a rare but known cause of malignancy-associated TMA as noted in the literature. RCC-associated TMA is quite severe leading to rapid progression to a fatal outcome. 2 1. George, J. N. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. Oncology 25, 908–14 (2011). 2. Seo, D. W. et al. Hepatocellular carcinoma associated hemolytic uremic syndrome unrelated to chemotherapy. J. Korean Med. Sci. 9, 254–8 (1994).

Thrombotic Microangiopathy Secondary to Hepatocellular Carcinoma

**PUB408**

Charcot Foot Syndrome in a Nondiabetic Hemodialysis Patient

Werner Kiezophas,1 2 Sebahat Sat,1 Barbara Klein,1 Andreas Westhoff,1 2 Frank Dellanna,1 2 Gerard Hetzel.1 2 1 Kitz-Devita Karlstrasse, Düsseldorf, Germany; 2 Heinrich-Heine Univ, Düsseldorf, Germany.

**Introduction:** The prognosis is very poor for diabetic hemodialysis (HD) patients with foot lesions. Foot lesions are associated with risk of systemic inflammation and cardiovascular (CV) morbidity. Severe cases of diabetic foot with neuropathic arthropathy, microvascular changes from medialclerosis, and alteration of foot architecture are known as Charcot Foot Syndrome (CFS). Since diabetic and nondiabetic HD patients may experience changes in calcium and phosphate metabolism and secondary hyperparathyroidism, the question arises whether CFS can occur in HD patients in the absence of diabetes.

**Case Description:** Presented is a decade-long case study of a male HD patient (DOB 1961) who was treated since Dec 1999 for biopsy-proven nephrotic syndrome due to glomerulosclerosis. The patient began thrice weekly HD in Sept 2005 without prior treatment for diabetes mellitus (A1C 4.9%). In Apr 2012 he presented with a painless inflammatory acute foot syndrome, then presented in Apr 2013 with a planar ulceration. After conservative wound management, prophylactic shoes were prescribed. In clinical examination he showed signs of chronic CFS and arthropathic changes in osa metatarsals 2 and 3 with ostolysis and luxation of tarsometatarsal joints. Lab results indicate secondary hyperparathyroidism: parathyroid hormone 465 pg/mL, phosphate 6 mg/dL, and calcium 2.2 mg/dL.

**Discussion:** ING with crescents has not been described in the literature. In a case series reported by Markowitz et al, patients with ING had renal failure with a mean sCr of 2.4 mg/dl and proteinuria. The main clinical predictors of progression included lack of angiotensin II blockade and continued smoking. 1 In retrospect, it is likely the severity of her intra-glomerular pressures which lead to proteinuria was exacerbated with steroid treatment and resolved with discontinuation.

Charcot Foot Syndrome in a Nondiabetic Hemodialysis Patient

**PUB409**

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

Underline represents presenting author.

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Discussion: We believe this is the first description of chronic CFS in a non-diabetic HD patient. Acute CFS diagnosis is important because its symptoms (red warm skin, foot edema) are similar to those of phlegmon and osteomyelitis, and thus may be considered a differential diagnosis. Further investigations are necessary to determine whether this is an authentic entity of a foot syndrome, and if it’s associated with CV morbidity.

Funding: Pharmaceutical Company Support - Davita

PUB410


Introduction: Crescentic GN is usually manifested by features of active glomerular disease in the urine and by progressive rapid loss of significant renal function. SLE can present as predominantly crescentic GN often as Class III or IV lupus nephritis (LN) usually resulting in rapid deterioration of renal function requiring RRT.

Case: 18 y/o female recently diagnosed with SLE, on SLA, Plaquenil presented to ER with nausea, vomiting and epigastric pain after consuming “tiny tea” and was found to have serum creatinine (SCr) 4.5 mg/dL, which further increased to 4.74 with 3+ protein (2.5g/day), 3+ blood and RBC casts on urinalysis. Other relevant lab data: ANA 1:600, negative dsDNA, positive RNP, anti-SM Ab and normal complements. She was initiated on IV fluids and SCr normalized within 2 days. Renal biopsy showed Pauci immune Crescentic GN, class IV-S (A/C) with minimal IF staining. The clinical course was complicated by seizures; the diagnostic considerations included lupus cerebritis vs. PRESS. She was put on valproate to be started on immunosuppression as outpatient. She was admitted a week later with acute liver failure due to valproate and Tyleenol at which time she was pulsed with IV Solu-Medrol and discharged on oral steroids with a plan to start MMF after normalization of LFTs.

Discussion: Crescentic and focally necrotizing GN can be infrequently present in the spectrum of diffuse proliferative LN. Such cases are generally ANCA negative. Normalization of SCr after hydration in this case suggest pre renal as the likely etiology which poses a treatment dilemma for biopsy proven crescentic GN. While there is not much literature available regarding the treatment of lupus with crescentic GN and normal SCr, a retrospective case series reported that even <50% crescents portend a significant renal risk despite clinically evident preserved renal function. We believe that intense immunosuppression should be used in patients with crescentic GN and preserved renal function, despite the absence of any controlled studies. Our patient was started on MMF and prednisone with improvement in proteinuria from 2.6 gm to 150 mg with normal SCr.

PUB411

Anti-Thymocyte Globulin Induced Non Cardiogenic Pulmonary Edema Jaya Kaia, Amit Lahoti. Nephrology, Univ of Texas MD Anderson Cancer Center, Houston, TX.

Introduction: Anti-Thymocyte globulin (ATG) is used in treatment of hematologic malignancies and solid organ transplantation. Immediate local and systemic reactions are known. There has been only one reported case of non cardiogenic pulmonary edema (NCPE) caused by ATG.

Case Description: Our patient was a 59-year-old man with Marginal Zone Lymphoma which had progressed to diffuse large B cell lymphoma. Despite Hyper CVAD and Rituximab his disease continued to progress. He received Matched Unrelated Bone marrow transplantation after conditioning with ATG and rituximab. The next day he was admitted to the ICU with respiratory distress and bilateral lung infiltrates initially thought to be pulmonary edema. He was started on Lasix drip but did not improve. His CVP was 5, and his echocardio gram showed normal ejection fraction. Based on these findings he was diagnosed to have NCPE. Bronchoscopy revealed pulmonary hemorrhage. His condition worsened and he was intubated and started on Continuous Renal replacement therapy. He was given additional doses of steroids but without improvement. His died due to respiratory failure after two days of ICU stay.

Discussion: Non cardiogenic pulmonary edema is a clinical syndrome characterized by presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph without evidence of left atrial hypertension, fluid overload or congestive heart failure. Drug related NCPE is usually diagnosed after other causes of pulmonary infiltrates such as gastric aspiration, sepsis and pneumonia are excluded. The presence of normal echocardiogram and pulmonary hemorrhage within a day of administration of ATG, pulmonary infiltrates which did not resolve after intense attempts of volume removal indicated that the patient had NCPE. ATG is known to cause acute respiratory distress syndrome, alveolar hemorrhage and rapidly progressive interstitial fibrosis likely secondary to Cytokine release syndrome. Providers need to be aware of such complications as even though rare these cause increased morbidity and mortality. It is beneficial to give ATG infusions slowly and accompanied by high dose systemic steroids.

PUB412

Hypomagnesemia After Treatment with Pertuzumab Lilian Saro-Nunez,1 Tiffany A. Traina,2 Karen A. Cadoo,3 Teresa Gilewski,1 Ilya Gleizerman.4 1Nephrology, NYP-Well Cornell Medical Center, New York, NY; 2Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY; 3Gynecologic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; 4Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.

Introduction: Hypomagnesemia is a known side effect of epidermal growth factor receptor (EGFR) inhibitors such as cetuximab and panitumumab. Pertuzumab blocks HER (human epidermal growth factor receptor) 2 dimerization with HER3 and EGFR, and is used in HER2+ breast cancer. We present two cases of hypomagnesemia with pertuzumab use.

Case Description: Case 1 58 year-old woman with history of breast cancer treated with trastuzumab (T), docetaxel, pertuzumab (two doses of 840mg and one dose of 420mg) and carboplatin (AUC6). Patient developed hypomagnesemia with serum magnesium (Mg²⁺) 0.7 (1.7-2.6)mg/dl and symptomatic hypomagnesemia of 5.9 (8.5-10.5)mg/dl. Since initiation of chemotherapy she experienced diarrhea controlled with loperamide. Fractional excretion of magnesium (FeMg) was 2%. Parathyroid hormone (PTH) was 309.2 (12-88)pg/ml. Pertuzumab and carboplatin were stopped. Mild hypomagnesemia persisted 6 months later.

Case 2 56 year-old woman with history of breast cancer on treatment with T, paclitaxel and pertuzumab (one dose of 840mg and 2 doses of 420mg) was admitted with Mg²⁺ of 0.3 (1.4-2.2) mEq/L and corrected calcium of 6.1mg/dl. She complained of chronic diarrhea which improved with loperamide and was receiving proton pump inhibitor (PPI). FeMg was 3%, PTH was 161 (12-88)pg/ml. PPI was stopped but patient received another dose of pertuzumab (840mg). She remained hypomagnesemic and required IV supplementation until her death from progression of disease 22 months later.

Discussion: Although there were other confounding factors that could have caused hypomagnesemia including diarrhea, PPI and carboplatin, hypocalcemia (a manifestation of hypomagnesemia) did not develop until patients were started on pertuzumab. Carboplatin has been associated with hypomagnesemia but not with the degree of hypomagnesemia seen in these two patients. We postulate that pertuzumab may interfere with reabsorption of Mg²⁺ similar to EGFR inhibitors.

PUB413

Acute Renal Infarction: Case Series Yelda Deligoz bildaci1, Rumeyza Kazancioglu.2 1Nephrology, Bezismalek Vakif Univ, Istanbul, Turkey; 2Nephrology, Bezismalek Vakif Univ, Istanbul, Turkey.

Introduction: Acute renal infarction (ARI) occurs from interruption of kidney’s blood supply either partially or totally. Causes of renal infarction include: thromboembolism (usually from injured or replaced heart valves, congenital heart defects etc.) vasculitic disorders, trauma to the kidneys or hypercoagulable state. We present five cases of ARI with different etiologies.

Case Description: Description of Cases: Two female, three male, mean age 52 (range 26-72) patients presented to the emergency department between 2013 and 2015 in a university based hospital setting. Presenting complaint was severe flank pain lasting between 2 to 5 days for all of them. At initial examination all patients had costo-vertebral angle tenderness at the affected side. Contrast enhanced abdominal tomography was useful for showing renal artery occlusion and also renal infarction. Trans thoracic echocardiography were all normal and were not adequate in identifying patients having had heart defects, trans esophageal echocardiography was obviously superior in finding cases with possible paradoxical embolism. All patients were treated with enoxaparin therapy. During follow-up there was neither further complication nor kidney damage.
CASE 1

26

FE- MALE

NEGATIVE

NORMAL

PATENT DUCTUS ARTERIOSUS

0.8

0.7

CASE 2

72

MALE

POSITIVE

NORMAL

- 4.2

3.8

CASE 3

69

MALE

POSITIVE

NORMAL

- 0.8

0.8

CASE 4

38

MALE

NEGATIVE

NORMAL

- 0.8

0.9

CASE 5

56

FE- MALE

POSITIVE

NORMAL

PATENT DUCTUS ARTERIOSUS

0.8

0.8

Discussion: ARI usually is a hidden disease, which can easily be missed without any specific suspicion for patients presenting with flank pain. It should be kept in mind that there is no specific biochemical test for ARI and diagnosis process must involve evaluation of cardiac pathologies preferably with trans esophageal echocardiography.

PUB414

Disseminated Cryptococcal Infection in a 24-Year-Old Man with Primary Focal Segmental Glomerulosclerosis

Introduction: Focal segmental glomerulosclerosis (FSGS) is commonly treated with high doses of corticosteroids and calcineurin inhibitors to induce remission of proteinuria, however immunosuppression carries with it the risk of infection. We present here the case of a 24-year-old African American man following seven months of intermittent treatment for biopsy-proven FSGS with high-dose prednisone and cyclosporine.

Case Description: Our patient initially responded to prednisone 80 mg daily with proteinuria reduced to 37 mg/g from 3.5 g/g, but then suffered frequent hospitalizations for infection necessitating interruption of immunosuppression, now with decreased responsiveness to prednisone. Cyclosporine was added but interrupted after he developed skin findings concerning for necrotizing fasciitis. A surgical wound became infected, and he developed Clostridium difficile diarrhea. He was placed on ethacrynic acid and stavudine because of a sulfa allergy. His albumin remained < 1.5 mg/dL. Renal function worsened, now with ascites requiring paracentesis and subsequently developed E coli peritonitis. He was admitted to our medical ICU with hypoxia seven months after initial presentation. Chest xray at this time demonstrated pulmonary edema versus multilobar pneumonia. White blood cell count was 18.5, and increased to 30.0 after beginning prednisone taper. Broad-spectrum antibiotics and hemodialysis were initiated with no improvement. Head CT after seizure demonstrated diffuse hemorrhaging. Fungal cultures were sent, and patient was started on empiric voriconazole. Cultures returned after he expired positive for Cryptococcus. Autopsy showed disseminated Cryptococcus with cause of death attributed to cryptococcal pneumonia.

Discussion: This case demonstrates the infectious risk of high dose immunosuppression in treating resistant focal segmental glomerulosclerosis and the need to balance efficacy of treatment against these risks.

PUB415

A Rare Case of Kidney Amyloidosis Caused by Heroin Abuse

Introduction: Secondary(AA)Amyloidosis nephropathy is a rare manifestation of IVDA, as a condition characterized by deposition of insoluble fibrils in various organs; most commonly the liver and kidneys. Occurs as a result of chronic inflammatory states such as RA, IBD, chronic osteomyelitis, or familial Mediterranean fever. Kidney involvement in amyloidosis is a significant source of morbidity as it can progress to CKD.

Case Description: A 40 y/o AA man with no past medical history just 20 years of IV heroin abuse presented to the ED with the CC: Worsening lower extremity edema and a weight gain of 20 lbs. in the past few months. Patient denied any other medical problems or complaints. On PE, afebrile, normotensive, with clear lungs, normal heart at auscultation and benign abdominal findings, but with 3+ lower extremity edema. Multiple skin popping in upper and lower extremities with aching, and no evidence of active inflammation. Creatinine 0.8 mg/dL on arrival. The UA showed >600mg/dL of protein and no hematuria. A 24 hour urine collection showed 55 gm of proteinuria and serum albumin 2.1 g/dL. Cholesterol 232mg/dL, LDL 192 mg/dL, and Trig 189mg/dL. JPT’s were normal and the rest of serologic workup including HIV, Hep B and C were negative. A biopsy showed a nodular increase in mesangial matrix material that was congophilic and stained positive with both amyloid A and P, consistent with AA amyloidosis. The EM showed the presence of nonbranching fibrils that measure 7 and 12 nm in size. The mainstay treatment for secondary renal amyloidosis consists of targeting the underlying cause. In this case of heroin induced amyloidosis, the patient was counseled extensively about heroin cessation. Per the literature, not many other treatment options exist. We started him on colchicine as there are studies indicating its efficacy on disrupting the amyloid fibrils and decreasing progression of disease. He was also started on anti-coagulants and diuretics, but we were unable to start him on ACEI’s/ARB’s due to low blood pressure.

Discussion: AA kidney amyloidosis is a rare manifestation of IVDA, especially after a prolonged exposure. We should always consider this diagnosis in chronic heroin users presenting with proteinuria.

PUB416

Addressing Fertility and Management of a Patient with PCOS and C1q Nephropathy

Introduction: C1q nephropathy is a rare disease that can present in a variety of ways. We present the case of a 26 year-old female with PCOS and borderline diabetes who developed non-nephrotic-range proteinuria with preserved renal function who wished to become pregnant.

Case Description: Her serologic workup was unrevealing. She did not have any classical symptoms of SLE and her ANA was only mildly positive at 1:40. Biopsy of the kidney revealed predominant immunofluorescent staining for IgG and C1q with mesangial deposits of IgG. There was no clear evidence of focal segmental glomerulosclerosis to portend a worse prognosis. Her decision to pursue pregnancy prompted further inquiry into the effects of pregnancy on her renal disease.

Review of existing literature, limited as it may be, suggested that C1q autoimmunogenicity may be associated with normal placental growth and development in the context of hormonal changes.

Discussion: Therefore, interpretation of typical parameters, including urinary protein excretion alone, may not be sufficient in determining disease status. This case demonstrates the importance of renal biopsy in defining the underlying pathology in young women with evidence of glomerular disease who wish to become pregnant as it can help guide prognosis.

Funding: Other NIH Support - NIH T32 award

PUB417

Outcomes of Calcific Uremic Arteriolopathy (CUA) Management: An Inner City Tertiary Center Experience

Introduction: CUA is a rare, necrotizing skin condition caused by medial calcification of subcutaneous arteries leading to tissue ischemia and eventual necrosis. It predominantly occurs in patients with chronic kidney disease, associated with high morbidity, mortality and variable outcomes– posing a difficulty in management.

Case Description: We conducted a retrospective chart review from 2010-15. 17 patients were diagnosed and treated for CUA in a tertiary university center. Diagnostic methods and multi-disciplinary treatment included parathyroidectomy, medical management of bone mineral disease, standard wound care, and sodium thiosulfate. We classified outcomes as No Improvement, Stable, and Improvement of Lesions related to the mean Calcium-Phosphate product (CaXPhos). Table 1 shows patient characteristics.

Characteristics

Subjects

Range (min-max)

Gender

Comorbidities

Female

13

17(100%)

7 (41.17%)

Male

4 (23.5%)

8(47.05%)

CVA

3 (17.66%)

Ethnicity

PAH

5.9% (5.9%)

DM

17 (100%)

African American

16 (94.1%)

81 (100%)

White

1 (5.9%)

DVT/PE

16 (94.1%)

8(47.05%)

Mean Age

56.68

81 (100%)

35-9262

Mean PTH

1244.68

35-9262

ESRD

16 (94.1%)

Mean Calcium

8.95

15(93.8%)

7.6-10.3

Mean PO4

5.75

10 (58.8%)

3.5-8.7

PD

16 (94.1%)

Mean CaXPhos product

51.3

19 (100%)

29.1-782

Renal Transplant

15(93.8%)

Mean Ferritin

829.7

19 (100%)

98-1640

Biopsy Proven Ds

15(93.8%)

Mean Tranferin Sat%

29%

10 (58.8%)

7.5-11.6

Outcome

17 (100%)

Cinacalcet use

10 (58.8%)

10 (58.8%)

Healing

5(29.4%)

Parathyroidectomy

1 (5.8%)

Stable

4(23.5%)

Wound Care Counsel

14 (82.4%)

Worsening

8 (47.1%)

Sodium thiosulfate

17 (100%)

Figure 1 shows mean CaXPhos product was higher in patients with no response vs. those that remained stable or improved.
Discussion: CUA management still remains multi-faceted, with unpredictable responses, and no definitive cure.

PUB418
A Case of Adult-Onset Segmental Membranous Glomerulonephritis
Mao Watanabe, Toshiyuki Iimasawa, Takahiko Kawaguchi, Takafumi Yanakawa, Maiko Nagata, Moritoshi Kadomura, Hiroshi Kitamura. Internal Medicine, National Hospital Organization Chiba East Hospital, Chiba, Japan.

Introduction: Generally, adult-onset membranous glomerulonephritis (MN) has diffuse and global glomerular changes. We experienced a rare case of segmental MN (SMN).

Case Description: A 66 years old Japanese male was firstly noted proteinuria in an annual health check-up. Serum creatinine was 0.76 mg/dl, urine protein excretion was 2.1 g/gCr, and 10-19 red blood cells/high-power field were observed in the urine sediment. A percutaneous renal biopsy revealed segmental spike formation on the glomerular basement membrane (GBM) and segmental subepithelial deposits in all glomeruli. Granular deposits of IgG, IgM, IgA, C3, C1q were segmentally positive with granular patterns at the same regions. In electron microscopy, electron dense deposits were also found segmentally. The glomerular tufts with deposits included inflammatory cells (mainly macrophages). Any autoimmune disease, malignancies, and infections were detected by further examinations. Because urine protein decreased less than 1 g/gCr during the hospitalization, only temocapril hydrochloride has been prescribed from 67 years old. He has never taken immunosuppressive drugs. In 68 years old, because urine protein increased to 3g/gCr, the second renal biopsy was performed. Similarly to the first biopsy, segmental spike formation on GBM and segmental staining of immunoglobulins and complements were observed. The percentage of glomeruli with subepithelial deposits decreased to 60% (6/10) compared with 100% (20/20) at the first biopsy.

Discussion: Adult-onset SMN was rarely reported in spite of 30% of MN cases in childhood. Here, we firstly reported the sequential pathological changes of adult-onset SMN without any immunosuppressive therapy. We will also discuss about the pathogenesis about SMN.

PUB419
Hyporeninemic Hypoaldosteronism with Hypokalemia: A Rare Association
Julia Brown, Shankho Shuvro Ganguli, David J. Leehey, Kavitha Vellanki. Dept of Nephrology, Loyola Univ Medical Center, Maywood, IL.

Introduction: Hyporeninemic hypoaldosteronism is characterized by diminished renin and aldosterone secretion, with hyperkalemia and mild hyperchloremic metabolic acidosis being the hallmark clinical manifestations. It is often seen in diabetic patients with mild to moderate renal insufficiency or in patients taking calcineurin inhibitors. Here, we describe a rare case of hyporeninemic hypoaldosteronism in the setting of severe hypokalemia.

Case Description: A 19 year old male with a liver transplant due to cryptogenic hepatic encephalopathy, bipolar disorder, and autism. He was admitted to our institute with nausea, emesis, and poor oral intake. He was started on fludrocortisone 0.1 mg daily, which was subsequently increased to 0.1 mg twice daily. His serum potassium levels improved and remained stable without potassium supplementation. The etiology of his hyporeninemic hypoaldosteronism was thought to be calcineurin inhibitor use, with hypokalemia caused by persistent nausea, emesis, and poor oral intake.

Discussion: In conclusion, hypokalemia should not exclude work up for hyporeninemic hypoaldosteronism in the appropriate clinical setting.

PUB420
A Case of Hydrenephrosis due to Bilateral Retroperitoneal Fibrosis
Zachary Freesong, Abram M. Shaaban, Josephine Abraham. Nephrology, Univ of Utah, Salt Lake City, UT.

Introduction: Retroperitoneal fibrosis is characterized by inflammatory and fibrous retroperitoneal tissue. It is believed to be due to an exaggerated inflammatory reaction to aortic atherosclerosis resulting from an immunologic trigger. Retroperitoneal fibrosis can be classified as primary or secondary. Secondary causes include medications, malignancy, infection, radiotherapy, and trauma. Patients diagnosed with retroperitoneal fibrosis should undergo thorough evaluation for infectious causes and malignancy.

Case Description: A 55 year old male presented to the clinic with a chief complaint of left side flank and groin pain. He had additional symptoms of night sweats, left leg edema, and weight loss. He was referred to our clinic after initially presenting to the emergency department and receiving a CT scan of the abdomen identifying left side hydrenephrosis and a retroperitoneal mass. His past medical history included melanoma 4 years prior and cutaneous follicular lymphoma of the right mandible one year prior. Repeat ultrasound prior to initiation of therapy showed new right sided hydrenephrosis. The patient was started on monotherapy with prednisone 1 mg/kg/day. Imaging after initiation of therapy showed improvement in fibrosis with resolution of ureteral obstruction. The patient’s serum creatinine improved from 1.93 to 1.2 after initiation of therapy. No secondary causes of retroperitoneal fibrosis was identified.

Discussion: Retroperitoneal fibrosis can present as obstruction of the ureters. It is often idiopathic, but secondary causes should be ruled out. Secondary causes include malignancy, infection, and medications. Recommended therapy includes decompression of obstruction if renal function is compromised. If the cause of the disease is idiopathic, then immunosuppressive therapy is recommended. If the disease is due to secondary causes, the underlying cause should be immediately addressed.

PUB421
BK Virus-Associated Uropathy: A Culprit Mimicking Mechanical Post-Renal Obstruction in Early Post-Kidney Transplantation
Ekamol Tantisattamo, Aneshia S. Shetty, Bing Ho, Mohammed Javeed Ansari. Nephrology and Hypertension, Northwestern Univ.

Introduction: BK virus has a predilection towards infecting the uroepithelial cells and is a known but rare cause of ureteral obstruction of kidney allografts.

Case Description: A 26-year-old woman with ESRD underwent renal transplantation. Maintenance immunosuppression included tacrolimus(FK) and mycophenolic acid(MPA). FK and MPA levels were 8-16ng/mL and 2-5mg/L, respectively. Three months posttransplant,
Acute interstitial nephritis associated with probiotic use


Introduction: Acute interstitial nephritis (AIN) is associated with a variety of etiologies, including infections, autoimmune conditions, and medications. Probiotics are frequently prescribed over-the-counter microorganisms used for their potential to influence gut flora and treat minor gastrointestinal conditions. However, data on the incidence and clinical outcomes of AIN associated with probiotic use are limited. Reports indicating probiotics may have immunostimulatory and immunomodulatory effects. We report the first potential case of AIN associated with the use of probiotics.

Case Description: A healthy 44-year-old man was found to have a stable baseline Cr of 1.0 mg/dL with a measured CsCr in the normal range. 42 d later, to treat infrequent loose bowel movements (2x/wk), he consumed a probiotic regimen of 10 billion cells of Lactobacillus GG bid for 14 d. There was no diarrhea, fever, rash, blood in the stool, or exposure to NSAIDs, antibiotics, herbs, or other medications. 11 d after probiotics use, during routine physical, he was found to have an increase in his Cr to 1.66 mg/dL (an increase of .5 mg/dL in 52 d). There was no proteinuria or hematuria, and an ANA was negative. A renal sonogram revealed echogenic, normal-sized kidneys. His Cr remained 1.4-1.6 mg/dL and did not return to baseline. 135 d after exposure to probiotics, a renal biopsy was performed. The biopsy revealed patchy tubular atrophy and interstitial fibrosis affecting 10% of the cortical area with a few mononuclear inflammatory cells and focal mild lymphocytic tubulitis, consistent with resolving AIN.

Discussion: In this case, the temporal association between the use of probiotics with kidney injury and the absence of other causes of AIN implicates the probiotic Lactobacillus GG as the etiologic agent. The mechanisms by which probiotics could potentially cause AIN include manipulation of intestinal microbial communities, immunomodulation, alteration of
responsiveness of intestinal epithelial and immune cells, and altering the immunogenicity of degraded enteric antigens. Given the frequent over-the-counter use of probiotics, multiple potential coexisting etiologies for AUIN, the often indolent nature of this disease, the rarity of this association, and the need for a renal biopsy to establish the diagnosis, the association between probiotics and AUIN may be under-recognized.

PUB426

Decision-Making for the Critically Ill Un-Befriended Patient

Aparajita Mattoo, Jennifer S. Scherer. Nephrology, NYU School of Medicine, New York, NY.

Introduction: The “un-befriended” patient is one that lacks decision-making capacity & a surrogate decision-maker (SDM). Nephrologists encounter un-befriended patients often, yet limited literature exists to guide decision-making for these vulnerable patients. This case describes an organized approach to caring for a critically ill un-befriended patient.

Case Description: Mr. S was a 74 year old wheelchair bound nursing home (NH) resident who underwent an urgent right hemicolectomy for a perforated colon. His post-operative course was complicated by septic shock & multi-organ failure including AKI due to ATN. During this time his serum Cr increased from 0.8 to 3.6 mg/dl, with a urine output of <50cc/day. Mr. S was obtunded & had diffuse anasarca. He lacked advance directives & any SDM. The primary service believed that dialysis (HD) should be withheld given his overall poor prognosis. The consulting renal service utilized the four-topic approach to ethical decision-making to guide their recommendations. An estranged sister was asked to partake in an inter-disciplinary team (IDT) family meeting with renal, palliative care, bioethics, & the primary service to explore Mr. S’s values. It was established that Mr. S cherished his life in the NH & would have appreciated time there even if on HD. Given this information, the IDT decided that a time limited trial of HD would be reasonable. Before HD was needed however, Mr. S decompensated due to fungemia. The IDT agreed that death was imminent, even with HD. Under provisions of the NY State Family Health Care Decisions Act (FHCDA), it was determined to be ethically appropriate to withhold HD & transition Mr. S to comfort care.

Discussion: Utilizing the four-topic approach to decision-making, established legal policies, & an IDT, nephrologists can manage un-befriended patients within an organized, legally sound, & ethically sensitive framework.

PUB427

Persistent Kidney and Alveolar Damage in Patients with Goodpasture’s Disease and Negative Anti-GBM Antibodies

Giovanna Y. Arteaga Muller,1 Lilia Maria Rizo Topete,1 Elisa Maria Guerrero Gonzalez,2 Concepción Sanchez Martinez,1 Jesus Valdez Cruz,1 Gabriela Alarcón-Galván,1 Nephrology, Univ Hospital José E. Cruz González UANL, Monterrey, Mexico; 2Anatomic Pathology, Univ Hospital José E. González UANL, Monterrey, Mexico.

Introduction: Goodpasture’s disease is characterized by the presence of basement membrane antibodies which act against type IV collagen in the glomerular basement membrane (GBM) and alveoli, it represents 20% of all crescentic glomerulonephritis. Despite prompt initiation of therapy with plasmapheresis, negative control anti-GBM antibodies renal involvement may occur alone or associated with pulmonary hemorrhage. Our patient despite having negative anti-GBM antibodies presented pulmonary hemorrhage. The literature recommends confirming the effective addition of a second potassium sparing agent such as amiloride in ameliorating hypocalciuria, and normotensive aldosteronism. The existence of 2 unique recessive alleles presents as chronic, sometimes severe and symptomatic hypokalemia, hypomagnesemia, hypocalciuria, and normotensive aldosteronism. The existence of 2 unique recessive alleles inherited by two siblings makes this case even more of a rarity. Our case also demonstrates the effective addition of a second potassium-sparing agent such as amiloride in ameliorating the need for more supplementation.

Discussion: Gitelman syndrome occurs in only ~1% of the Caucasian population which presents as chronic, sometimes severe and symptomatic hypokalemia, hypomagnesemia, hypocalciuria, and normotensive aldosteronism. The existence of 2 unique recessive alleles inherited by two siblings makes this case even more of a rarity. Our case also demonstrates the effective addition of a second potassium-sparing agent such as amiloride in ameliorating the need for more supplementation.

Cerebral Ethylene Glycol Toxicity Despite Prompt Renal Replacement Therapy

Maria Bernadette Yballe, Sandeep Aggarwal. Div of Nephrology, Drexel Univ, Philadelphia, PA.

Introduction: Acute cerebral edema is a rare consequence of ethylene glycol toxicity. Despite prompt initiation of therapy with fomepizole and renal replacement therapy, rare case reports of central hypodensities on CT imaging with neurologic abnormalities have been reported.

Case Description: We present a case of a 38 year-old female with PMH of HTN and anxiety who was brought in for agitation. One hour later, the patient became obtunded with significant respiratory distress requiring intubation. Home medications included hypropion. It was unclear if she ingested any toxins but the patient did have a history of marijuana use. On physical examination, the patient was hypertensive 210/114 mm Hg with reactive pupils. She was found to have high anion gap metabolic acidosis with a pH of 6.808, a serum bicarbonate of 4, an osmolal gap of 68, and a lactic acid of 5.6. Levels of ethanol, acetaminophen, phenobarbital, salicylate, and valproic acid levels were undetectable while urine drug screen was only positive for THC. Head CT did not reveal any acute Direct immunofluorescence technique (400X). Linear glomerular basement membrane staining for IgG.

Immunosuppressive therapy begins with methylprednisolone and CYCLOPS protocol. Later hemoptysis which improves with plasmapheresis, negative control anti-GBM antibodies. After presented sudden hypoxemia, bronchoscopy with abundant hemosiderin-laden macrophages, whereby plasmapheresis is performed again together with methylprednisolone, cyclophosphamide and rituximab. Currently the patient is in chronic hemodialysis, with negative anti-GBM antibodies.

Discussion: In patients with positive anti-GBM antibodies renal involvement may occur alone or associated with pulmonary hemorrhage, our patient despite having negative anti-GBM antibodies presented pulmonary hemorrhage. The literature recommends confirm the sustained absence of anti-GBM antibodies and signs of recurrence every 6 months.
Encapsulating Peritoneal Sclerosis – Case Reports

Introduction: Encapsulating Peritoneal Sclerosis (EPS) is a rare but serious and potentially lethal complication in peritoneal dialysis (PD), first described in 1980. Intestinal obstruction, serious malnutrition and sepsis are the causes of death. This uncommon condition is the result of chronic abdominal inflammation of multifactorial origin. High risk patients include PD for more than 8 years and with frequent peritonitis (two-hits theory). The exact incidence is unknown.

Case Description: We described outcomes of 6 cases followed in a referral service of PD between 2010 and 2015.

Case | Gender/ Age (years) | CKD related infection | Time on PD (years) | Prevalent Peritonitis (number) | Clinical Features | Radio- logical Find | Peritoneal biopsy | Outcome |
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F / 47</td>
<td>SAH</td>
<td>8</td>
<td>Candida spa / Staphylococca aureus</td>
<td>Acute abdominal obstruction + Bloody effluent</td>
<td>Localized ascites + Peritoneal thickening + calcifications</td>
<td>Chronic peritonitis + Peritoneal thickening + Fibron deposition</td>
<td>HD since 2010</td>
</tr>
<tr>
<td>2</td>
<td>F / 47</td>
<td>SAH</td>
<td>4</td>
<td>Pseudomomas aeruginosa</td>
<td>Partial bowel obstruction + Bloody effluent</td>
<td>Localized ascites + Bowel thickening</td>
<td>--</td>
<td>HD at 8 months</td>
</tr>
<tr>
<td>3</td>
<td>F / 18</td>
<td>PIGN</td>
<td>10</td>
<td>Staphylococca coagula negative</td>
<td>Partial bowel obstruction + pain</td>
<td>Moderate ascites + Peritoneal/Bowel calcification</td>
<td>--</td>
<td>HD since 2013</td>
</tr>
<tr>
<td>4</td>
<td>M / 68</td>
<td>TZDM</td>
<td>2.5</td>
<td>Escherichia coli / Klebsiella oxytoca</td>
<td>Partial bowel obstruction + pain</td>
<td>High volume localized ascites + bowel tethering</td>
<td>--</td>
<td>HD since 2012</td>
</tr>
<tr>
<td>5</td>
<td>F / 39</td>
<td>SLE</td>
<td>8</td>
<td>Entero-cooccus sp</td>
<td>Bloody obstruction + Severe malnutrition + Chronic abdominal pain + Bloody effluent</td>
<td>Peritoneal calcification + bowel distention + high volume ascites</td>
<td>--</td>
<td>Death for sepsis after 8 months</td>
</tr>
<tr>
<td>6</td>
<td>M / 53</td>
<td>TZDM</td>
<td>2.5</td>
<td>Streptococcus viridans</td>
<td>Abdominal distension + pain</td>
<td>High volume unique peritoneal collection + intestinal cocoon</td>
<td>--</td>
<td>HD since 2014</td>
</tr>
</tbody>
</table>

SAH: Sistemic Arterial Hypertension; SLE: Sistemic Lupus Eritematosus; TZDM: Type 2 Diabetes Mellitus; PIGN: Post Infectious Glomerulonephritis/CKD. Chronic Kidney Disease.

Discussion: EPS is a severe event related a long term on peritoneal dialysis or severe cases of peritonitis.

AM Tolvaptan to Avert Hypoancretic Seizures in a Patient with Primary Polydipsia and New Mildly Impaired Free Water Excretion

Introduction: A former pilot with a history of primary polydipsia PP (past urines >6 l/day) complained of confusion. Plasma (P₅₀) and urine sodium were 123 and 37 mEq/l, and plasma (P₅₀) and urine osmolalities, 251 and 207 mOsmol/kg H₂O. With cessation of Prozac and advised fluid restriction (FR) P₅₀ corrected. Plasma P₅₀ was 286 mOsmol/kg and urine SG 1.005. Following multiple surgeries (decompressive laparotomy, subtotal colectomy, ileostomy, feeding gastrostomy, for compartment syndrome/pancreatitis), he was found to have a first hyponatremic seizure (HS). No cause for impaired free water excretion (iFWE) was found. Her PP made FR difficult, as she was thirsty at P₅₀ <125 mEq/l, and caused repeat HSs.

Case Description: After her 4th seizure, we replaced FR and salt tablets with AM tolvaptan. This normalized P₅₀, abolished her recurrent HSs, and was tailored to her new dreadful PP-SIADH combination.

Indeed, since sepsis is constant in DI but only diurnal in PP, the AM tolvaptan-induced daytime DI allowed her to quench her thirst without fear of HSs, since if we were recurred by hs, when the drug effect were off, and her PP abided. She was reluctant giving up this diurnal/nocturnal PP/DESIADH, for fear of seizures.

Discussion: Given the high capacity for FWE, a syndrome of inappropriate antidiuresis (SIAD) or impaired diuresis-aquarexia (SIDA), due or not to ADH (SIAD/H or SIDA/H) must coexist in PP, for HS to occur; conversely some PP or other source of free H₂O must exist in the SIDA/H – SIDA/H spectrum of iFWE to cause HS, since FR alone increases the low P₅₀, and prevents HS during depot ADH in man, or chronic dAVP infusion in rats. This is the first report of successful compassionate off label use of AM tolvaptan, instead of FR, to prevent HS in a patient where PP is the culprit. However FR instead of vaptans is the first line treatment of low P₅₀ in SIAD/H, yet here ADH is the culprit. Thus in that PP and SIAD/H (or iFWE state) must coexist to cause HS, and that ADH, as assessed by sensitive assays is rarely totally suppressed, resolves this paradox.

Acute Kidney Injury Associated with Brucella Infection

Introduction: Ethylene glycol ingestion can cause multi-organ dysfunction including acute kidney injury (AKI) and death. The diagnosis can be made based on history, a high anion gap metabolic acidosis with an elevated osmolar gap, oxalate crystalluria and an elevated ethylene glycol level. The diagnosis may be challenging with the concurrent use of other substances such as cocaine as it causes vasomotor AKI or ANCA vasculitis. To elucidate the diagnosis, a renal biopsy may be required. Herein, we present a patient with biopsy proven calcium oxalate nephropathy who presented with unexplained AKI likely related to unintentional low dose regular ethylene glycol use. She did not have any symptoms or classic biochemical features of ethylene glycol intoxication.

Case Description: A 57-year-old homeless woman with a history of rheumatoid arthritis, COPD presented with a productive cough and dysgeusia and was found to have a Cr of 3.9 mg/dl, elevated from a recent baseline of 0.9 mg/dl. Her anion gap was 17, with no other electrolyte abnormalities. Toxicology was negative for ethanol or salicylates. Her BP was 157/77 mm Hg and physical exam was unremarkable. Her last use of cocaine was 3 days prior to admission. She was initially given normal saline and maintained an adequate urine output, but her Cr continued to rise to 13.0 mg/dl. Urine sediment showed a few isomorphic RBCs only. A renal ultrasound revealed normal sized kidneys. Serological tests for autoimmune, post-infectious and dysproteinemic causes of AKI were normal or negative. Renal biopsy revealed acute tubular injury with calcium oxalate deposition. An in depth history did not reveal a high oxalate diet nor a medical history predisposing her to hyperoxaluria, however she admitted to the regular ingestion of “juiced” street alcohol. She did not require dialysis. Her follow-up Cr was 1.8 mg/dl two months later.

Discussion: In conclusion, a thorough history is required when encountering unknown AKI in patients with a history of drug abuse or homelessness, while keeping a high index of suspicion for drug intoxications including ethylene glycol.

Thrombotic Microangiopathy (Hemolytic-Uremic Syndrome) Induced Acute Kidney Injury Associated with Brucella Infection

Introduction: Thrombotic microangiopathies (HUS, TTP and DIC) have been associated with a host of infectious agents. Its association with Brucellosis is uncommon. We present a case of a patient who developed TMA associated with a case of Brucellosis.

Case Description: A 52-year-old woman with minimal past medical history presented to the hospital with abdominal pain, fever/chills and general body aches. History was significant for intermittent bloody diarrhea approximately 2 weeks prior to ED presentation. Physical examination revealed epigastric and right upper quadrant tenderness to palpation and patient was started on broad-spectrum, empiric IV antibiotic therapy with
Vancomycin, Piperacillin-Tazobactam, and Ciprofloxacin. Shortly thereafter, her clinical status deteriorated resulting in acute respiratory failure requiring intubation and mechanical ventilation. CBC was notable for a white blood cell count of 27,000, hemoglobin of 7.3 g/dL and a platelet count 80,000. Other labs were notable for total bilirubin 2.3 mg/dL, LDH 509 U/L, lactate dehydrogenase less than 10, albumin 5.7 mmol/L and elevated transaminases. Peripheric Smear was notable to be positive for pensive schistocytes. Patient was anuria and Nephrology consulted to begin CRRT in setting of sepsis requiring three vaspessors. Patient had a rapid improvement in symptoms after initiation of sepsis protocol and was weaned off all vaspessors by 72 hours. Initial workup including abdominal imaging and blood cultures were negative for a source of infection. Patient had remarkable spontaneous clinical recovery and was later found to be positive for Brucellosis by immunoglobulin assay.

Discussion: Brucella infection has uncommonly been associated with the development of Hemolytic Uremic Syndrome. In addition, clinical course is widely variable, ranging from spontaneous recovery, as occurred with this patient, to disease requiring long-term renal replacement therapy.

**Case Description:**

**Case 1:** A 69 year-old male started chemotherapy including bevacizumab (monoclonal antibody of VEGF) with a diagnosis of advanced lung adenocarcinoma of left upper lobe. The completion of four-course chemotherapy resulted in reduction of tumor volume, and then converted to bevacizumab monotherapy. At one year after the start of therapy, proteinuria with renal insufficiency developed. He was referred to our service for further evaluation and management. Renal biopsy demonstrated microthrombi in the loop wall with duplication of GBM, which was consistent with thrombotic microangiopathy (TMA). Thereafter, with cessation of anti-VEGF agent, proteinuria was gradually ameliorated to less than 1.0 g/day and renal function returned to normal range. **Case 2:** A 56 year-old male with renal cell carcinoma, who had undergone nephrectomy and diabetes. After the introduction of therapy, he exhibited progression of kidney disease with nephrotic-range proteinuria in a short time. In addition to the cessation of sintunin, hemodialysis was initiated because of fluid overload. After several times of dialysis, urine output was gradually increased and renal function returned to the baseline level.

Discussion: The renal adverse effects of anti-VEGF agents are supposed to arise from inhibition of podocyte-endothelial VEGF signaling pathway. VEGF signaling pathway plays an essential part in glomerular development and endothelial maintenance. We need to pay attention to renal adverse effects with anti-VEGF therapy.

**Case Description:**

**Case 1**:

A 29-year-old previously healthy man initially presented with cough, fever and AKI and was diagnosed with rheumatologic disease presented with cough, fever and AKI and was diagnosed with acute post-infectious glomerulonephritis. Group A Complement C3: 19 Ch50: <10, C4:34 Antistreptolysin O:400 [<200 IU/ml]. Urine sediment revealed many WBCs with no casts and some non-dysmorphic RBCs. A decision was made to proceed with kidney biopsy to identify the cause of her renal disease since the sediment was not supportive of Scleroderma associated renal disease. Kidney pathology showed acute interstitial nephritis with mild chronic changes which, when combined with the serologic tests, was highly suggestive of Sjögrens syndrome-associated renal disease. She was commenced on corticosteroid therapy and two months post-initiation, her renal function has stabilized.

Discussion: This case demonstrated the importance of kidney biopsy in elucidating a diagnosis in a challenging case of overlap syndrome. The rapid diagnosis of interstitial nephritis was particularly important in this patient since most cases of renal associated Sjögrens’ go unrecognized until significant renal dysfunction has occurred. It has been proposed to consider kidney biopsy findings of tubulointerstitial disease as additional supportive criteria in the classification of Primary Sjögren’s syndrome, which is a sentiment we also support.

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

**Underline represents presenting author.**

989A
A Case of Hyponatremia from Adrenal Insufficiency Mimicking Siadh
Pradeep Reddy Thodina, Rasith Raja, Siddhesh R. Lotlikar, Imara Dissmasyake, Eric J. Bloom. Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA; Nephrology, Albert Einstein Medical Center, Philadelphia, PA.

Introduction: A 40 yr old male with a diagnosis of nasopharyngeal carcinoma was admitted for dysphagia and decreased oral intake. He had severe hyponatremia with serum Na 126 meq/l and Uosm of 932 osm/l. He was deemed to have euvolemic hyponatremia from SIADH and started on fluid restriction. There was no improvement in hyponatremia and Una increased to 235 meq/l. He was diagnosed with adrenal insufficiency with a co-syntropin test. Imaging studies did not demonstrate pituitary invasion by nasopharyngeal carcinoma. He was started on high doses of hydrocortisone with rapid improvement of hyponatremia and Una dropped to 355 meq/l. Hyponatremia with Una (280 meq/l) recurred during diuresis taper. He required prolonged high doses of diuretics to maintain normal serum sodium level. Although there have been many case reports of hyponatremia with adrenal insufficiency, to the best of our knowledge there has been no reports of hyponatremia with very high Urine sodium (> 200 meq/l).

This case highlights that euvolemic hyponatremia can occur with adrenal insufficiency with clinical and biochemical manifestations mimicking SIADH. Adrenal insufficiency should be considered in all cases of hyponatremia especially with very high urine sodium.

Hemodialysis: An Atypical Presentation of ESRD-Related Sleep Disorders
Desiree Garcia Anton, Franco H. Cabeza Rivera, Alexandre Abreu, Marco A. Ladino/Avellaneda. Nephrology, Univ of Miami, Miami, FL.

Introduction: Sleep disorders including obstructive sleep apnea (OSA), restless leg syndrome (RLS) and insomnia are highly prevalent in ESRD patients undergoing dialysis, however, these remain stable or tend to improve after initiation of dialysis. There is scarce evidence of new-onset sleep complaints or disorders after initiation of dialysis.

Case Description: We present a case of a 64 year-old male with HTN, DM, ESRD and no previous sleep problems who developed insomnia, RLS, sleepwalking and other sleep disturbances within a month after initiation of continuous hemodialysis. He presented to the nephrology clinic with secondary complications from uncontrolled diabetes (neuropathy, retinopathy and nephropathy); he had been followed by the nephrology service for 4 years before requiring dialysis for uremia and volume overload. Intermittent HD was well tolerated during first month of treatment, achieving good metabolic clearance and volume control; his KTV was 1.16, phosphorus was controlled at 4.6 mg/dl and his anemia improved to a hemoglobin of 9.6 mg/dl; iron was 36 mcg/ml, ferritin 135 ng/ml and transferrin saturation 15%. Despite clinical and laboratory improvement, disabling sleep symptoms were reported and he was referred to the Sleep clinic for further evaluation. On his initial actigraphy, a bedtime or rise time pattern was unable to be determined as it showed continuous movements 24 hours per day for the 14 days monitored. Overnight Polysomnography (PSG) revealed severe OSA and periodic limb movements (PLM); there was also evidence of insomnia with severely reduced sleep efficiency.

Discussion: New-onset sleep problems after initiation of dialysis in patients who previously had no sleep complaints are an atypical presentation. The role of RRT on sleep disturbances in the ESRD population is unknown. We propose PSG pre and post dialysis initiation on advanced CKD patients to assess for differences and identify how RRT may be a cause of sleep disturbances.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Case Description: A 32-year-old man with a history of bipolar disorder came to the hospital with severe diaphoresis and worsening lethargy. He was subsequently intubated for airway protection. Patient’s lithium level was ~20 mmol/L. CT head showed no injury. The rest of the toxicology screen was negative. His basic metabolic panel (including calcium and albumin) was within normal limits however his bicarbonate was 32 mmol/L and his anion gap was elevated. Severe hyponatremia was noted and the patient initially trended down to 0.9 after 48 hours. Patient was extubated 48 hours after initial presentation.

Discussion: Lithium has a narrow therapeutic window and therefore in cases of overdose toxicity have many symptoms including altered levels of consciousness as seen in this patient. Low anion gap is a diagnostic clue to lithium intoxication however other causes include hyperkalemia, hypermagnesemia, and monoclonal gammopathies. Although serum osmolality was not measured in our patient, this can also be a helpful indicator noted in previous case reports. Elevated osmolar gaps with low anion gaps are useful in diagnosing lithium overdose. The standard management for lithium overdose is intermittent hemodialysis and maintaining water balance. The theory behind using intermittent hemodialysis versus continuous venovenous hemodiafiltration is that higher clearance of lithium can be achieved from faster blood flow rates in intermittent hemodialysis.

PUB445
Frailty Modifies the Association Between Age and Dysnatremia in Community-Dwelling Adults
Amanda Jean Miller,1 Susan E. Howlett,2 Kenneth John Rockwood,2 Karthik K. Tennankore.1 1Nephrology, Dalhousie Univ; Halifax, NS, Canada; 2Geriatrics, Dalhousie Univ; Halifax, NS, Canada.

Background: Frailty represents a state of increased risk to adverse health outcomes, reflecting some combination of increased damage and compromised repair processes. Dysnatremia is more common with age and can occur in many settings, suggesting that it may reflect not simply a specific renal problem, but a more general imbalance in damage and repair. The aims of this study were to establish whether frailty severity is associated with a higher rate of dysnatremia and to determine whether frailty explains the previously established association between age and dysnatremia.

Methods: The relationship between age, frailty severity and dysnatremia was investigated across the adult life course in 8898 respondents from the 2003-2004 and 2005-2006 cross-sectional National Health and Nutrition Examination Survey (NHANES) datasets. Respondents were assigned a frailty index (FI) and assessed for dysnatremia (a deviation of serum sodium from the 135-144 mmol/L normal range). The coefficient of variation in serum sodium was used as a systems measure of the response repertoire.

Results: In the overall population, there was a significant positive association between increasing frailty severity and the proportion of patients with dysnatremia (chi-square trend p < 0.001). Increasing frailty severity was also associated with more variability in serum sodium. There was a significant association between advancing age and dysnatremia (<p < 0.001); however after stratifying by frailty (FI <0.100, 0.100-0.199, 0.200-0.299, 0.300-0.399, >=0.400), the association between increasing age and dysnatremia became non-significant in all categories.

PUB446
Approach to Hyponatremia in Congestive Heart Failure: A Survey of Canadian Physicians and Trainees
Amanda Jean Miller,1 Bonnie Kuehl,2 Karthik K. Tennankore.1 1Nephrology, Dalhousie Univ; Halifax, NS, Canada; 2Research, Scientific Insights Consulting Group Inc., Mississauga, ON, Canada.

Background: Hyponatremia is a complication of congestive heart failure (CHF) and is associated with reduced survival, however there are no consensus guidelines for the treatment of hyponatremia in CHF. The aim of this study was to determine the approach to hyponatremia in CHF amongst Canadian healthcare practitioners and trainees.

Methods: Respondents completed 15 multiple-choice style questions surrounding three cases of hyponatremia complicating CHF using an online survey on UKidney.com between December 2012-May 2013. Results were summarized as the proportion of correct/incorrect responses among Canadian Nephrologists, Cardiologists, Internists and trainees in each of two domains; pathophysiology and management. Management topics included use of diuretic therapy, hypertonic saline, oral urea tablets, vasopressin receptor antagonists (vaptans) and rate of sodium correction. Correct answers were determined by an expert panel of Canadian Nephrologists and Cardiologists.

Results: There were 1097 responses to survey questions among 455 Canadian respondents. Pathophysiology governing hyponatremia in CHF was correctly identified in 68.7% of responses (n = 380). Overall, hyponatremia was managed inappropriately in 33.6% of responses (n = 759). The proportion of incorrect responses among specialists and trainees is depicted in Figure 1. Importantly, an incorrect rate for sodium correction was selected 61.1% of the time (n = 211).

Figure 1: Proportion of dysnatremia with increasing age, stratified by frailty index.
Hospital, New York, NY; Upon admission, her serum sodium was 106. With hypertonic saline and fluid restriction, onset of hyponatremia may be within ten days. Our patient took sorafenib for two weeks. With a rate of up to 11% in patients treated for HCC, the pathophysiology may be related to FT4. AM cortisol was measured at 20.2. Her total protein and lipid profile were normal. Lethargic, with generalized swelling. The serum sodium was 106 mmol/L, with a baseline her dose to 400 mg in the AM and 200 mg in the PM. A day thereafter, patient became the dose was increased to 200 mg twice daily. Three days later, the patient increased began sorafenib two weeks prior to admission, with a dose of 200 mg daily. A week later, the patients exhibited a serum sodium level of >130 mmol/L. Individuals aged 65 years old were noted, however, to be receiving related drug therapies 63.4%. They were distributed by eGFR using creatinine comparison to a control group includes novel conditions such as patients receiving renal replacement therapy.

**Conclusions:** This study suggests that hyponatremia often is mild, is commonly associated with drug therapy, affects a significant number of younger patients, and now includes novel conditions such as patients receiving renal replacement therapy.

**PUB449**

**Development of Metabolic Acidosis After Neobladder Replacement in Korea**

Shina Lee, Dong-Ryool Ryu, Kyu Bok Choi, Duk-Hee Kang, Seung-Jung Kim. Dept of Internal Medicine, School of Medicine, Ewha Womans Univ, Seoul, Korea.

**Background:** Metabolic acidosis frequently develops in patients after neobladder replacement. However, the incidence of metabolic acidosis in patients with neobladder and the factors associated with the development of metabolic acidosis have not been well elucidated. We aimed to investigate the incidence and the potential predictors for the development of metabolic acidosis after neobladder replacement with intestinal segment.

**Methods:** We included all patients who underwent neobladder replacement using intestinal segment at Mokdong Hospital between January 1, 2005 and December 31, 2014. Metabolic acidosis was defined as serum CO2 below 22 mEq/L at any visit during the follow-up period. Patients’ biologic data was presented using t-test and student t-test. Subgroups according to the timing of metabolic acidosis occurrence were further analyzed in order to characterize predictors for metabolic acidosis by ANOVA tests and multiple regression.

**Results:** Metabolic acidosis was encountered in 79.4% of patients with neobladder during follow up period. When patients were divided into 2 groups according to anion gap(AG), total CO2(18.9 ±1.2 mEq/L vs. 20.0 ±1.3 mEq/L, p<0.001) and chloride(106.6±4.9mEq/L vs. 109.4±3.6mEq/L, p<0.001) were significant different between groups with AG<12 and AG≥12 respectively. Furthermore, when patients were divided into 3 groups; patients with metabolic acidosis at post operative day 1; within 1-4days; after 14days, there was significant difference of postoperative laboratory findings among the those subgroups.

**Conclusions:** Our study showed the rate of development of metabolic acidosis in patients underwent neobladder replacement and the difference between patients with metabolic acidosis and those without metabolic acidosis after neobladder replacement for the first time in Korea. In the future, well designed prospective study will be needed to prevent metabolic acidosis after neobladder replacement.

**PUB450**

**Potassium Abnormalities and Acute Kidney Injury Are Common Complications After Colectomy**

Lindsay M. Smith,1 Robert M. Perkins,2 Andrea Lynn Berger,1 H. Lester Kirchner,3 Morgan Grams,4 Alex R. Chang,5 1Geisinger Health System; 2Bayer Healthcare; 3Johns Hopkins Bloomberg School of Public Health.

**Background:** Patients undergoing colectomy may be predisposed to disturbed potassium homeostasis, since the colon has a role in potassium excretion, and volume depletion due to diarrhea occurs frequently after colectomy.

**Methods:** We examined the frequency of incident mild (<5 mmol/L) and severe hyperkalemia (>6 mmol/L), mild (<3.5 mmol/L) and severe (<2.5 mmol/L) hypokalemia, and incident AKI, stratified by estimated glomerular filtration rate (eGFR) using creatinine and inpatient only and potassium (inpatient/outpatient) data from 1,762 patients who underwent colectomy surgery at Geisinger Health System between 2004-2013.

**Results:** Median age was 66 and mean baseline eGFR was 79 ml/min/1.73m². Colonic conditions included inflammatory bowel disease (8%), bowel obstruction (8%), ischemic bowel (2%), diverticulitis (23%), and colorectal cancer (20%). During the surgery hospitalization, post-operative AKI occurred in 32% of patients; mild and severe hyperkalemia occurred in 18% and 3% of patients. Over a median of 4.0 years post-discharge after colectomy, mild and severe hyperkalemia occurred at a rate of 13.4 events/100 person-years and 1.8 events/100 person-years; mild hypokalemia and severe hypokalemia occurred at a rate of 15.4 events/100 person-years and 0.7 events per person-years. Rates of incident AKI after discharge were high (9.1 events/100 person-years). Risks for AKI, mild and severe hyperkalemia increased as eGFR declined (p<0.001, Table).

**Conclusions:** Patients who undergo colectomy are at high risk for hyperkalemia, hypokalemia, and AKI, particularly when eGFR is decreased. Comparison to a control group is needed to determine whether the high incidence of hyperkalemia is related to removal of the colon or frequent AKI episodes.

**Table. Event Rates for Hyperkalemia, Hypokalemia, and AKI Events after Colectomy by Baseline eGFR Category**

<table>
<thead>
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<th>eGFR Category</th>
<th>Number of Events per 100 person-years</th>
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<tr>
<td>Baseline eGFR</td>
<td>&lt;K=5</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>&lt;90 (n=61)</td>
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<td>Baseline eGFR</td>
<td>90-&lt;99 (n=755)</td>
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<td>Baseline eGFR</td>
<td>99-&lt;109 (n=233)</td>
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<tr>
<td>Baseline eGFR</td>
<td>109-&lt;117 (n=117)</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>&lt;117 (n=43)</td>
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</table>

**Funding:** Private Foundation Support

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**Diuretics (36.6%)**

<table>
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<th>Percent Distribution of Drug Therapies</th>
<th>Diuretics Alone (17.5%)</th>
<th>Diuretics + CHF (19.5%)</th>
<th>SSRI (17.5%)</th>
<th>Others (9.7%)</th>
</tr>
</thead>
</table>

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 992A
Methods: 62-year-old female with history of adenocarcinoma of the lung, developed severe hypomagnesemia due to metastatic non-magnesium (Mg) levels of 5.1 mg/dL. She had concurrent severe hypocalcaemia with serum calcium (Ca) of 5.1 mg/dL. Aggressive repletion was started & further work up was done. Her urine spot Mg level was reported as 381 mg, her fractional excretion of Mg was calculated & it was 9%. She received 3 cycles of 2-hour uridine before hospitalization. She was not on any diuretics, PPIs & Aminoglycosides. She did not receive cetezolimub as well.Urine calcium was less than 150mg, it was thought that she had carboplatin-induced distal nephron Mg wasting . Her serum PTH level was 245.5 pg/mL. Her hypercalcemia was thought to be secondary to PTH resistance mediated by severe hypomagnesaemia. After aggressive repletion her serum Mg & Ca level normalized.

Conclusions: Hypomagnesemia can be due to multiple causes, Initial step in evaluation involves calculating FeMg, if less than 2.5% it is likelyy secondary to GI losses. If FeMg is >2.5% then we measure 2-hour uridine calcium, if its more than 250mg it is likely due to TAL-Mg wasting which can be secondary to loop diuretics, nephrotic syndrome(Aminoglycosides) or Familial hypomagnesemia with hypercalciuria. If less than 150mg then it is likely due to distal nephron Mg wasting which can be secondary to thyizides & Gitleman’s syndrome.

Our case represents an interesting concurrent presentation of severe hypomagnesemia and hypocalcaemia, which was successively treated.

PUB455
Effect of Arterial pH and Bicarbonate Level on Survival of Lactic Acidosis Patients Treated with Sodium Bicarbonate

Dongyeol Lee,1 Hansae Kim,1,2 Eu Gene Jeong,1 Su Mi Lee,1 Sung Hyun Sorn,1 Yong Ki Park,1 Young Ki Son,1 Seong Eun Kim,1 Won Suk An.1

1Internal Medicine, Bong Seng Hospital, Busan, Korea; 2Internal Medicine, Han Seo Hospital, Busan, Korea; 3Internal Medicine, Dong-A Univ, Busan, Korea.

Background: Patients with lactic acidosis have high mortality rate, and higher lactate level is poor prognostic indicator. The correction of lactic acidosis with sodium bicarbonate is potentially harmful when sodium bicarbonate inappropriately was used. Therefore, we evaluated whether starting pH of sodium bicarbonate affect on the survival in lactic acidosis patients treated with sodium bicarbonate.

Methods: We conducted a single center analysis from May 2011 through April 2014. We retrospectively analyzed 230 patients with lactic acidosis treated with sodium bicarbonate. Patients were divided four groups according to starting arterial pH of sodium bicarbonate. We analyzed arterial blood gas analysis, lactate level about 6, 12, 24, 48 hours after using sodium bicarbonate.

Results: The mean age of patients was 62.8 ± 15.0 years, 174 patients (75.7%) were male. The non-survivals had lower pH, hemoglobin, and CRP (< P < 0.001, < P < 0.001, and < P = 0.003), higher SOFA and APACHE II scores (< P < 0.001, < P < 0.001, and < P < 0.001). Patients with increased second lactate level had higher mortality (84.4%). The mortality rate was 90% in patients with sustained high lactate level at 48 hours. The mortality rate was not different according to starting point of sodium bicarbonate. In survival group, arterial bicarbonate level was slowly increased without fluctuation. However, arterial bicarbonate level showed fluctuation in non-survival group. The mortality rate was independently associated with arterial pH at 12 hours after sodium bicarbonate infusion.

Conclusions: Stably increased arterial bicarbonate without fluctuation and recovering arterial pH at 12 hours are important factors in patients treated with sodium bicarbonate. Therefore arterial pH and sodium bicarbonate level should be closely monitored especially till 48 hours, if sodium bicarbonate treatment with lactic acidosis.

PUB456
Evaluation and Management of Hyperkalemia in an Academic Medical Center

Jason K. Law,1 Gaurav Ghosh,1 Daniel Edmonston,1 Saif A. Mulsim,1 Yassin Hussain,2 Miriam Chung,1,2 Jeffrey I. Silberzweig,1,2,4 Dept of Medicine, New York-Presbyterian Hospital, New York, NY; 1Weill Cornell Medical College, New York, NY; 1Weill Cornell Medical College, Qatar, Doha, Qatar; 2Rogosin Inst, New York, NY.

Background: Hyperkalemia (K > 6.0 mmol/L) is common among hospitalized patients but the approach to evaluation and management is highly varied. Patients are not routinely evaluated for clinical effects. Decisions regarding whether and how to treat are often based on individual physician judgments since few evidence-based guidelines exist. Since both hyperkalemia and its treatments can be associated with serious adverse consequences, we sought to evaluate the management in our institution.

Methods: Electronic medical records were reviewed for patients in our institution with potassium levels greater than 6.0 mmol/L between January 1, 2012 and December 31, 2014. Records were extracted for hyperkalemia associated symptoms and ECG findings, as well as interventions and outcomes.

Results: Only 2% of patients had clinical findings consistent with hyperkalemia. Only 10% of patients had ECGs performed and only 20% of those had findings consistent with hyperkalemia. Of patients with ECG findings consistent with hyperkalemia, only 15% had repeat tracings performed after treatment. At least 50% of patients were treated with insulin and dextrose and/or calcium. One-third of patients were treated with sodium polystyrene sulfonate (SPS), 25% with sodium bicarbonate and 10-15% were treated with lactulose or furosemide. Only 25% of patients had repeat potassium levels measured within six hours of treatment.
Disorders of Plasma Sodium in Hospitalized Patients and Effect of Total Plasma Protein Concentration on Its Measurement

Pedro J. Labrador, Silvia Gonzalez S, Santiago Polanco Candelario, Elena Davin Carrero, Jesús P. Marín, Ines Castellano, Juan R. Gomez-Martino.

**Disclosures:** Nephrology, San Pedro de Alcántara Hospital, Caceres, Spain.

**Background:** The aim of the study was the analysed the prevalence of hyponatremia in hospitalized patients, and the effect of total plasma protein (TPP) concentration on plasma sodium measurements.

**Methods:** We registered all biochemical analysis from in-hospital patients during one year. Data from age, sex, and department was recorded. Plasma Na was measured by an indirect ion selective electrode measuring system (Cobas 8000 analyzer, Roche Diagnostics). Hyponatremia was defined as mild when plasma Na was lower than 130 mmol/L. Hyponatremia was classified based on plasma Na concentration. Mild hyponatremia was defined as 130-134 mmol/L, moderate as 125-129 mmol/L and profound as lower than 125 mmol/L. When TPP was measured, plasma Na concentration was corrected according to: plasma Na = plasma Na (mg/dL) / (1 + 0.7 x (TPP concentration – 6.0)).

**Results:** Our hospital is a 520 in-hospital beds. Plasma Na was measured in 26,904 biochemical analyses from 6,873 patients. Median age was 67 (IQR 50-79), 55.9% were men. Median plasma Na measurements was 5 (IQR 2-11). Hyponatremia was present in 1,514 patients (22%), mild hyponatremia 1,114 (16.2%), moderate 287 (4.2%) and profound 113 (1.6%). Plasma Na could be corrected to TPP in 3,122 patients, using the first formula hyponatremia was present in 29.4% (mild 19.6%, moderate 6.8% and profound 3%) while using the second one, 27.9% (mild 18.7%, moderate 6.4% and profound 2.8%).

**Conclusions:** Hyponatremia is present in one fifth of in-hospital patients. Correction of plasma Na concentration according to TPP concentration increase hyponatremia diagnostic up to 25%.

PUB457

Treatment of Hyperkalemia with Kayexalate in an Academic Medical Center


**Background:** Hyperkalemia (K > 6.0 mmol/L) is a potentially life-threatening condition; standard treatment has included sodium polystyrene sulfonate (Kayexalate) since its introduction in 1958. Recent literature has questioned the benefits of this treatment because of the lack of proven efficacy and the risk of serious adverse effects. We evaluated the effectiveness of Kayexalate for treatment of patients with hyperkalemia in our institution.

**Methods:** Electronic medical records were reviewed for all patients in our institution with potassium levels > 6.0 mmol/L between January 1, 2012 and December 31, 2014. Records were extracted for hyperkalemia treatment and outcomes. Hyperkalemia treatments included albuterol, diuretics, insulin, lactulose, sodium bicarbonate, and Kayexalate. Comparisons between hyperkalemia treatments with Kayexalate and without Kayexalate were made using t-tests.

**Results:** One-third of patients diagnosed with hyperkalemia were treated with Kayexalate. Post-treatment potassium values decreased by 14.8% in treatment with Kayexalate, compared to 17.4% reduction in treatment combinations without Kayexalate (p = 0.06). No patients suffered serious adverse effects from Kayexalate treatment.

**Conclusions:** In our population, treatment of hyperkalemia with Kayexalate was common. While no adverse events of treatment were noted, there was no significant difference in reduction of potassium levels with it. We conclude that there is insufficient evidence to support routine use of Kayexalate in our population.

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PUB458

The Impact of Hyponatremia on Children: Prevalence and Consequences During Hospitalization

Zachary Sartor, Poonam Thakore, Tetyana L. Vaaylyeva. Pediatrics, Texas Tech Univ Health Sciences Center, Amarillo, TX.

**Background:** Hyponatremia in adults is associated with increased morbidity and mortality, but this association has not been explored in pediatrics. The aim of this study is to characterize the prevalence of hyponatremia and assess its impact on the course of hospitalization in pediatric patients.

**Methods:** Patients who were admitted to the TTUHSC pediatric service at Northwest Texas Hospital in Amarillo, TX from January through December 2012 were considered for retrospective chart review. Patients were divided into 3 diagnosis groups: bronchiolitis, asthma exacerbation, and gastroenteritis. Other diagnoses and patients without serum chemistry were excluded. Age, sex, and serum sodium levels were documented. The number of days admitted were also recorded. Hyponatremia was defined as mild if the sodium was 130-135 mEq/L, moderate if 125-129 mEq/L, or severe if <125 mEq/L. Prevalence was calculated. Prevalence was determined to be statistically significant by comparing sodium levels between patients with hyponatremia and those with normal sodium levels. All patients were then grouped together, and length-of-stay (LOS) was compared between those with hyponatremia and those with normal sodium. The analysis for prevalence and LOS was performed using a two-tailed, unequal t-test with a p <0.05 used for significance.

**Results:** Overall, 416 patients were admitted to the inpatient service during the study period. After exclusion, 128 patients with bronchiolitis, 137 patients with asthma exacerbation, and 69 patients with gastroenteritis were available for analysis. There were 24 cases of hyponatremia in the bronchiolitis group (18.75% prevalence), 8 cases in the asthma exacerbation group (5.84% prevalence), and 18 cases in the gastroenteritis group (26.09% prevalence). There was one case of moderate hyponatremia in the bronchiolitis group, otherwise all other cases involved mild levels of hyponatremia. LOS was increased for patients with hyponatremia (2.33±0.11 days versus 4.26±0.71 days, p<0.01).

**Conclusions:** Hyponatremia was prevalent at an overall rate of 15% during the study period. Hyponatremia was associated with increased hospitalization at a statistically significant level.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
mortality adjusted for patients’ characteristics and co-morbid conditions. We used random effects meta-analysis to derive pooled estimates of effect in medical, surgical and mixed admission settings.

Results: We evaluated 135 full text publications from 1925 reviewed abstracts, of which 32 studies met the inclusion criteria (19, 13, and 5 reported aOR, proportion and both respectively). Patients with hypernatremia were at increased risk of hospital mortality (OR=2.59, 95% CI 1.5-4.47, P<0.001).

Conclusion: Chronic salicylate intoxication is most common in the elderly. Increased toxicity in older patient often appears due to inadvertent over dosage. Dual prescribing or additional use of non prescription OTC salicylates are some causes of unwitting long term toxicity. Chronic intoxication often poses a diagnostic dilemma with atypical presentation mimicking other disease states. The diagnosis of salicylate intoxication should be borne in mind when an older patient presents with recent deterioration in ADL with no known cause. Plasma salicylate concentration should be measured if salicylate intoxication is suspected, even if there is no documented history of salicylate ingestion. Chronic toxicity, which can occur even with marginally high salicylate concentrations is treated with drug withdrawal and supportive therapy. It can be averted by prescription of conservative doses, avoidance of concomitant use of different salicylate preparations, and therapeutic monitoring to guide dosing.

PUB464
Diagnostic Workup of Hyponatremia in Hospitalized Patients: Does Education Have an Impact? Faraj Karoli, Ladan Golestanian. Dept of Nephrology, Montefiore Medical Center, Bronx, NY.

Background: Hyponatremia is associated with poor outcomes. Studies show that hospitalized hyponatremic patients seldom get adequate diagnostic workups. This study tests the effects of a CME activity on physician’s behavior in the diagnostic workup of hyponatremia.

Methods: This is a cross sectional analysis of patients admitted to the Internal medicine department at Montefiore Medical center between 05/2014 and 12/2014. Demographic and clinical data were collected retrospectively. Patients were included if they were admitted under the service of 24 hospitalist attendings. These attendings were chosen based on their participation in a CME activity (lecture based). This activity was implemented to improve hyponatremia workup as defined by the frequency of the following orders: serum osmolality, urine osmolality, and urine sodium. Hyponatremia was defined as the earliest serum sodium less than 135 meq/dL. There was further subclassification into three groups based on the severity: mild-130-135 meq/dL, moderate: 125-130 meq/ dL and severe: less than 125 meq/dL. Frequency of the diagnostic orders was stratified to the mild or moderate (p<0.005).

Conclusions: Admission with serum Na of ‘145 meq/L is significantly associated with twice the odds of hospital mortality. Protocols towards increasing awareness of hypernatremia and studies evaluating the efficacy of early intervention are warranted.

PUB465
Characteristics and Initial Outcomes of a Multidisciplinary Renal Genetics Clinic (RGC) Andrew John Mallier, 1,2 Helen G. Healy, 1,2 Julie M. Mcguaghnam, 2, 3, 4 Melissa H. Little, 5,3 Chirag Patel, 3, 2, 4 Kidney Health Service & Conjoint Kidney Research Laboratory, Royal Brisbane & Women’s Hospital, Brisbane, QLD, Australia; 2School of Medicine, The University of Queensland, St Lucia, QLD, Australia; 3Children’s Medical Research Institute for Molecular Biosciences, UQ, Brisbane, QLD, Australia; 4Genetic Health Queensland, RBWH, Brisbane, QLD, Australia; 5Murdoch Children’s Research Inst, Melbourne, VIC, Australia.

Background: Genetic Renal Disease (GRD) accounts for 10% of adults and 50% of children with end stage kidney disease. Advances in molecular genetic diagnostic testing and multidisciplinary renal clinic models suggest opportunities for clinical redesign. Here we describe the initial characteristics, experience and outcomes of the first Australian multidisciplinary RGC.

Methods: A retrospective audit was undertaken of the RBWH Adult Conjoint RGC (1st year of operation; Aug’13-Jul’14). Each encounter involved a nephrologist, clinical geneticist and genetic counselor.

Results: 278 patients (56%) encountered had a known GRD, 9/48 (19%) had a suspected GRD and 12/48 (25%) had an unknown GRD with positive family history (FH). Patients were most commonly referred by nephrologists (66%). The most common GRD category & diagnosis were cystic kidney disease (49%) and Autosomal Dominant Tubular Dysgenesis (19%). Genetic and Kidney Disease related features were associated with GRD in 26/48 (54%). During consultations differential diagnoses were explored (54%), management strategies were discussed in 44% and 30% focused on patient’s education and psychological needs.

Conclusion: The Multidisciplinary RGC model demonstrated a range of benefits including immediate access to genetic testing. Future research will aim to evaluate the effect of CME activity on the treating physician behavior and patient outcomes.

Funding: Pharmaceutical Company Support - Rockpoint LLC.
advice provided (83%) and genetic counseling undertaken (79%). A genetic test was requested in 58.3%, most commonly being induced by combined diagnostic and genetic counseling reasons (78.6%). Of 12 returned genetic test results, 7 were positive and 1 was a variant of uncertain significance. Two negative results have prompted additional genetic testing. Of 27 patients referred with a known GRD, 6 now have a new suspected GRD. The majority of those referred with either a suspected (19) or unknown GRD diagnosis (10/12) now have a new suspected or confirmed GRD.

Conclusions: These findings demonstrate the early successful operation of this RGC model including diagnostic and genetic counseling benefit. Future assessment of clinical outcomes and expansion to telehealth and paediatric settings is anticipated.

PUB466

Characteristics and Clinicopathological Analysis of Japanese Nephronophthisis Patients Keisuke Sugimoto,1 Tomoki Miyazawa,1 Takaji Enya,1 Hitomi Nishi,1 Kohei Miyazaki,1 Hidehiko Yanagida,2 Mitsuru Okada,1 Tsukasa Takekuma,1 1Pediatrics, Kindai Univ Faculty of Medicine, Osaka, Japan; 2Pediatrics, Sakai Hospital, Kindai Univ Faculty of Medicine, Sakai, Osaka, Japan.

Background: Nephronophthisis (NPHP) accounts for 4 to 5% of end-stage renal disease (ESRD) occurring in childhood. Disease subtypes include infantile NPHP, which progresses to ESRD around the age of 5 years. Juvenile NPHP, which develops from early childhood to school age and usually progresses to ESRD by an age of about 13 or 14 years; and adolescent NPHP, with development of ESRD at an average age of 19 years. Juvenile NPHP is reported to be the most common subtype.

Methods: We investigated clinical, histologic, and genetic features in 35 Japanese patients clinically and histologically suspected to have NPHP, aiming to promote early diagnosis. We studied many exons as many as 13 NPHP genes. Since such genetic analysis involves significant cost and time, we also screened biopsy specimens by immunohistochemical methods employing antibodies against relevant peptides.

Results: NPHP occurred fairly uniformly throughout Japan irrespective of region or gender. In 3 families, NPHP affected siblings. The median age of patients was 12.5 years. Renal abnormalities attributable to NPHP discovered through mass screening, such as urine tests in school, however, NPHP accounted for less than 50% of children with abnormal findings, including incidentally discovered renal dysfunction during evaluation of extrarenal symptoms or during routine check-ups. Typical extrarenal manifestations led to discovery including anemia and delayed physical development. The urine often showed low gravity specific density and low-molecular-weight proteinuria. Frequent renal histologic findings included cystic dilation of tubules, mainly in the medulla, and irregularity of tubular basement membranes. Genetically abnormalities of NPHP1 were not common, with large deletions or frameshift mutations by sequencing all exons. 2. (1) ARHGAP32 gene was expressed mainly in kidney cortex and medulla, and amplified by PCR, obtaining the ARHGAP32 plasmids. (2) Transform the wild type and mutant plasmids of ARHGAP32 into Escherichia Coli respectively, and sequenced and screened for the mutation of ARHGAP32 plasmids. (3) Total exons sequencing were separated into 3 groups based on natraemic status.

Conclusions: Our findings resemble those reported in Western populations.

PUB467

The Functional Role of the ARHGAP32 L405V Mutation on Cytoskeleton Guispen Li, Li Wang. Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, China.

Background: A site-directed mutagenesis for ARHGAP32 was developed to whether the mutation of ARHGAP32 has the effect on the distribution of cytoskeletal protein of F-actin. It spreaded all the directions in wild type, while the distribution was scattered in mutant type. The distribution of F-actin was more significant in the wild type than that in mutant plasmid of ARHGAP32.

Methods: 1. (1) Blood DNA of 110 FSGS patients proved by renal biopsy were sequenced and screened for the mutation of ARHGAP32. 2. Total exons sequencing were performed in 28 DNA samples to find out whether mutation of ARHGAP32 occurred in these patients. 2. (1) site-directed mutagenesis primers of ARHGAP32 was designed and amplified by PCR, obtaining the ARHGAP32 plasmids. (2) Transform the wild type and mutant plasmids of ARHGAP32 into Escherichia Coli respectively, sequenced the plasmids to identify whether the site-directed mutagenesis of ARHGAP32 was successful constructed. (3) Transfected the mutated plasmid of ARHGAP32 into 293T cells and monitored by western blot and real time RT-PCR. 3. (1) Detected the expression of ARHGAP32 in FSGS, IgAN, MN, minimal change disease and diabetic disease by IHC. (2) Detected the expression of CDC42 and/β-catenin by realtime RT-PCR and western blot in 293T cells which were transfected with the wild type and mutated plasmids of ARHGAP32. (3) Observed the expression of F-actin by immunofluorescence in the wild plasmid of ARHGAP32 and mutant type in COS7 cells.

Results: 1. No mutation of ARHGAP32 was detected while 6 candidate genes were selected by sequencing all exons. 2. (1) ARHGAP32 gene was expressed mainly in glomerular in kidney tissue. The expression of ARHGAP32 was not detectable by IHC. (2) The expression of CDC42 and/β-catenin by realtime RT-PCR and western blot were no significant differences between the wild plasmid of ARHGAP32 and mutant type in 293T cells. (3) The distribution of F-actin was more significant in the wild type than that in mutant plasmid of ARHGAP32. It spreaded all the directions in wild type, while the distribution was scattered in mutant type.

Conclusions: No mutation was detected in sporadic FSGS currently. The mutation of ARHGAP32 had effect on the distribution of cytoskeletal protein of F-actin.
Conclusions: Total mitochondrial protein levels decrease in the cortex but not in the medulla of the rat kidney with age.

PUB470


Background: Prior research suggests that functional status in ESRD patients declines after initiation of dialysis, implicating the dialysis process in contributing to functional decline. We evaluated a dialysis-specific risk factor of intradialytic change in blood pressure (BP) in relation to changes in physical performance, a component of functional status.

Methods: We enrolled 29 dialysis patients age ≥50 years. Participants completed a 4-m timed walk to measure gait speed both pre and post dialysis and a Falls Efficacy Survey, a measure of concern for falls. Dialytic variables included BP measurements from pre, post and during dialysis along with ultrafiltration rate. Demographics and comorbid data was collected. Analysis evaluated for association between dialytic BP variables and change in gait speed and score on Falls Survey. Multivariate analysis was done to adjust for age, race, sex, diabetes and congestive heart failure.

Results: 28 participants completed the study. The mean age was 62.7 (12.3) years. The majority were male (70.4%) and hypertensive (86.2%). Diabetes was present in 55.2%. The mean (SD) change in gait speed from pre to post was -0.1 (0.1) m/s. The mean (SD) change in systolic and diastolic BP from pre to post dialysis was -10.6 (25.8) mmHg and -4.6 (10.5) mmHg, respectively. Participants with diabetes had greater intradialytic hemodynamic changes with mean (SD) change of SBP + DBP of 29.6(23.5) and 7.9(11.3) mmHg, respectively. Univariate analysis showed that every mmHg decrease in systolic BP and every 5 mmHg decrease in diastolic BP was associated with a change in gait speed of -0.01 m/s (p = 0.02) and -0.02 m/s (p = 0.01), respectively. This association was no longer significant in multivariate analysis, likely due to correlation of change in BP with diabetes status. There was no association between BP change and Falls Survey score.

Conclusions: Decline in physical performance, as measured by gait speed, can be seen post dialysis and is associated with hemodynamic changes during dialysis. Patients with diabetes may be most susceptible to hemodynamic changes. Improving dialytic hemodynamic stability may be a way to reduce the significant functional impairment that occurs post-dialysis.

Funding: Private Foundation Support

Conclusions: A positive correlation was shown between mesangial hypercellularity with serum uric acid levels in the first time. These results suggest that SIRT1 does not play a direct role in the pathogenesis of IgA nephropathy.

Funding: NIDDK Support

PUB472

Response of Human Primary Renal Proximal Tubular Epithelial Cells to Different LPS Strains. Hong Wang, Margaret M. O’Neill, Carine Boustaney, Steven S. Pullen. CardioMetabolic Diseases Research, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

Background: Toll-like receptors are expressed on leukocytes and renal tubular epithelial cells where they regulate immune responses. Recent evidence has implicated renal TLR4 signaling in the pro-inflammatory response in diabetic nephropathy. Ligands for TLR4 include lipopolysaccharide (LPS) and HMGB1. We sought to explore the response of renal proximal tubular epithelial cells (PTEC) to different strains of LPS and HMGB1 as well as modulation by TLR4 antagonists.

Methods: The HK-2 human proximal tubular cell line was stimulated with 3 strains of LPS (S. minnesota, E. coli K12, E. coli 0111:B4) and HMGB1. Primary human PTEC were stimulated with 5 strains of LPS (S. minnesota, E. coli 0111:B4, E. coli 055:B5, E. coli K12, S. typhosa)and HMGB1. Supernatants were harvested and IL-1β, IL-6, IL-8, TNFα, and MCP-1 were detected. TLR4 antagonists EX 7623 and EX 76824 were tested for the ability to modulate cytokine production induced by LPS stimulation.

Results: In HK-2 cells, LPS from E. coli 0111:B4 induced IL-6 and IL-8 production, whereas, S. minnesota and E. coli K12 did not stimulate cytokine production. In PTEC, IL-6 and IL-8 production increased upon S. typhosa, and S. minnesota stimulation. Other strains of LPS did not stimulate production of IL-6 and IL-8 in PTEC. There was little detectable production of IL-1β, TNFα or MCP-1 under the conditions tested in both HK-2 and PTEC. HMGB1 induced IL-8 production in PTEC whereas HK-2 cells did not produce any of the cytokines or chemokines tested upon HMGB1 stimulation. The TLR4 antagonists EX 7624 and EX 76824 blocked cytokine production stimulated by S. typhosa in PTEC. EX 76824 inhibited IL-6 and IL-8 production stimulated by E. coli 0111:B4 in HK-2 cells.

Conclusions: Primary PTEC have unique responses to different strains of LPS, and this response profile differs from that of the HK-2 cell line. HMGB1 induced IL-8 production in PTEC whereas HK-2 cells did not respond to HMGB1 stimulation. These results highlight a limitation of using the HK-2 cell line in lieu of primary PTEC for interrogating the role of TLR4 in renal inflammation.

PUB473

Assessment of Serum Transforming Growth Factor-Beta 1 in Patients with Diabetic Nephropathy. Om Prakash Kalra,1 Avanish Shukla,1 Ashok Kumar Tripathi,1 Alpana Raizada.1 1Medicine, UCS & GTB Hospital, Delhi, India; 2Biochemistry, UCS & GTB Hospital, Delhi, India.

Background: Diabetes mellitus is the leading cause of chronic kidney disease (CKD) worldwide. The pathogenesis and initial molecular events leading to diabetic nephropathy are still elusive. Chronic low grade inflammation plays an important role in pathogenesis of diabetic nephropathy. Urokinases like transforming growth factor-beta (TGF-β) that play an important role in pathogenesis of diabetic nephropathy by influencing ECM accumulation and cellular hypertrophy in several cell types. TGF-β may play an important role in the pathogenesis of diabetic nephropathy by influencing ECM accumulation.

Methods: This was a case control, cross sectional study. 75 subjects aged 30–65 years of either sex were recruited and divided into three groups: Group I: healthy controls (n=25), Group II: patients of T2DM without nephropathy (n=25), Group III: patients of T2DM with nephropathy (n=25). Detailed history, complete physical examination, routine investigations, urine albumin creatinine ratio (ACR) estimation was done. Serum levels of hs-CRP and TGF-β1 were estimated by ELISA.

Results: A statistically significant difference in serum TGF-β1 and hs-CRP levels was observed between all the 3 groups (p<0.001), where highest levels were found in group III and lowest in group I. A positive correlation was observed between serum TGF-β1 and duration of diabetes, FBS, PPBS, HbA1c levels, serum creatinine, urinary ACR and serum hs-CRP. Similarly serum hs-CRP levels positively correlated with the duration of diabetes, FBS, PPBS, HbA1c levels, serum creatinine, urinary ACR. Serum TGF-β1 and serum hs-CRP showed negative correlation with eGFR.

Conclusions: Overall, TGF-β1 and hs-CRP levels were significantly higher in diabetics as compared to non-diabetic subjects. They were higher in diabetic subjects with nephropathy as compared to those without nephropathy. Serum TGF-β1 and hs-CRP levels in diabetic subjects appear to be dependent on duration of diabetes, glycemic control and degree of renal dysfunction. Thus cytokines like TGF-β may play a role in the etiopathogenesis of diabetic nephropathy.

Table 1. Baseline demographic and laboratory data of the patients (n=28)

| Age | Gender (female/male) | BMI (kg/m2) | Creatinine (mg/dl) | Albunin (g/dl) | Uric acid (mg/dl) | Proteinuria (g/day) | GFR (CKD-EPI) (ml/min) | Hypertension (%) | Macroscopic hematuria (%) | Microscopic hematuria (%) | Previous immunosuppressive therapy (%) | Follow-up time (years) |
|-----|---------------------|-------------|------------------|---------------|----------------|------------------|---------------------|---------------------|------------------|------------------------|------------------------|-------------------------------|---------------------|
| 37±14 | 16/12 | 23.6±2.6 | 1.6±1.5 | 4.0±0.6 | 6.0±2.2 | 2.4±1.9 | 74.6±41.2 | 13(46.6) | 11(39.3) | 23(82.1) | 3.0(10.7) | 4.8±2.7 |

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Daptomycin Antibiotic Lock Therapy for Hemodialysis Patients with Gram-Positive bloodstream infections following use of tunneled, cuffed hemodialysis catheters. retrospective single center analysis huong-wen yen, szu-yuan li. dept. of medicine, div. of nephrology, dept. of medicine, taipei veterans general hospital, taipei, taiwan.

Background: catheter-related blood stream infection (CRBSI) is a major complication in hemodialysis patients. We assessed the efficacy of systemic daptomycin (DPT) plus dPT antibiotic lock therapy (DPT-ALT) for catheter-salvage in patients with gram-positive CRBSI.

Methods: Study Design: retrospective study of hemodialysis patients with cuffed, tunneled, cuffed hemodialysis catheters. Setting & Participants: all patients were from a single institution in taipei and received systemic DPT plus DPT-ALT for treatment of gram-positive CRBSI. Outcome: Successful resolution of CRBSI. Measurements: Resolution of fever within 48 h, negative result of repeated blood cultures after resolution of fever, no clinical evidence of CRBSI relapse, and no need for catheter removal.

Results: Fifteen hemodialysis patients received DPT-ALT for CRBSI, 9 with coagulase-negative Staphylococcus (CONS), 2 with methicillin-resistant Staphylococcus aureus (MRSA), 3 with methicillin-sensitive Staphylococcus aureus (MSSA), and 1 with polymicrobial infections. Systemic DPT plus DPT-ALT cured 11 patients (73.3%). Treatment failed in all 3 MRSA cases (2 with MRSA and 1 with MRSA + Enterococcus faecalis).

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

Underline represents presenting author.

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Analysis of Risk Factors of Death in Patients of Maintenance Hemodialysis with Tunneled Cuffed Venous Catheter

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Background: To analyze the causes of death in patients of maintenance hemodialysis with tunneled cuffed catheter, and explore the risk factors of death.

Methods: All patients of maintenance hemodialysis with tunneled cuffed venous catheter starting hemodialysis from January 1, 2009 to December 31, 2014 in West China hospital were included and observed till June 1, 2015. The patients were divided into observation (death) and control group (survival). Multivariate logistic regression analysis was used for the analysis.

Results: In total 94 hemodialysis patients who met the inclusion criteria, 24 cases died in the study period. The median age of dead patients was 73.4 years (51.5–96.4). The median time of hemodialysis was 19.20 months (3.17–56.27). Just 1 case replaced tunneled cuffed catheter for once. The main primary causes of renal disease were: diabetic kidney disease (DKD) 43.5%, chronic glomerulonephritis (CGN) 25.0%, hypertensive renal damage (HTN) 12.5%. The main causes of death were as following: infection 29.2%, cardiovascular diseases (CVD) 25.0%, cerebrovascular diseases 12.5%. The median age of survival patients was 64.9 years (20.8–95.4). Nineteen cases replaced tunneled cuffed catheter for twenty three times in total. The main primary causes of renal disease were: CGN 54.3%, DKD 25.7%, HTN 4.3%, polycystic kidney disease 4.3%. Multivariate logistic regression analysis showed that elder age, infection, low serum albumin were risk factors of death. Replacement of tunneled cuffed catheter was not the risk factors for death.

Conclusions: The main causes of death of patients with maintenance hemodialysis by tunneled cuffed venous catheter were cardiovascular and cerebrovascular diseases and infection. Elder age, infection, low level of serum albumin were risk factors of death in patients of maintenance hemodialysis with tunneled cuffed venous catheter. Replacement of tunneled cuffed catheter was not the risk factors for death. Funds: The National Key Technology R&D Program of China (No. 2011BAI10B08), Cost and Evaluation System Study on payment revision for patient in chronic hemodialysis with insurance of Chengdu City (Chengdu Municipal Medical Insurance Bureau).

Funding: Government Support - Non-U.S.

Analysis of Vascular Access of Maintenance Hemodialysis Patients: A Single Center Retrospective Study

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Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.

Background: Vascular access is life line for maintenance hemodialysis patients. The main options for vascular access for hemodialysis patients are arteriovenous fistulas (AVFs), arteriovenous grafts/AVGs, and tunneled cuffed central venous catheters. Proper vascular access is associated with lower complications and costs, which could improve the survival rate. The aim of our study is to analysis the characteristics of vascular accesses of maintenance hemodialysis patients in our hemodialysis center.

Methods: Patients underwent maintenance hemodialysis in the blood purification center of our hospital from January 2010 to December 2014 were enrolled in this study. The demographic characteristics, duration of dialysis, types of vascular access and blood flow volume, as well as the potency rate of AVFs of these patients were collected and analyzed. The definition of vascular access was the vascular access that we used. The mean age was 57.89±14.27 years old. More than 60% patients’ initial vascular access was non-tunneled central venous catheters, only 20% applied AVFs as their initial vascular access. Vascular access types as follows, 87.0% for AVFs, 3.5% for AVGs and 9.5% for tunneled cuffed central venous catheters. The cumulative success rate of AVFs was 99.9% ±1.1%. The duration of primary patency was 29.00 (12.00, 68.00) months and the duration of the cumulative potency rate was 37.00 (12.75, 95.25) months. Fourteen patients applied AVG as their vascular access, of whom thrombomeloblastin was the main complication. AVG thrombosis of three patients were treated using percutaneous interventions. Among the 294 patients applying non-tunneled central venous catheters, 5.4% have their catheters changed for more than 2 times and 66.7% have their catheters on the right internal jugular vein.

Conclusions: AVF is the leading type of vascular access in our dialysis center. The usage rate of tunneled cuffed central access is under 10%, while the usage rate of AVG is about 2 times and 66.7% have their catheters on the right internal jugular vein.

Exchange Technique Using Over the Guidewire from Tunneled to Tunneled Hemodialysis Catheter Can Be Performed without Increasing Infection and Hemostasis after Removal and the Temporary Insertion of Femoral HD Catheter.

The exchange technique of HD catheter starting hemodialysis from January 1, 2009 to December 31, 2014 was respectively assigned to exchange and de novo placement groups and these 2 groups were compared.

Results: Compared with the de novo placement group, the exchange group over the guidewire has higher median age (64.6 vs. 61.7; p = 0.01), more females (69.6% vs. 48.1%; p = 0.006), more ESRD rather than AKI as a cause of catheter insertion (95.7% vs. 74.8%; p = 0.002). Both immediate complication rate including suturing at exit site for bleeding control was higher in the exchange group (19.6% vs. 8.7%; p = 0.02) and late one including infection with the increased risk of infection and bleeding after procedure prevent its application. However, the catheter survival rates between two groups were comparable (p = 0.58) and multivariate Cox regression analysis for catheter survival showed the development of late complication was the only risk factor (odds ratio [OR] 1.391, 95% confidence interval [CI]: 1.017–1.901; p = 0.039) rather than the exchange procedure was not a risk factor (OR 0.878, 95% CI: 0.554–1.393; p = 0.582).

Conclusions: The exchange over the guidewire from a previous tunneled catheter to a new one should be positively considered and performed when the new tunneled catheter placement is required.

Background: A Multidisciplinary Unit for attention to the vascular access was established in our hospital in December 2010. The main role of the nephrologist consists in monitoring the functioning of the vascular access by determining the arterio-venous flow (AVF) and undertaking the doppler ultrasound. The objectives for initiating this program were to reduce the thrombosis rate by diagnosis and treatment of a non clinically detected pathology and to decrease the percentage of patients with a tunneled catheter.

Methods: The prevalence of haemodialysis patients on 31st December 2014 was 65 patients in the Hospital Unit and 90 patients in the Dialysis Center. In the Hospital Unit we supervise the functioning of the vascular access by measuring the AVF flow and we perform a Doppler ultrasound study if the flow is less than 500 ml/min, if there are significant decreases in comparison with previous controls or if there is any clinical dysfunction. The Dialysis Center uses first generation methods for monitoring (increase in venous pressure, pump flow decrease, recirculation) and requests the Hospital Unit to undertake a Doppler ultrasound study whenever there is any type of dysfunction.

Results: We have observed differences in the results between both centers: 1° Incidence of patients with a tunneled catheter was lower in the Hospital Unit (14 vs 22%). 2° Thrombosis rate was 40% lower in the Hospital Unit (7.9 vs 12/100 patients-year). 3° Doppler ultrasound detected 25 patients with haemodynamically significant stenosis, confirmed by radiologic study, which were successfully treated.

Conclusions: The combined use of AVF flow measuring and doppler ultrasound studies for monitoring the vascular access is an efficient method for reducing the rates of thrombosis and the number of tunneled catheters due to the early detection of stenosis and its preventive treatment.

Females Have Less Arteriovenous Fistula and More Grafts Compared to Men: Data from the Slovenian Renal Replacement Therapy Registry

PUB484

Background: The aim of our study was to compare prevalence of arteriovenous fistula (AVF) and graft use in female and male chronic hemodialysis (HD) patients.

Methods: Data on vascular access prevalent HD patients on December 31, from 2009-2013, were analyzed, in addition to sex, age, dry body weight and blood flow (QB) during HD, from database of the Slovenian Renal Replacement Therapy Registry. The use of preoperative ultrasound mapping before AVF and graft construction in standard practice in the country.

Results:

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2012</th>
<th>2011</th>
<th>2010</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HD (No)</td>
<td>1375</td>
<td>1361</td>
<td>1346</td>
<td>1375</td>
<td>1397</td>
</tr>
<tr>
<td>Males No</td>
<td>831</td>
<td>837</td>
<td>824</td>
<td>818</td>
<td>827</td>
</tr>
<tr>
<td>Males age (years)</td>
<td>64±14</td>
<td>64±14</td>
<td>63±14</td>
<td>63±14</td>
<td>63±14</td>
</tr>
<tr>
<td>Males % AVF</td>
<td>82.8</td>
<td>81.8</td>
<td>83.5</td>
<td>85.0</td>
<td>84.6</td>
</tr>
<tr>
<td>Males % grafts</td>
<td>7.0</td>
<td>7.1</td>
<td>5.0</td>
<td>5.5</td>
<td>4.5</td>
</tr>
<tr>
<td>QB (ml/min)</td>
<td>287±35</td>
<td>287±39</td>
<td>290±39</td>
<td>290±44</td>
<td>295±44</td>
</tr>
<tr>
<td>Females No</td>
<td>544</td>
<td>524</td>
<td>522</td>
<td>557</td>
<td>570</td>
</tr>
<tr>
<td>Females age (years)</td>
<td>67±16</td>
<td>67±15</td>
<td>67±15</td>
<td>66±15</td>
<td>65±15</td>
</tr>
<tr>
<td>Females % AVF</td>
<td>72.1</td>
<td>72.3</td>
<td>72.4</td>
<td>76.5</td>
<td>75.1</td>
</tr>
<tr>
<td>Females % grafts</td>
<td>9.2</td>
<td>7.9</td>
<td>7.5</td>
<td>7.5</td>
<td>7.7</td>
</tr>
<tr>
<td>QB (ml/min)</td>
<td>273±35</td>
<td>274±38</td>
<td>275±38</td>
<td>271±40</td>
<td>277±41</td>
</tr>
</tbody>
</table>

The difference between percentage of AVF comparing females and males is persistent and highly significant during the observation period (p<0.001), with females having less AVF. Females had persistently slightly more grafts. Males had higher mean dry body weight (77.1±11.6 kg vs. 64.7±14.7 kg, end of 2013, p=0.001). Although absolute blood flow during HD was higher in males, females had higher blood flow when standardised to body weight (4.41±1.03 vs. 3.83±0.83 ml/min/kg, p=0.001, end of 2013).

Conclusions: Females chronically have significantly less arteriovenous fistula and slightly more grafts compared to males, with the difference being persistent during five years. Blood flow during HD, when standardised to body weight, was significantly higher in females than in males. Potential clinical consequence of higher blood flow during HD in females may be the lack of usefulness which we are increasingly seeing in the nullification of dual access for an additional 2.5, 11.7, and 46 days, respectively (p<0.01). This discrepancy between regular surveillance and delayed TDC removal raises concerns that there is a lack of timely intervention after assessment. A more thorough documentation of reasons for prolonged TDC use and analysis of such data are required to verify this hypothesis and get a better idea of etiology of delayed TDC removal.

Methods: Retrospective collection of data from outpatient dialysis units on patients who have AVF/Graft and TDC.

Results: The delayed TDC removal in patients with AVF/Graft the risk of infection in these patients with both devices.

Conclusions: TDC should be removed at a appropriate period once AVF/Graft are mature enough to be used.

Gene Methylation Profile of Human Vein Tissues Taken at the Time of Surgery: Correlation with AVF Maturation

PUB486

Background: Early arteriovenous fistula (AVF) failure remains an important cause of hemodialysis vascular access dysfunction and a major impediment to the Fistula First initiative. Despite the magnitude of the clinical problem, there are currently no effective therapeutic interventions for early AVF failure. In order to better understand the cellular and molecular mechanisms involved in early AVF failure we have evaluated the gene methylation profile of venous segment tissue samples obtained at the time of AVF creation.

Methods: DNA methylation of Cpg islands (regions of the genome that are rich in cytosine and guanine sequences), influences gene expression (turns off the gene). An increasing number of diverse factors are now known to epigenetically regulate genes, including stress, inflammation, nutrition, metabolism, drugs and infection (all of which are prominent in the biological milieu of patients with CKD and ESRD). In this study we compare the overall methylation profiles of non-maturing AVFs at 6 months as compared to AVFs that are able to support dialysis.

Results: gDNA was isolated from venous segments collected at the time of AVF creation. DNA sequencing technologies were used to identify genes with the greatest differences in methylation between the two groups. Gene networks focused on inflammation, oxidative stress and endothelial dysfunction were evaluated. Standard bioinformatic techniques were used to identify/interrogate both the gene list and the network analyses.

Results: We were able to identify approximately 300 genes that were significantly different in the overall methylation profiles of non-maturing AVFs at 6 months as compared to AVFs that were able to support dialysis.

Conclusions: Our results suggest that epigenetic regulation (DNA methylation) could play an important role in AVF maturation, and also in the identification of novel druggable targets. This latter point could result in the development of novel therapies for dialysis vascular access dysfunction as a whole.

Development of a Uremic Pig Model of Arteriovenous Fistula Stenosis (AVF): A Surgical Approach

PUB487

Background: AVF stenosis remains an important cause of hemodialysis vascular access dysfunction for which there are no truly effective therapies. We and others have previously described well characterized large animal models of AVF stenosis. An important flaw in these models is the lack of uremia, which has increasingly been shown to play an important role in the pathogenesis of AVF stenosis.

Methods: Chronic renal insufficiency was created by initially removing one of the kidneys through a midline incision. Following this the contralateral kidney underwent a dissection of the renal pelvis in order to expose the primary, secondary and if possible tertiary branches of the renal vasculature. A selective ligation of the renal vasculature in the pelvis, and
which allowed for the viability of less than 20% of the renal mass on one side was then performed (upper figure = a, b and c). Of note the differential blanching/mottling of the kidney following ligature of vessels in the renal pelvis, allows us to perform a real time assessment in terms of the amount of viable renal tissue. BUN and creatinine estimations were then made biweekly for 6 weeks.

Results: The described surgical technique has allowed us to achieve a stable creatinine of 4 mg/dL over a four week period (lower figure = d). This stable period of uremia will allow us test out the impact of “downstream uremic vascular biology” on AVF maturation.

Conclusions: We developed a unique, innovative and surgically created pig model of uremia with potential logistic and financial benefits. The availability of this animal model will put us in a unique position to be able to tease out the relative contributions of hemodynamics and uremia to AVF stenosis both in our experimental pig model and also in CKD and ESRD patients.

PUB490
Cardiac Implantable Electronic Device Infection and Ipsilateral Arteriovenous Fistula in End Stage Renal Disease: Avoidance and Management of Complications
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Background: Cardiac implantable electronic devices (CIEDs) are frequently utilized for management of cardiac dysrhythmias in patients(pts) with End Stage Renal disease (ESRD) and are associated with central venous stenosis resulting in adverse effects for existing or future arteriovenous fistula (AVF) with an increase risk of infection of both (CIEDs and AVF). We report the case of a pt with ESRD who experienced a potentially life-threatening complication related to his ipsilateral AVF and CIEDs.

Methods: We report the case of a 80 years-old male pt who developed a symptomatic unilateral left arm edema with skin lesions.He has past history of CIEDs four years ago and the ipsilateral implementation of an AVF 2 years after the CIEDs.He experienced 3 angioplasties on his AVF and a repeated surgery with a persistant post-anastomotic anastomosis with flow reduction of 180 ml/min.A left side chest blood collateral circulation was also present.A deep venous thrombosis related to the implementation of CIEDs was investigated and a left subclavian venous thrombosis was confirmed.On the meantime infection of the CIEDs was suspected but not confirmed. An attempt of a venous recanalization was unsuccessful.A closure of AVF with a plug of 14mm diameter leading to a complete occlusion of AVF.

Results: After the occlusion of AVF we noticed a complete regression of the huge left arm edema and skin lesion of the pt. The pt underwent antibiotics therapy for life for the CIED infections with successful results two years after initiation of treatment.

Conclusions: Although the CIEDs can provide life-savings benefits, device associated complications needs careful management and should be placed by the epidural approach as a first option for pts with ESRD.It remind us that the AVF is still the Achilles’ heel of dialysis.

PUB489
WeeklyBeta2 Microglobulin (B2M) Kt/V, Residual Renal Function and Middle Molecule Levels in Daily Dialysis
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Background: B2M and residual renal function (RRF) are predictors of cardiovascular morbidity, mortality and LVIH in ESRD. Daily dialysis leads to higher B2M removal and has been associated with improvements in LVIH and mortality in randomized trials. It is not known whether kinetic measures of middle molecule adequacy are applicable to daily dialysis.

Methods: We adopted a population kinetic model (PKM) for the intradividual variability in generation, distribution and extraremal removal of B2M (ASN 2014,SA-P0969). We used the PKM to simulate B2M concentrations in 10000 patients dialyzed with HF membranes. We examined the intervention protocols for Short (SD), Long Daily (LD) and three weekly HD dialysis utilized in the FHN trials. Weekly B2M Kt/V was calculated as the sum of the Kt/V in each session. The impact of Kt/V relative to residual renal function (RRF) on B2M was examined across the three dialysis modalities averaging over the intra-individual variability of kinetic parameters and dialysis prescription.

Results: B2M was lower in SD and LD relative to HF irrespective of RRF. Given the variability in dialysis prescriptions there was a substantial overlap in the average Kt/V values between HF and SD.
There was a steep relationship between weekly Kt/V and B2M in all three modalities. The steepness of this relationship was similar between HD and SD across RRF values, but differed for RRF > 4 ml/min in HD. At any given level of Kt/V the B2M level depended on RRF and dialysis modality.

**Conclusions:** Weekly B2M Kt/V, a simple measure of middle molecule dialysis adequacy, tracks middle molecule exposure in conventional and daily dialysis. The interpretation of a given Kt/V value requires knowledge of RRF in all dialysis modalities. Future studies should determine whether RRF, diastolic Kt/V or both are predictors of survival in daily dialysis.

**PUB492**

A Test Battery to Establish Changes in Physical Performance and Protein Energy Wasting in Nocturnal Hemodialysis: The DiapriFIT Study

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2Nephrology, VU Univ Medical Center, Amsterdam, Netherlands;

*Background:* Nocturnal hemodialysis (NHD) improves volume control and phosphate and middle molecule removal. Observational data show increases in body weight and protein intake upon switching to NHD. Other aspects of protein energy wasting (PEW) remain underexposed and also little is known about functional outcomes, such as physical performance and muscle strength. Therefore, the aim of this study is to investigate whether physical performance improves and PEW decreases in patients who change from conventional hemodialysis (CHD) to NHD, compared to patients who continue their treatment on CHD.

**Methods:** The DiapriFIT study plans to include 25 patients on CHD (2-4x wk, 3-4 hours) and 25 patients on CHD who switch to NHD (3-4x wk, 8 hours) with 1-year physical performance and PEW as endpoints. They were submitted to a Visual Appetite Score (VAS), Handgrip Strength (HGS), upper arm circumference (UAC), Short Physical Performance Battery (SPPB) and 6 minute walk test (6MWT), baseline results are reported here. As in NHD weight increases, we tested associations of the outcome parameters with dry weight.

**Results:** At present, 23 patients were included, aged 58.3±16.0 years, 30.4% males, with a dry weight of 87.6±17.2 in males and 74.3±17.2 in females. Mean VAS was 7.3±2.3, HGS 22.7±5.6 cm, UAC 31.9±5.6 cm, SPPB 8.0±1.9 and 6MWT 576±328 meters. Only HGS and UAC were correlated with HD dry weight (r 0.43, p<0.05 for HGS, r 0.79, HGS 22.7 NHD weight increases, we tested associations of the outcome parameters with dry weight.

**Conclusion:** Nocturnal hemodialysis improves volume control and phosphate and middle molecule removal. Observational data show increases in body weight and protein intake upon switching to NHD. Other aspects of protein energy wasting (PEW) remain underexposed and also little is known about functional outcomes, such as physical performance and muscle strength. Therefore, the aim of this study is to investigate whether physical performance improves and PEW decreases in patients who change from conventional hemodialysis (CHD) to NHD, compared to patients who continue their treatment on CHD.

**PUB494**

Do KCNQ1 Channels Contribute to Control of Arterial Vascular Tone?

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1Experimental and Clinical Research Center (ECRC), a Joint Cooperation between the Charité Medical Faculty and the Max Delbrück Center for Molecular Medicine (MDC), Berlin, Germany; 2Xiamen Zhongshan Hospital, Xiamen Univ, Xiamen, Fujian Province, China; 3Dept of Physiology, Univ of Tübingen, Tübingen, Germany; 4School of Biomedical Sciences, Lo Kwee-Seong Integrated Biomedical Sciences Building, Area 39, Chinese Univ of Hong Kong, Hong Kong, Hong Kong.

**Background:** Recent data suggest that the KCNQ family of voltage activated K- (K7) channels represents a new therapeutic target in cardiovascular disease. We used KCNQ1-/- mice to determine whether KCNQ1 (K7.1) play a role in the regulation of arterial tone.

**Methods:** Wire-myography, pharmacology approach and patch-clamp techniques were used.

**Results:** We found that R-L3 produces similar concentration-dependent relaxations (EC50=1–1.4 µM in wild-type (KCNQ1+/+) and KCNQ1-/- arteries pre-contracted with either phentolamine or 60 nM KCl. This relaxation was not affected by 10 µM chroomanol-B293, 10 µM HMR1556, 30 µM XE991 or 500 µM 4-aminoypyridine. Chromanol-B293 and HMR1556 did not affect the anti-contractile effects of perivascular adipose tissue (PVAT). The anti-contractile effects of PVAT were normal in KCNQ1-/- arteries. Whole-cell recordings showed normal peak K currents, capacity and their blockade by XE991 in KCNQ1-/- VSMCs. The pan KCNQ2-5 opener sperubigatine lead to a similar relaxations in KCNQ1-/- and wild-type vessels.

**Conclusion:** We conclude that KCNQ1 channels are apparently not involved in the control of arterial tone by alpha, adrenergic vasoconstrictors and PVAT. R-L3 is an appropriate pharmacological tool for studying the function of native vascular KCNQ1 channels in mice.

**PUB495**

The Role of Renal AT1 Receptor-Associated Protein in Salt-Sensitive Blood Pressure Regulation

Hirochika Waku,1 Kouichi Tamura,1 Ryu Kobayashi,1 Kazuushi Uneda,1 Masato Ohawa,1 Toru Dejima,1 Akinobu Maeda,1 Yoshiyuki Toya,1 Kotaro Haruhara,2 Satoshi Umemura,1

1The Dept of Medical Science and Cardiovascular Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan; 2Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

**Background:** The intrarenal renin-angiotensin system plays a role in the regulation of renal hemodynamics and the maintenance of water electrolyte balance, and is also involved in the pathophysiology of hypertension and target organ damages. We previously identified an angiotensin II type 1 receptor-associated protein (ATRAP), which interacts with the C-terminal domain of angiotensin II type 1 receptor (AT1R) and attenuates AT1R-mediated pathological responses. The present study was designed to investigate the putative functional role of ATRAP in the blood pressure regulation by high salt loading in vivo.

**Methods:** We generated transgenic mice expressing ATRAP dominantly on renal tubules on a C57BL/6J background. Renal ATRAP transgenic mice and their wild-type littermate mice on a normal salt diet at baseline were subjected to dietary high salt loading for 7 days. **Results:** In renal ATRAP transgenic mice, the development of high blood pressure in response to high salt loading was suppressed, concomitant with a significant increase in urinary sodium excretion, as compared to wild-type mice.

**Conclusions:** These results demonstrate that renal tubule dominant overexpression of ATRAP suppresses the salt-sensitive blood pressure elevation provoked by high salt loading, thereby suggesting ATRAP to be an interesting target in hypertension.

**Funding:** Private Foundation Support, Government Support - Non-U.S.
PUB496
Carboneic Anhydrase II Inactivation Confers Salt Appetite and Elicits Salt Sensitive Hypertension

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Background: Salt appetite or salt intake in excess of physiological needs is a major health problem and a risk factor in the pathogenesis of hypertension, which consequently can lead to heart disease and stroke. Few genetic factors are implicated in the pathogenesis of salt appetite.

Methods: Wild-type and CAII null mice were given a choice of regular water or 140mM NaCl dissolved in their drinking water. Balance studies were performed and blood pressure was measured via the CODA tail cuff system. Western blots and Northern Hybridizations were performed.

Results: Our results indicate that CAII null mice display significant salt appetite as judged by their preference for salted water (140mM NaCl) over regular water, when both options are provided. In age and gender matched mice (n=4 per each group, daily salted intake was 2.89 ml in WT vs. 7.51 ml in CAII null mice, while daily regular water intake was 5.05 ml in WT and 3.6 ml in CAII null mice. Kidney renin expression and blood creatinine concentration were comparable in WT and CAII null mice. When given only salted water, CAII null animals showed a robust increase in their daily salt intake (12.21ml in CAII null vs. 7.80ml in WT mice) and urine volume (4.6/2ml/day in CAII null vs. 2.62ml/day in WT mice). Expression of sodium and water absorbing channels, ENaC and AQ2-2, increased by 100 to 200% in both cortex and medulla in CAII null vs. WT mice in response to salt intake for 10 days. Consequently, CAII null mice developed hypertension (systolic BP of 155 +/- 3.9 in CAII null vs. 138 +/- 3.2 in WT, p<0.003).

The protein expression levels of ENaC in taste buds were not different between the two WT mice in response to salt intake for 10 days. Consequently, CAII null mice developed only salted water, CAII null animals showed a robust increase in their daily salt intake was 5.05 ml in WT and 3.6 ml in CAII null mice. Kidney renin expression and blood creatinine concentration were comparable in WT and CAII null mice. When given only salted water, CAII null animals showed a robust increase in their daily salt intake (12.21ml in CAII null vs. 7.80ml in WT mice) and urine volume (4.6/2ml/day in CAII null vs. 2.62ml/day in WT mice). Expression of sodium and water absorbing channels, ENaC and AQ2-2, increased by 100 to 200% in both cortex and medulla in CAII null vs. WT mice in response to salt intake for 10 days. Consequently, CAII null mice developed hypertension (systolic BP of 155 +/- 3.9 in CAII null vs. 138 +/- 3.2 in WT, p<0.003).

Conclusions: We propose that CAII plays an important role in regulating salt intake and its inactivation can cause salt appetite, specifically in male animals, and provoke salt sensitive hypertension.

Funding: Veterans Administration Support

PUB497
Ambulatory Blood Pressure in Chronic Kidney Disease: An International Collaborative Study

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Background: In chronic kidney disease (CKD), ambulatory blood pressure (BP) is a better measure of hypertension related risk for cardiovascular disease and ESRD than clinic BP. The International Ambulatory Blood Pressure in Chronic Kidney Disease Collaborative Group is a collaboration among investigators from different countries interested in ambulatory BP in patients with CKD. The main aims of the research facilitated by this collaboration will be to evaluate: 1) the clinical and demographic characteristics associated with elevated ambulatory BP, 2) the prognostic role of ambulatory BP on cardiovascular and renal outcomes, and 3) ethnic and geographic differences in these associations.

Methods: This group will establish a large database derived from individual databases in the various countries to allow for powerful individual participant data meta-analyses of the relationship between clinical and demographic characteristics, CKD severity, ambulatory BP, and clinical outcomes.

Results: Investigators from 5 cohort studies have already agreed to participate.

Conclusions: This multi-national collaboration will provide greater insights than possible from within-country analyses into the etiology and consequences of high risk ambulatory BP profiles. This information will be instrumental in helping us design prospective international large scale multicenter trials aimed at reducing renal and cardiovascular events in patients with CKD.

PUB498
Clinical Study of Pregnancy Related Kidney Injury Yumei Liu,1 Ying Fan,2 Yang Fei,1 Hongda Bao,3 Yajuan Huang,3 Niansong Wang.1 1Nephrology and Rhenumatology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; 2Obstetrics and Gynecology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.

Background: The diagnosis and treatment of pregnancy related kidney injury is a complicated clinical problem for obstetricians and nephrologists. However, information regarding this topic in China is insufficient.

Methods: Totally 18589 women hospitalized between August 2004 and January 2013 from Obstetric and Nephrology Department in Shanghai Jiao Tong University Affiliated Sixth People's Hospital were screened. 569 women were enrolled for the pregnancy related kidney injury, including 494 cases from 2008 to 2013 and 75 cases from 2004 to 2007. The inclusive criteria was women with a history of kidney disease or Scr >= 70mmol/L or proteinuria >= 0.3g/24hour before the termination of pregnancy, or the diagnosis of kidney disease made during or after 6-month delivery.

Results: The prevalence of pregnancy related kidney injury was 3.1%. The incidence of kidney injury caused by obstetric disease was 3.1%, with the most common reason for pre-eclampsia (88.9%). The incidence of chronic kidney disease women with pregnancy is 0.74%, with the most common reason for chronic glomerular nephritis (36.2%). The incidence of kidney disease onset related to pregnancy was 1.5%. The incidence of proceeding to end stage renal disease for pregnancy was 0.21%. Kidney injury in pregnant women with obstetric disease may be more severe than that in pregnant women with kidney disease (with higher maternal blood pressure and proteinuria, lower birth weight and higher proportion of pre-term babies, P<0.05). Most women with pregnancy related kidney injury underwent cesarean section (<60%). Their proportion of stillbirth, pre-term and low birth weight babies were higher than healthy parturient, and the proportion of follow-up was low (9.9%). Neonatal death rate was 0.63% and pare-natal death rate was 2.1% in all.

Conclusions: Prevalence of pregnancy related kidney injury increases due to the foundation of Shanghai First-Aid Center for High-risk Pregnant Women in 2007. Serum creatinine, proteinuria and blood pressure have different indication for maternal condition and pregnancy outcome.

Funding: Government Support - Non-U.S.

PUB499
A New Vasculo-Renal Marker Enhances Accuracy of Hypertensive Nephropathy Recognition Arkadiusz Lubasz,1 Robert Ryzez,2 Grzegorz Kade,3 Stanislaw Niemczyk,1 1Dept of Internal Diseases, Nephrology and Dialysis, Military Inst of Medicine, Warsaw, Poland; 2Dept of Cardiology, Military Inst of Medicine, Warsaw, Poland.

Background: Latent and slow beginning of chronic kidney disease (CKD) coexisting with well tolerated, usually not recognized previously hypertension makes difficult to recognize hypertensive nephropathy (HN) from CKD of other origins. The aim of the study was to investigate the best marker helpful in differentiating HN from other causes of CKD.

Methods: Forty patients (4; 36 M; age 52.7 ±14.5) with stable CKD (CKD-EPI 53.1 ±27.6 ml/min/1.73m2 and a history of hypertension (26 with HN) were enrolled in the study. Serum Creatinine (Cre), Cystatin C (Cys), NT-pro brain natriuretic peptide (NTProBNP), Troponin I (TNI) and urinary albumin to creatinine ratio (UACR) were tested. Renal function was estimated according to Cre and Cys based CKD-EPI formula. Echocardiographic examination, carotid Intima-Media Thickness (IMT), ABPM, Renal Resistive Index (RRI) were performed. Vasculo-Renal Index (VRI) was calculated as IMT to UACR ratio.

Results: Groups with HN and CKD of other origins did not differ in renal function (CKD-EPI 46,2 vs 57,1 ml/min/1,73m2; P=0,22), NTProBNP, TNI, intimal medial (LV) ejection fraction, LV mass index and mean arterial pressure. Patients with HN were older (56,4 ±15,1 vs 45,9 ±14,1; p =0,039), had lower UACR (0,264 ±0,48 vs 0,814 ±0,564 mg/mg; p<0,001), but higher IMT (0,588 ±0,217 vs 0,652 ±0,380; p=0,009) and VRI (m. 28,8 [0,36; 1030,00] vs m. 0,78 [0,34; 12,50] p<0,0001). In ROC analysis VRI ≥ 1,91, UACR ≤ 0,199, and IMT ≥ 0,87 could recognize HN with sensitivity of 85%, 73% and 62% respectively, specificity of 79%, 93% and 86% and accuracy of 82.5%, 80% and 70% (AUC 0,874, 0,849 and 0,749; p<0,05).

Conclusions: A new Vasculo-Renal Index recognizes HN more accurately, but UACR and IMT are not significantly worse.

Funding: Government Support - Non-U.S.
Background: In patients with chronic kidney disease (CKD), impaired urinary sodium excretion (UNa) may cause nocturnal hypertension and pressure natriuresis to compensate for daytime sodium retention. The aim of this study was to determine the renal histological lesions which associated with nocturnal blood pressure (BP) and UNa in patients with CKD.

Methods: We analyzed 64 patients biopsyed in our institutions from Sep 2010 to Apr 2014 (Forty IgA nephropathy, 6 Purpura nephritis, 4 membranous nephropathy and 14 the others). During the same hospitalization period of renal biopsy, ambulatory BP monitoring and evaluation of UNa were performed simultaneously. The association of histological findings such as global sclerosis (%GS), arteriolar hyalinosis (%hyaline), and interstitial fibrosis (IF), with nocturnal BP and night/day ratio of UNa were assessed using linear regression analysis.

Results: Twenty three patients were male, mean age was 40.5 ± 15.9 years, and mean estimated glomerular filtration rate (eGFR) was 79.0 ± 28.9 mL/min/1.73m². Both nocturnal BP and night/day ratio of UNa positively associated with %GS, %hyaline, and IF, and negatively associated with eGFR. Multiple regression analysis adjusted for age, sex, eGFR, and usage of antihypertensive drugs showed that %GS was significantly associated with nocturnal systolic BP (β = 0.38, p = 0.012), nocturnal diastolic BP (β = 0.34, p = 0.031) and night/day ratio of UNa (β = 0.52, p = 0.005).

Conclusions: We found that night/day ratio of UNa and nocturnal BP closely related to the percentage of global sclerosis. These findings could be the morphological evidence that elevated night/day ratio of UNa may indicate the increase in glomerular hypoperfusion to compensate for daytime sodium retention resulting in elevation of nocturnal BP in patients with CKD.

**Conclusions:** This meta-analysis suggests that the bedtime dosing regimen drug therapy benefits CKD patients in terms of hypertension especially those with non-dipper BP pattern.

**Funding:** Government Support - Non-U.S.

**PUB503**

**The Impact of Glomerular Collapse in Hypertensive Emergency Patients**

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Background: The prognosis of kidney disease with hypertensive emergency (malignant glomerulonephrosis) is still worse compared with benign nephrosclerosis. Here, further to assess the reasons of worse prognosis and to reconsider more appropriate therapy for malignant nephrosclerosis, we compared pathological parameters between malignant and benign nephrosclerosis.

Methods: 8 patients diagnosed as hypertensive emergency with acute renal failure were performed renal biopsies from October 2005 to May 2015. We selected all patients with the benign nephrosclerosis (n=8), who were performed renal biopsies during same period, as controls. We compared changes in clinical and pathological data using the paired t-test and the Mann-Whitney U-test.

Results: All 8 patients with hypertensive emergency had characteristic pathological changes of malignant hypertension, such as fibronoid necrosis, onion-skin thickening and edematous-appearing matrix in arteries. These changes were never observed in benign nephrosclerosis. The rates of global sclerosis and segmental sclerosis had no statistical differences between these two groups. Interestingly, when glomerular collapsing rate was counted by GCR (number of glomerular collapse/ total number of glomeruli), GCR scores were much higher in hypertensive emergency cases compared with those in benign nephrosclerosis cases (42.9 ± 23.8 % vs. 6.5 ± 7.4 %; p < 0.05). These patient's clinical characteristics showed a high level of plasma renin activity (PRA) (14.9 ± 5.8 ng/ml/1h) and low aldosterone (3.5 ± 2.8). Two of 8 patients reached to end stage kidney disease requiring dialysis.

Conclusions: Glomerular collapse and hyper-renin mean glomerular hyperperfusion. Therefore, if therapy accelerate this glomerular hyperperfusion, it might affect renal prognosis. We should reconsider the way of therapy, such as the selection of anti-hypertensive drugs, and the speed of declining blood pressure and volume control by thinking glomerular hyperperfusion.

**PUB504**

A Study of Early Treatment with Benazepril in SHR at Different Doses

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Background: To investigate whether early treatment with super high dosage ACEI can reverse glomerulonephrosis in SHR.

Methods: 30 SHRs were randomized and divided into three groups (n=10): model control group (SHR), 10 mg·kg⁻¹·d⁻¹ Benazepril treatment (HT group), 50 mg·kg⁻¹·d⁻¹ Benazepril treatment (SHT group), 10 Wistar-Kyoto rats were studied as normal control group (N group), placebo , 10 mg·kg⁻¹·d⁻¹ Benazepril and 50 mg·kg⁻¹·d⁻¹ Benazepril were given through intragastric administration starting from 0 week of the experiment, rats were killed until 12 week of the experiment. Blood pressure(Bp), 24 hours urinary protein(24hUpr) and serum creatinine(Scr) were detected in the 0, 4, 8, 12 week of the experiment. Renal pathology damage was evaluated with paraffin wax section of kidney tissue through HE, MASSON stain; the protein levels for TGF-b1 and PAI-1 were tested through immunohistochemical staining method.

Results: Compared with model control group, Bp, 24hUpr of HT and SHT groups decreased obviously (P<0.05), the protein levels for TGF-b1 and PAI-1 in kidney tissue of HT group and SHT group were inhibited(P<0.05), glomerular collagen deposition of HT group and SHT group reduced evidently (P<0.05).

**Conclusions:** This meta-analysis suggests that the bedtime dosing regimen drug therapy benefits CKD patients in terms of hypertension especially those with non-dipper BP pattern.
Conclusions: This study shows that high dosage ACEI and super high dosage ACEI all can decrease blood pressure, reduce proteinuria, depress the expressions of TGF-β and PAI-1 protein in SHR, and delay glomerulosclerosis. But super high dosage ACEI can not reverse glomerulosclerosis in SHR.

PUB505


Background: Scleroderma renal crisis (SRC) is a rare cause of atypical hemolytic uremic syndrome (aHUS) and differentiating it from other causes of thrombotic microangiopathies can be challenging. A 53-year old Caucasian male, with no past medical history was found unresponsive. BP was elevated to 207/141 mm Hg. Skin examination showed diffuse telangiectasia and edema of his extremities with bilateral sclerodactyly (Figure 1). Fundoscopy revealed bilateral retinal hemorrhage and exudates. Labs showed a hemoglobin=5gm/dl, platelet=25×10⁹/μl, creatinine=6mg/dl, LDH=11221U/L, bilirubin=1-6mg/dl, haptoglobin<5%, reticulocyte count=10.4% and schistocytes. ANA and anti-RNA Polymerase III antibody were positive (C3 and C4, coagulation profile, fibrinogen were normal; Coombs negative). CT head showed severe microvascular changes throughout the white matter of the cerebrum and MRI showed evidence of punctuate chronic micro-hemorrhages in the left thalamus and cerebellar tonsils. The presence of MAH, acute renal failure and thrombocytopenia raised suspicion for possible aHUS/TPP. Serum ADAMTS13 was ordered. Because of the possibility of SRC, the patient was started on captopril. A dramatic improvement in BP, hemoglobin and platelets count along with the normalization of LDH and schistocytosis disappearance was observed. However, there was no improvement in kidney function requiring hemodialysis. ADAMTS13 activity returned at 40% (cut-off for TTP is <5%). Patient did not pursue eculizumab therapy. A significant portion of patients with Scleroderma can develop aHUS. In this case, hypertension might have served as a complement amplifying condition.

Methods: Clinical presentation/course of the patient.

Results: Despite therapy with ACE inhibitors patient ended up on RRT.

Conclusions: Patient presenting with Malignant HTN and MAH was found to be in scleroderma crisis.

PUB506


Background: Only a few studies with a very limited sample size have evaluated the impact of neck irradiation on baroreflex failure and blood pressure (BP) abnormalities. We investigated 60-patients, with head/neck cancer, who received neck irradiation between 2005 to 2010. IRB approval was obtained. Median for age was 61.5 years (range 24-90 years). We used the same cohort of patients, before the received neck irradiation as a control for BP. Mean systolic BP before neck irradiation was 129.1±1.802 mm Hg. Skin examination showed diffuse telangiectasia and edema of his extremities with bilateral sclerodactyly (Figure 1). Fundoscopy revealed bilateral retinal hemorrhage and exudates. Labs showed a hemoglobin=5gm/dl, platelet=25×10⁹/μl, creatinine=6mg/dl, LDH=11221U/L, bilirubin=1-6mg/dl, haptoglobin<5%, reticulocyte count=10.4% and schistocytes. ANA and anti-RNA Polymerase III antibody were positive (C3 and C4, coagulation profile, fibrinogen were normal; Coombs negative). CT head showed severe microvascular changes throughout the white matter of the cerebrum and MRI showed evidence of punctuate chronic micro-hemorrhages in the left thalamus and cerebellar tonsils. The presence of MAH, acute renal failure and thrombocytopenia raised suspicion for possible aHUS/TPP. Serum ADAMTS13 was ordered. Because of the possibility of SRC, the patient was started on captopril. A dramatic improvement in BP, hemoglobin and platelets count along with the normalization of LDH and schistocytosis disappearance was observed. However, there was no improvement in kidney function requiring hemodialysis. ADAMTS13 activity returned at 40% (cut-off for TTP is <5%). Patient did not pursue eculizumab therapy. A significant portion of patients with Scleroderma can develop aHUS. In this case, hypertension might have served as a complement amplifying condition.

Methods: Clinical presentation/course of the patient.

Results: Despite therapy with ACE inhibitors patient ended up on RRT.

Conclusions: Patient presenting with Malignant HTN and MAH was found to be in scleroderma crisis.

PUB507

Sympathetic Nervous System Activity Reflected by Renalase and Catecholamines in Different Aged Patients with and without Chronic Kidney Disease Edrya Zbolski, Dominika Maciorkowska, Ewa Koc-Zorawska, Jolanta Czarnecka, 1Department of Nephrology and Hypertension with Dialysis Centre, Medical Univ, Bialystok, Poland; 21st Dept of Nephrology and Transplantation, Medical Univ, Bialystok, Poland.

Background: Sympathetic nervous system activity is elevated in patients with chronic kidney disease (CKD) as well as in older persons. It contributes to hypertension and cardiovascular diseases. It is due to a reduction of catecholamines clearance and in elderly also to an increased sympathetic discharge from different organs. Renalase may play a role in the renin-angiotensin-aldosterone system. The aim of the study was to assess the sympathetic nervous system activity, according to serum renalase and catecholamines concentration in a cohort of 211 patients with hypertension and with or without chronic kidney disease.

Methods: The study group was divided according to age below and above 65 years. The older persons (61) was also divided into group with (75%) and without CKD stage 5. The serum renalase, dopamine and noradrenaline concentration as well as pressure control, residual renal function rate and echocardiography were assessed.

Results: The older group had higher renalase (p=0.02) and dopamine (p=0.001) concentration and it was elevated in patients with CKD comparing to those without. They also had advanced abnormalities in echocardiography, like thicker interventricular septum (p=0.03) and lower ejection fraction (p=0.001) as well as CKD patients comparing to those without CKD – pronounced left ventricular hypertrophy (p=0.007) and lower ejection fraction (p=0.004). They more often suffered from coronary artery disease. The residual renal function was less in older patients with CKD. The main used hypotensive drugs in studied group were beta-blockers. There was the significant correlation between age and renalase, noradrenaline and dopamine concentration.

Conclusions: The advanced age especially combined with chronic kidney disease is associated with elevated renalase and dopamine level. It may reflect the sympathetic nervous system hyperactivity due to impaired kidney function and reduction of residual diuresis. It may have an impact on the development of cardiovascular complications.

PUB508

Heart Rate Variabilities During Day and Night Can Alter the Circadian Blood Pressure (BP) Rhythm Toshiyuki Miura,1 Michio Fukuda,1 Yoshiaki Ogyama,1 Ken Kiyono,3 Yoshiharu Yamamoto,1 Junichiro Hayano,1 Nobuyuki Ohite,1 Nagoya City Univ, Japan; Osaka Univ, Japan; Toyo Univ, Japan.

Background: We previously reported in patients with chronic kidney disease (CKD) that the circadian rhythms of BP and urinary sodium excretion (UnV) were both impaired into non-dipper pattern as renal function deteriorated. Elevated salt-sensitivity of BP and inappropriate activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system play important roles in high BP and the high incidence of cardiovascular diseases in patients with CKD.

Methods: In 39 patients with CKD, we analyzed HRV in 24-h electrocardiography, BP monitoring and urine collection, separately for daytime and nighttime. Patients, who took antihypertensive agents, were excluded. We evaluated the relationship between systolic blood pressure (SBP) and UnV. The Non-Gaussianity index of HRV(UnV), which reflects the probability of intermittent large deviations of heart rate (HR) from the trend, and the power of high frequency (HF, 0.15-0.40 Hz) obtained by frequency domain analysis of HRV was used as a marker of sympathetic cardiac overdrive, and as vagal nerve activity, respectively.

Results: As renal function deteriorated, 24h-β and daytime β increased. 24h-SBP showed significant relationships with daytime (r=0.40, p<0.01) and night-time (r=0.37, p=0.02). Night/day ratios of SBP and UnV were also elevated as GFR was reduced. Night/day ratios of SBP correlated inversely with night-time HR(r=−0.36, p=0.02). When analyzed by stepwise multiple regression analysis, the main determinants of 24h-SBP were 24h-UnV, daytime β, and night-time HR. Night/day SBP ratios was determined by night/day ratio of UnV, rather than any HRs.

Conclusions: Our study clearly demonstrated that as renal function deteriorated, sympathetic nerve activity is activated during the day, and vagal activation was impaired during the night, both of which can contributes to high BP in patients with CKD. However, the increase type of circadian BP rhythm was associated with the circadian UnV rhythm rather than sympathetic or vagal nerve activity, even though the sympathetic activity can stimulate tubular sodium reabsorption.

PUB509

The Effects of the Insight Meditation Practice on Blood Pressure Reduction in Buddhist Exemplary People Tutamas Varesangthip,1 Kriengsak Varesangthip,2 1Dhamma Communication Div, Graduate School, Mahachulalongkornrajavidyalaya Univ, Bangkok, Thailand; 2Renal Div, Dept of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.

Background: Hypertension (HTN) is a leading risk factor for preventable cardiovascular disease, with over one in five adults affected worldwide. Lifestyle modification is the key strategy for the prevention and treatment of HTN. It is often associated with greater cardiovascular risk, and stress management is a recommended intervention for hyperventilators. For many patients, maximal medical therapy is insufficient

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

Underline represents presenting author.

1005A
to adequately treat refractory hypertension. Lifestyle modification remains an important approach in management. Buddhist meditation encompasses a variety of meditation techniques that aim to develop mindfulness, concentration and insight.

**Methods:** We aimed to study whether Buddhist Insight Meditation (IM) Practice, composing of Walking Meditation and Sitting Meditation, could reduce the level of blood pressure in Buddhist Exemplary People. 65 exemplary people were divided into 3 groups according to the schedule they performed IM Practice. Group 1 (n = 25) performed 30 minutes of the Walking and 30 minutes of the Sitting Meditation, group 2 (n = 20) performed 45 minutes in each Meditation and group 3 (n = 20) performed 60 minutes in each Meditation. Their blood pressures (BP), pulse pressures (PP) and pulses (P) were measured before and after Walking and Sitting Meditations.

**Results:** The results clearly showed that systolic BP, PP and P were significantly decreased after the Walking Meditation at 30-45-60 minutes. After IM Practice schedule, an artesunate-elad has significantly been decreased in all 3 groups, PP has been significantly decreased in group 2 and systolic BP has been significantly reduced in group 3.

**Conclusions:** In conclusion, the Buddhist IM Practice could meaningfully reduce the sympathetic activities including systolic BP, PP and P. Therefore, this Buddhist Practice should be added to be one modality of the standard hypertensive treatments.

**PUB510**

**ENA as a Novel Mechanism for Hypertension and Volume Expansion in Type 2 Diabetes**

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**Background:** Renal Na retention and extracellular fluid volume expansion are hallmarks of type 2 diabetes. There is evidence that this occurs even in the absence of activation of hormones that are known to stimulate renal Na transporters. Recent studies suggest that plasmnin-dependent activation of ENaC may be responsible for renal Na retention in the setting of nphropathy. We hypothesized that the ENaC inhibitor amiloride would be an effective therapeutic agent in inducing a natriuresis and lowering blood pressure in individuals with macroscopic proteinuria.

**Methods:** We conducted a pilot double-blind randomized cross-over study comparing the effects of daily administration of either oral amiloride (10 mg/day) or HCTZ (Na,Cl co-transporter inhibitor) to patients with type 2 diabetes and macroscopic proteinuria. We examined safety and feasibility of amiloride by monitoring kidney function, adherence, blood pressure, weight, urinary Na excretion and serum electrolytes during diuretic administration.

**Results:** 9 subjects were enrolled in the trial. Systolic blood pressure (SBP) decreased in both treatment groups, but there was not a significant difference between HCTZ and amiloride (P = 0.53). Amiloride treatment was associated with a 1.1 ± 0.4 kg decline in weight (P = 0.02), and a 0.70 ± 0.18 mmol/L greater increase in serum potassium (P = 0.002) over the low dose portion of the study. 2 subjects developed acute kidney injury and hyperkalemia when treated with amiloride. 5 subjects had readily detectable levels of urinary plasmninogen/plasmin, and 4 did not. Among those receiving amiloride, the low plasmin group experienced a change of 1.1±4.6 mmol/L in SBP and the high plasmin group experienced a change of -13.9±8.7 mmol/L, although there was insufficient evidence to conclude that there were differential treatment effects by high/low plasmninogin status (P = 0.113).

**Conclusions:** Among patients with type 2 diabetes, normal renal function, and proteinuria, there was suggestion of increased naturalis for those treated with amiloride vs. HCTZ, however, acute kidney injury severe hyperkalemia was a safety concern.

**Funding:** Private Foundation Support

**PUB511**

**Serum Phosphorus Control and Reduced Phosphate Binder Pill Burden Among Hemodialysis Patients Who Switched from Sevelamer to Sucroferric Oxyhydroxide**

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**Background:** Clinical management of hyperphosphatemia among hemodialysis (HD) patients (pts) can present challenges. A retrospective database analysis was conducted to study the effectiveness of sucroferric oxyhydroxide (SO) among in-center HD pts who switched from sevelamer to SO as part of routine clinical care.

**Methods:** Pts who switched from sevelamer and had 1 serum phosphorus (sPhos) measured during SO treatment were included. Changes in sPhos, serum calcium (sCa), intact parathyroid hormone (iPTH), transferrin saturation (TSAT), ferritin (FER), and pill burden were assessed at baseline (3-months prior to SO) and at follow-up (3-months during SO treatment).

**Results:** Pts (n = 1487) were, on average, 54 years old, with dialysis vintage of 4.4 years and hyperphosphatemia (baseline sPhos=6.94 mg/dl). Figure shows sPhos distribution at baseline and follow-up. Pts within-range sPhos (3.5-5.5 mg/dl) increased from 12% to 20.1% (68% increase). Mean sPhos decreased from 6.94 to 6.7 mg/dl (p = 0.001) and mean sCa decreased from 9.3 to 9.25 mg/dl (p = 0.001). There was a significant decrease (47 pills/day, p = 0.001) in pill burden (8.5 to 3.7 pills). No significant change in iPTH levels was observed in Baseline to follow-up in 461.3 to 637.6 pg/ml). TSAT and FER significantly increased (p = 0.001) from 33.7% to 35.3% and 983.5 to 1051.4 ng/ml, respectively. In pts not receiving IV iron (n=149), there were no significant changes in TSAT (36.3% to 35.9%) or FER (1221.5 to 1177.4 ng/ml).

**Conclusions:** Correlations of variables with sFe ultimately reflect correlations with ETr/Cr, TR/Cr or both (Clin Nephrol 83:167). As expected, sTr/Cr was closely associated with ETr/Cr. The other y-variables, which depicted comparisons of sTr/Cr, were inversely related to ETr/Cr as a specific indicator of P influx and a surrogate for [P], in the CDN. As [P] fell in the CDN, the difference rose between actual and maximal P reabsorption in the proximal nephron. We did not identify an endocrine mediator of this interaction.

**Funding:** Veterans Administration Support, Pharmaceutical Company Support - Genzyme Corporation
Observational Study at the Mexican Institute for Social Security and Services for State Worker’s National Medical Center 20 de Noviembre Nephrology Department Outpatient Clinic Using Cinacalcet as Renal Replacement Therapy for Secondary Hyperparathyroidism Caused by Chronic Kidney Disease

**Results:** We have found by western blot that there is an increase in intestinal NaPi-2b protein abundance and EvertedSac studies showed increased NaPi transport in the Alport Ileum compared to the WT littermate controls. Cardiac echo studies revealed that Alport mice have decreased ejection fraction (EF: 67±2% compared to 75±3% in the WT littermate) and diastolic dysfunction (mitral Doppler flow E/A ratio: 1.2±0.1 compared to 1.6±0.1 in the WT littermate, p<0.05), which could be corrected by treatment with Niacin (intestinal phosphate uptake inhibitor). In the treated Alport mice EF increased to 78±2% (p<0.05) and E/A ratio improved to 1.3±0.1 (p<0.05). In addition, there were significant decreases mRNA relative expression in β-MHC (0.08±0.02 in control vs. 2.19±0.34 in Alport, p<0.001, vs. 0.2±0.01 in Alport+Niacin, p<0.05). PAI-1 (0.12±0.01 in control vs. 1.05±0.15 in Alport, p<0.05, vs. 0.15±0.05 in Alport+Niacin, p<0.05), and TGF-β (0.03±0.01 in control vs. 0.77±0.23 in Alport, p<0.01, vs. 0.07±0.23 in Alport+Niacin, p<0.01), markers of heart failure and cardiac fibrosis.

**Conclusions:** Inhibition of intestinal phosphate transport with Niacin therefore improves systolic and diastolic cardiac dysfunction in CKD.

**Funding:** Pharmaceutical Company Support - Daichi Sanko

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Establishing Regulatory Networks of Phosphorus Metabolism in HD Patients – A New Path of Treating Hyperphosphatemia

**Background:** The clinical efficiency of current treatment of hyperphosphatemia in HD varies widely on different patients. We assume that it is due to phosphorus regulation in vivo. In physiological conditions, phosphorus is regulated by a biological network consisting of interacting hormones and minerals. In HD, the networks change dramatically and affect serum phosphorus. This study aims to establish the regulatory networks of phosphorus in HD and identify the key factors that may have a causal effect on circulating concentrations of phosphorus.

**Methods:** 30 MHD patients were enrolled and divided into three groups (n=10, PTH<300 ng/ml; n=10, 300 ng/ml<PTH≤600 ng/ml; n=10, PTH>600 ng/ml). Predialysis blood samples were obtained on the mid-week dialysis day for detection of PTH, FGF23, 25(OH)D3, Klotho, and Ca every week for 12 weeks each patient. Causal inference, a widely used process of concluding a causal connection, was adopted to establish the regulatory networks of phosphorus metabolism within different PTH levels.

**Results:** The networks show that when PTH<600 ng/ml, FGF23 can stimulate the increase of serum Pi, Ca, and PTH, in turn, serum Ca and Pi can also stimulate the increase of FGF23. When PTH>600 ng/ml, FGF23 becomes the stimulator of only serum Ca, and serum Pi has a positive causal effect on PTH, besides, the rise of PTH increases serum Pi level, too. So, serum Pi is affect by FGF23 when PTH<600 ng/ml and by PTH when PTH>600 ng/ml. Since FGF23 promotes the increase of PTH when PTH>600 ng/ml, FGF23 becomes the key factor in disorders of phosphorus metabolism. The figures also shows that Klotho and 25(OH)D3 may be not important in the therapy of hyperphosphatemia.

**Conclusions:** Reducing FGF23 levels might contribute to the control of phosphorus.

**Funding:** Government Support - Non-U.S.
Results: Sample 0.3% CKD1, 4.8% CKD2, 28.6% CKD3, 38.1% CKD4 and 22.2% CKD5. Mean serum Ca 9.47 mg/dL, mean serum phosphate P 3.77 mg/dL, PTH level 174 ng/dL, VD3 27 mg/dL. Mean Ca excretion 126 mg/day. Mean P excretion 477 mg/dL. PTH level 174 mg/dL. Ca bound 22.2% on calcium, 12.7% on calcium and 26.8% on paricalcitol. 70% of the sample had Ca excretion > 100 mg/dL. When classifying by stages of the disease, increases the amount of patients with Ca excretion > 100 mg/dL: CKD1 25%, CKD2 50%, CKD3 50%, CKD4 80%, CKD5 83%. Decreasing the mean Ca excretion. The subgroup of patients with lower Ca excretion had a higher PTH level (155 vs 111 pg/mL, p < 0.05). 94% of patients treated with Ca based binders had a Ca excretion > 100 mg/dL with no difference in serum Ca. Patients on calcitriol, paricalcitol or calciotriol had lower Ca excretion than those without treatment.

Conclusions: According to our results, patients with CKD show a decrease in renal Ca excretion that become exacerbated as the renal disease progresses. Supplementation with hypercalciemic drugs is not balanced out with the expected increase of renal Ca excretion. Therefore, we think that CKD patients are exposed to a chronic Ca overload, sometimes underestimated, with the resulting negative impact in morbidity and mortality.

PUB518

effect of Parathyroid Hormone on Serum Magnesium Level: The Neglected Relationship in Hemodialysis Patients with Secondary Hyperparathyroidism

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Background: Chronic kidney disease-mineral and bone disorder (CKD-MBD) is an important complication in patients with end-stage kidney disease which is associated with cardiovascular morbidity and mortality. Since recent studies have shown that serum magnesium plays an important role in secondary hyperparathyroidism, vascular calcification and cardiovascular mortality, the interest on magnesium has grown.

Methods: This cross-sectional study was conducted on 111 patients with end-stage renal disease on maintenance hemodialysis who was hospitalized for secondary hyperparathyroidism. The interventional study was conducted on 23 patients underwent total parathyroidectomy.

Results: In our study, hypermagnesaemia (>2.5 mg/dL) occurs in up to 44% of cases and hypomagnesaemia did not present. No significant correlations were found between serum magnesium and parathyroid hormone (r = -0.143, p = 0.134). Correlation analysis and logistic regression analysis suggested that the derangement of magnesium between serum magnesium and parathyroid hormone (r = -0.143, p = 0.134). Correlation cases and hypomagnesemia did not present. No significant correlations were found

Conclusions: There is an increased prevalence of hypermagnesaemia in hemodialysis patients with secondary hyperparathyroidism. The derangement of magnesium between serum magnesium and parathyroid hormone was correlated with the derangement of calcium/phosphate homeostasis. Therefore, we think that CKD patients are exposed to a chronic Ca overload, sometimes underestimated, with the resulting negative impact in morbidity and mortality.

PUB519

Calciphylaxis in Patient with Chronic Renal Disease Not Dialytic and Multiple Myeloma

Patricia Junqueira Freitas, Aline Lourenço Baptista, Clóvis Antonio lopes Pinto, Joubert Araujo Alves, Pedro Caruso, Benedito Jorge Pereira, Fernanda Lemos Moura, Marina Harume Imanishi, Luis Andre Andrade, Germana Alves Brito. Nephrology, AC CAMARGO, Sao Paulo, Brazil.

Background: Calciphylaxis, also known as calcifying urerteral fibrosarcoma, is a rare medical condition, which is normally diagnosed in patients with terminal CKD who are already in renal replacement therapy (RRT). Objective report the presence of calciphylaxis in CKD, in patient with oncologic disease.

Methods: Female patient, 71 years old, caucasian, conducted to AC Camargo Hospital for etiological investigation of injuries in lower limbs associated with renal failure, hypercalcemia, anemia and astenia. Has history of hypertension and obesity. Physical examination: poor general state, dyspnea, respiratory and cardiovascular systems without changes, ulcerated lesions of necrotic center in lower limbs (FIGURE). Laboratory tests: Creatinine 8.8 mg/dL, Urea 169 mg/dL, K 4.1 mEq/L, HC03:16.3 mEq/L, pH 7.29, Ca: 1.58 mmol/L, PTH: 295 pg/ml, P: 3.6 mg/dL, total Ca 12.9 mg/dL, albumin 1.8 g/L, Renal US: regular, Parathyroid US: regular, Left biopsy(Bx) of skin, chronic inflammatory process, scar, thickened subcutaneous tissue, dermal necrosis, ulcerated lesions of lower limbs (FIGURE). Noninvasive hemodynamic evaluation was performed before, during and after dialysis. Results: Comparing with group 2, cardiac index (CI) was higher (P=0.252) while systemic vascular resistance index (SVRI) was lower (P=0.05) in group 1. The mean thoracic fluid capacity (TFC) of the two groups were similar (P=0.424) before dialysis. Before PTX, spheric blood pressures (SBP) of all the 12 patients were above 90 mmHg. Decreasing the mean Ca excretion. The subgroup of patients with lower Ca excretion had a higher PTH level (155 vs 111 pg/mL, p<0.05). The frequency of Ca > 2.60 mM and Ph > 1.5 mM are not modified at M6/M0. We compared M6’s biologic data with M0’s data.

Conclusions: At M6, Ca magnesium intake is reduced by 57% vs M0. Ph is similar vs M0. Mean serum calcium is not altered. The frequency of Ca > 2.60 mM and Ph > 1.5 mM are not modified at M6/M0. We compared M6’s biologic data with M0’s data. The only difference is related to a decrease of Calcium Intake (g/d) from M0 (1.51 +/- 1.13) to M6 (0.63 +/- 0.31, P<0.05).

Funding: Private Foundation Support

PUB521

Calcium Binders Are They All Equal? Comparison Calcium Acetate (CA) versus Carbonate Calcium (CC) in CKD 5D: Multicentric Study

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Background: CA’s phosphate binder is available since 2010 in France. A monocentric study indicates that CA is equivalent to CC based on phosphatemia reduction while reducing calcium intake by 60%. This study compare CA to CC in different dialysis centers i.e different CKD MBD protocols.

Methods: 28 hemodialysis centers are involved. CC is switched to CA at M6 with 6 months follow up (M1, M2). We compared M6’s, biologic data with M1’s, data.

Results: 293 patients (70+/-14 y) in 28 centers. At M1, CA dosage was 3.8 +/- 2 pills/day. Demographic characteristics are consistent with our National French registry. At M6, mineral values are similar to M0: Ph mM (1.54 +/- 0.55 vs 1.52 +/- 0.65, NS), Ca mM (2.23 +/- 0.17 vs 2.21 +/- 0.15, NS), PTH pg/ml (221 +/- 204 vs 262 +/- 217, NS), Vit. D mM (75 +/- 32 vs 79 +/- 24, NS), % pts with no calcium binder (43 vs 49, NS), % pts w. Ca > 2.6 mM (2 vs 1, NS), % pts w. Ph > 1.5 mM (39 vs 38, NS). The only difference is related to a decrease of Calcium Intake (g/d) from M0 (1.51 +/- 1.13) to M6 (0.63 +/- 0.31, P<0.05).

Conclusions: At M6, Ca intake is reduced by 57% vs M0, while Ph is similar vs M0. Mean serum calcium is not altered. The frequency of Ca > 2.60 mM and Ph > 1.5 mM are not modified at M6/M0. We compared M6’s biologic data with M0’s data. The only difference is related to a decrease of Calcium Intake (g/d) from M0 (1.51 +/- 1.13) to M6 (0.63 +/- 0.31, P<0.05).

Funding: Private Foundation Support

PUB520

Hemodynamic Changes in Maintenance Hemodialysis Patients with Hypotension After Parathyroidectomy

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Background: Parathyroidectomy (PTX) is applied to treat secondary hyperparathyroidism in hemodialysis patients. Some patients suffered from hypotension after PTX although hypocalcemia was corrected. The aim of this study was to demonstrate the hemodynamic changes in hemodialysis patients after PTX.

Methods: Twelve patients were included in this study. Among them 4 have hypotension after PTX (Group 1) and the other have their blood pressure remained after PTX (Group 2). Before PTX, systolic blood pressures (SBP) of all the 12 patients were above 90 mmHg. Noninvasive hemodynamic evaluation was performed before, during and after dialysis.

Results: Comparing with group 2, cardiac index (CI) was higher (P=0.252) while systemic vascular resistance index (SVRI) was lower (P=0.05) in group 1. The mean thoracic fluid capacity (TFC) of the two groups were similar (P=0.424) before dialysis. Serum Ca, PTH, ALP, ventricular ejection fraction and vascular calcification score of thoracic aorta, abdominal aorta and heart valve before PTX, as well as the weight of the removed parathyroid glands, serum Ca, ALP, hemoglobin after PTX of the patients were determined. No statistical differences were found. However, the phosphorus level was lower in group 1 both before and after PTX. CI, SVRI and TFC were similar in both groups during hemodialysis.

Conclusions: Patients with hypotension after PTX have a lower systemic vascular resistance index and a higher cardiac index, which might be associated with serum phosphorus level.

Funding: Government Support - Non-U.S.
PUB522

Cost of Medications Used in the Management of Secondary Hyperparathyroidism (SHPT) in Patients with End Stage Renal Disease (ESRD) Mark E. Bensink,1 Leigh Darryl Quarles,2 Vasily Bele佐off,1 Kerry Cooper,1 Jonathan D. Campbell,3 'Amgen Inc., Thousand Oaks, CA; 2Univ of Tennessee, Memphis, TN; 3Univ of Colorado, Aurora, CO.

Background: Management of SHPT associated with ESRD is complex, typically requiring combinations of medications. Eighty-five percent of the ESRD population is covered by Medicare with detailed drug expenditures reported annually by the US Renal Data System. For the remaining 18% covered by commercial health plans, drug expenditure information is unknown. The purpose of this study is to estimate the cost of medications used in the management of SHPT in ESRD patients from the US commercial health plan perspective.

Methods: Economic analysis with one-year time horizon to estimate per-member-per-month (PMPM) cost for SHPT related medications: calcium and non-calcium-based phosphate binders, calcitriol or active vitamin D analogs, and calcimimetics. Input parameters include: prevalence of ESRD in commercial health plans (MarketScan®); medication utilization and non-adherence (IMS Health for oral medications and Outcomes Plus for intravenous [IV] medications); and medication wholesale acquisition costs (WAC) (AnalysSource.com) with one-way sensitivity analysis.

Results: The total PMPM (2014 US Dollars) cost of SHPT-related medications is $0.34: cinacalcet $0.06, phosphate binders $0.16, oral vitamin D $0.02, and IV vitamin D $0.10.

Figure 1. Total PMPM Cost Breakdown

Calcimimetic 18.7%
Calcitriol 13.6%
Phosphate Binders 46.2%
Oral Vitamin D 6.6%
IV Vitamin D 2.9%

Results are most sensitive to variation in ESRD prevalence and cinacalcet WAC parameters.

Conclusions: Results indicate that the collective cost of medications for the management of SHPT in commercial health plans is substantial with the cost of cinacalcet being lower compared to phosphate binders and IV vitamin D, but higher compared to oral vitamin D.

Funding: Pharmaceutical Company Support - Amgen Inc.

PUB523

Medullar Compression by Bone Tumor: Case Report Cinthia Sobral Vieira, Nicole D.T. Carvalho. Nephrology Unit- Cliniefo, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

Background: The presentation of vertebral tumors may have different kinds of manifestation. They can mimic nonploc, inflammatory and congenital diseases. The following report is about a patient with a lytic bone lesion in the thoracic spine causing medullar compression symptoms.

Methods: A 66 years old masculine patient, with chronic renal disease in hemodialysis for 5 years, non-adherent to treatment or diet, had his levels of phosphor, calcium/phosphor, alkaline phosphatase and parathyroid hormone (PTH) elevated in the last year. He did not take the medication prescription: Calcitriol and Sevelamer. The patient came to the ER of a general hospital referring constipation and abdominal distention. During the hospitalization he started to refer paresthesia in inferior members with progressive march dysfunction. The neurological exam showed ataxic/calcaneal gait and strength reduction (4+/5+) in the inferior members.

Results: After 5 years, non-adherent to treatment or diet, had his levels of phosphor, calcium/phosphor, alkaline phosphatase and parathyroid hormone (PTH) elevated in the last year. He did not take the medication prescription: Calcitriol and Sevelamer. The patient came to the ER of a general hospital referring constipation and abdominal distention. During the hospitalization he started to refer paresthesia in inferior members with progressive march dysfunction. The neurological exam showed ataxic/calcaneal gait and strength reduction (4+/5+) in the inferior members.

Conclusions: The presentation of vertebral tumors may have different kinds of manifestation. They can mimic nonploc, inflammatory and congenital diseases. The following report is about a patient with a lytic bone lesion in the thoracic spine causing medullar compression symptoms.

PUB524

Rescue-Therapy with Lanthanum-Carbonate (LC) in Uncontrolled Hyperphosphoremia in Dialysis Nicola Giotto, Angela maria Marino. Dept of Medicine, Nephrology and Dialysis Unit, Cardinal Massaia Hospital, Asti, AT, Italy.

Background: Control of hyperphosphatemia in hemodialysis provides an approach based on changes in diet, dialysis efficiency improvement, and use of phosphate binders. The latter, however, in some patients do not prove effective, conditioning the indirect increase of mortality and morbidity of the subject on dialysis. The objective of this study was to evaluate the difference in efficacy of a regimen of lanthanum carbonate plus standard therapy (LTS) compared to standard therapy alone (TS) in the treatment of patients with persistent hyperphosphatemia, as rescue-therapy.

Methods: We conducted an observational study of data on consecutive patients in hemodialysis who have presented more than four phosphorus values greater than 6 mg/dL in three months. Patients treated with TS, have varied therapeutic scheme introducing LC. Patients treated with sevelamer have outstanding this therapy and were treated with LC. The data analysis has been done considering a retrospective phase (FR) of three months and a prospective phase (FP) of six months, for each subject analyzing the effectiveness of therapy before and after enrollment.

Results: In a cohort of 163 patients on hemodialysis, we have selected for the study, 14 patients who had a mean age of about 65 years and length of dialysis than 6 years. The combination of LC plus TS produced a significant increase in the proportion of patients achieving the therapeutic targets as defined by the K/DOQI Guidelines. Reduction of 2.12 mg/dL (-32.7%) than the average of the P phase prospective (4.55 mg/dL) than the retrospective phase (6.77 mg/dL), was statistically significant (p <0.001), is associated with the reduction of 19:21 mg/dL (-32.9%) of the average value of CaXP in the prospective phase (39.07 mg2/dL2) compared to the retrospective phase (58.28 mg2/dL2), also statistically significant (p <0.001). The patients at the target of the FR accounted for 92.31% for P and 100% for the CaXP, respectively vs. the 7.14% and 50% of FR.

Conclusions: The introduction of the LC-as rescue therapy in the treatment of hemodialysis patients with uncontrolled hyperphosphatemia resulted very effective allowing more easily reach the therapeutic objectives.

PUB525

Glucocorticoid-Induced Osteoporosis in Renal Patients Gabrielle Goldet,1 George Greenhall,2 Alan D. Salama.3 'Basildon and Thurrock Univ Hospital; 2Royal Free Hospital, London; 3Royal Free Hospital, London.

Background: Glucocorticoid-induced osteoporosis (GIO) is associated with severe morbidity due to fragility fractures as well traumatic fractures and 50-90% of patients on long term steroids are affected by GIO. GIO is relevant in the renal context as steroids are widely used to treat renal disease and as part of immunosuppression in transplant. Also, renal patients are already at higher risk of fractures in association with renal bone disease.

Methods: We designed and undertook an audit to assess screening and management of GIO in nephrology outpatients in a university hospital in London, using national guidelines as a benchmark for our performance. We then presented the results at a local meeting, produced posters and leaflets on GIO to be placed in the outpatient waiting area for patients so as to raise awareness of this issue and provided a simple algorithm to be followed by clinicians in all the clinic rooms. We then re-audited after 6 months.

Results: 100 patients were audited in each audit cycle. Measures audited were a) whether all patients over 65 were treated with bone protection; b) whether all patients with documented fragility fracture were treated with BSA; c) whether all patients under 65 without fragility fracture underwent DXA scan; d) whether all patients with T-score under -2.5 were treated with BSA; e) whether all patients with T-score 0 to -1.5 underwent DXA scan; f) whether all patients under 65 without fragility fracture underwent DXA scan; g) whether all patients are managed according to national guideline (cycle 1: 29%; cycle 2: 41%). See table for breakdown of results.

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Conclusions: Our intervention has improved performance as measured against national guidelines, though the rate of GIO screening remains low. Many patients could potentially benefit from bone protection, though larger studies would be needed to demonstrate an effect on fracture incidence.

Funding: Government Support - Non-U.S.
The Kidney Stone and Increased Water Intake Trial in Steel Workers:

PUB526

**Results:** A total of 1443 workers were randomized to receive standard-dose (38.5 mg daily) or low-dose cinacalcet (25 mg alternate day) for 16 weeks. At 8 weeks, doses of cinacalcet could be increased to achieve a target of 30 mg daily for 12 weeks. The changes in serum iPTH, calcium, phosphorus, and alkaline phosphatase were compared between the two groups. The study found that low-dose cinacalcet was effective in reducing iPTH levels without significant changes in serum calcium or phosphorus. The study also found that low-dose cinacalcet was well tolerated and did not increase the risk of hypocalcemia.

**Conclusions:** Low-dose cinacalcet is effective in reducing iPTH levels in hemodialysis patients without increasing the risk of hypocalcemia. It is an alternative to standard-dose cinacalcet and may be a suitable option for patients who are at risk of hyperparathyroidism.

PUB527

**Methods:** The study was an open, randomized controlled trial (RCT) involving 1443 patients with secondary hyperparathyroidism. The patients were randomized to receive either standard-dose cinacalcet (38.5 mg daily) or low-dose cinacalcet (25 mg alternate day) for 16 weeks. The primary outcome was the percentage of patients achieving the KDIGO target at 16 weeks.

**Results:** The study found that low-dose cinacalcet was effective in reducing iPTH levels without significant changes in serum calcium or phosphorus. The study also found that low-dose cinacalcet was well tolerated and did not increase the risk of hypocalcemia.

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PUB528

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Parathormone Stability in Hemodialyzed Patients: Comparison on Non-Centrifuged EDTA and Serum Samples with 2nd and 3rd Generation Assays
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Background: PTH stability is of importance. Many studies have shown divergent results between EDTA and serum, mainly linked to differences in protocols or cut-offs used to decipher whether PTH remained stable or not. No studies have yet compared PTH as measured by 2nd and 3rd generation assays on the same samples in hemodialyzed (HD) patients.

Methods: Five pairs of samples (EDTA and gel tubes) were obtained in 10 HD patients before session. One pair was centrifuged and run immediately to establish the “T0”. Two pairs were kept at 4°C and +25°C. They were centrifuged after 4 and 18 hours. Supernatant was kept at -80°C for one week. Then, all samples were measured in a single batch, on Roche Cobas and DiaSorin XL 2nd and 3rd generation PTH assays. Samples were considered as stable if 90% of subjects had a decrease lower than a total change limit (TCL) that takes both analytical and biological variability into consideration. All determinations were run in duplicates.

Results: At T0, no difference was observed between plasma and serum for any of the methods. PTH decreased in all samples and degradation was the same with 2nd or 3rd generation assays, whatever the method used. Percentages of decrease were systematically lower in EDTA plasma compared to serum and none of our subjects presented a decrease higher than the TCL with EDTA plasma. In serum, PTH was not considered as stable, but only when kept at 25°C for 18 hours.

Conclusions: PTH stability is of paramount importance for correct interpretation of the results. Many studies have tried to evaluate this stability but are not free from criticisms, mainly due to a poorly defined T0 and questionable acceptation limits. In this study, we used an unfrozen T0 and decision limits based on analytical and biological variations. Moreover, we tested 2nd and 3rd generation PTH on two automated platforms. Our results show that, if PTH is basically more stable in EDTA plasma than in serum, this advantage is only clinically significant when samples are stored for a long period (18h) at +25°C.

Vitamin D Metabolism Is Incompletely Restored After Kidney Transplantation
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1Univ of Warwick, United Kingdom; 2Univ of Cambridge, United Kingdom; 1Massachusetts General Hospital, Boston; 2Queen’s Univ, Kingston, Canada.

Background: Vitamin D deficiency is widely reported in patients with renal impairment and is associated with adverse outcomes. The extent and rate of recovery of vitamin D metabolism after kidney transplantation is uncertain.

Methods: We enrolled 175 dialysis patients (HD) listed for kidney transplantation, and 85 hypertensive but otherwise healthy controls (HTN). We determined blood markers of mineral metabolism including intact FGF23 and vitamin D metabolites at entry (or immediately pre-transplantation), and 2 months. As a surrogate for vitamin D deficiency, we assessed the 25(OH)D3: 24.25(OH)2D3 ratio (D-ratio, normal 5:25).

Results: Of 175 dialysis patients, 76 were transplanted (TXR) during the study. TXR were transplanted with a lower BMI than controls. FGF23 was higher in HD patients than HTN at base-line, but normalised after 12 months (p<0.13). At baseline, vitamin D insufficiency (defined as 25(OH)D3 <30 ng/mL) was present in 82% of subjects and did not differ between groups. However, vitamin D deficiency (defined as 25(OH)D3 <10 ng/mL) was more common in dialysis (15% versus 4%, p=0.49). The baseline D-ratio was higher in HD (48, IQR 27-67) than in HTN (16, IQR 14-18, p<0.0001) patients. Transplantation resulted in significant reduction in D-ratio after 2 and 12 months compared to HD (p=0.0008 and p=0.005 respectively). The slope of D-ratio vs 25(OH)D3 increased after transplantation, but remained lower than for HTN controls, suggesting reduced expression or activity of the catalytic CYP24A1 (25-OH-D3-24-hydroxylase) in kidney failure.

Conclusions: Vitamin D insufficiency is highly prevalent in patients on dialysis and in hypertensive controls, and only partially resolves after kidney transplantation.

Low Time-Averaged Serum Intact Parathyroid Hormone Level Is an Independent Risk Factor for Overall Mortality and Major Adverse Cardiac and Cerebrovascular Events in Incident Dialysis Patients
Sul A Lee,1 Mi Jung Lee,1 Kyoung Sook Park,1 Jong Hyun Jee,1 Jae Eun Um,1 Meiyan Wu,2 Hyung Jung Oh,1 Jung Tak Park,1 Seung Hyoek Han,1 Shin-Wook Kang,1,2 Tae-Hyun Yoo.1
1Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; 2Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Chronic kidney disease-mineral bone disorder (CKD-MBD) is known as a major risk factor for cardiovascular disease in end-stage renal disease (ESRD) patients. CKD-MBD is classified into low turnover and high turnover bone disease according to the bone dynamics, both of which are related with vascular calcification in ESRD. To evaluate the prognostic value of abnormal serum parathyroid hormone (PTH) levels on ESRD patients, we investigated the effects of time-averaged serum intact PTH (TA-iPTH) levels on overall mortality and major adverse cardiac and cerebrovascular events (MACCEs) in incident dialysis patients.

Methods: In this prospective observational study, 413 patients who started dialysis between January 2005 and September 2010 at Yonsei University Health System were enrolled. Patients were divided into three groups according to TA-iPTH levels during the 12 months after initiation of dialysis (group 1:<65pg/mL, group 2: 65 to 300 pg/mL, group 3: >300pg/mL). Cox regression analysis was performed to determine the prognostic value of TA-iPTH on overall mortality and MACCEs.

Results: The mean age was 56.5±14.5 years and 222 patients (53.8%) were male. During a median follow-up of 50.8 months, 49 patients (11.9%) were dead and MACCEs were occurred in 55 patients (13.3%). Multivariate Cox regression analysis demonstrated that low TA-iPTH level was an independent risk factor for both overall mortality [group 2 as reference; group 1, hazard ratio (HR)=2.08, 95% confidence interval (CI)=1.2-3.8, P=0.02] and MACCEs (HR=1.88, 95% CI=1.04-3.40, P=0.04) in incident dialysis patients after adjusting confounding factors.

Conclusions: This study demonstrates that low TA-iPTH is an independent risk factor for overall mortality and MACCEs in incident dialysis patients.

Combined Analysis of Hypercalcemia and PTH Levels as Clue to Unveil Persistent Transplant Hyperparathyroidism
Melani Custodio,1 Maria Julia C. L. N. Araujo,1,2 Wagner Dominguez,1 Rosa M. A. Moyaes,1 Elias David-Neto,1 Vanda Jorgetti.1
1Nephrology Div, Univ de Sao Paulo; 2Transplant Unit, Univ de Sao Paulo; 1UNINOVE, Sao Paulo, Brazil.

Background: Mineral and bone metabolism disorders in chronic kidney disease (CKD-MBD) are not always corrected after kidney transplantation (TxR). The persistence of hyperparathyroidism may have a negative impact on patient and graft outcome. Our objective was to evaluate the evolution off CKD-MBD and the incidence of hyperparathyroidism after 12 months of TxR.

Methods: In this study, we included all consecutive patients submitted to a TxR during the period between Jan 2010 and Dec 2014 in a University based center. We excluded patients with a PTH <300 pg/mL before TxR, multi-organ transplants, patients with an eGFR<30mL/min and those who underwent parathyroidectomy after TxR. Twelve-month eGFR, plasma levels of total calcium (Ca), phosphorus (P), alkaline phosphatase (AlkP), magnesium (Mg), parathormone (PTH), and 25-hydroxy vitamin D (25-OH vit D) were compared to baseline values. A PTH >100pg/mL and a total calcium >10.2mg/dL were considered abnormal. We defined high PTH, with or without hypercalcemia as the primary endpoints for the analysis.
Results: During the observation period, 408 patients were evaluated. There was a significant increase in eGFR and in calcium levels 12 months after the TxR. Compared to the baseline, PTH, AlkP, and P significantly decreased. 25-OH Vit D also did not change during the period. Fifteen percent of patients presented both PTH and Ca above the reference levels, while 37% presented isolated high PTH and 8% hypercalcemia only. Multivariate analysis disclosed that post-TxR hyperparathyroidism was dependent on pre-transplant PTH (OR 1.001; CI 95%: 1.001-1.002) and Ca (OR 1.233; CI 95%: 1.036-1.468).

Conclusions: Monitoring Ca and PTH before and after TxR may be important to detect patients at high risk of persistent hyperparathyroidism, and to identify patients in need of treatment to prevent its complications.

PB534

Predictors of FGF23 and Soluble Klotho in HIV Infection
Rubin Wang,1 Michael Shlippik,2 Joachim H. Ix,3 Michelle M. Estrella,1 Johns Hopkins Univ;1UCSF, UCSD.

Background: In the general population, FGF23 and its co-receptor, soluble klotho (sKlotho), have been implicated in the aging process. HIV+ individuals are at higher risk of age-related comorbidities compared with HIV- persons. We evaluated whether FGF23 and sKlotho levels differed by HIV status and determined clinical factors associated with each hormone in HIV+ men.

Methods: 384 HIV+ and 225 HIV- men in the Multicenter AIDS Cohort Study (MACS) were randomly selected for FGF23 and sKlotho measurements from samples stored in 2008-2010. We compared FGF23 and sKlotho levels by HIV status, adjusted for age and race. Multivariable linear regression models were used to determine predictors of FGF23 and sKlotho levels among HIV+ men.

Results: Mean age was 53y; 34% were black; and median eGFR was 90mL/min. 99% of HIV+ men were antiretroviral-treated. FGF23 and sKlotho were not significantly correlated (r=0.09). In adjusted analyses, HIV was associated with 11% (p=0.002) higher sKlotho but not FGF23 levels (-1%; p=0.84). Among HIV+ men, diabetes was associated with 3% (p=0.68) and HCV (34%); 95% CI: -14%, -49%); and cumulative tenofovir (TDF) exposure (-4%/year; 95% CI: -1%, -7%) were associated with 30% (95% CI: 3-65%) higher FGF23, whereas HCV (34%); 95% CI: 7%, 36%) [Figure] Neither CD4 count nor HIV RNA were associated with FGF23 or sKlotho concentrations.

Conclusions: HIV+ individuals had similar FGF23 but higher sKlotho levels compared to HIV- counterparts. Among HIV+ men, clinical predictors associated with FGF23 differed from those associated with sKlotho. Mechanisms by which HIV treatment and co-morbid conditions may impact these hormone levels need further study.

Funding: NIDDK Support, Other NIH Support - NIAID, NCI, NHLBI, NIDCD

PB535

Response of Fibroblast Growth Factor 23 to Sodium Interventions in Diabetic Nephropathy and Arterial Hypertension
Selmer K. Humalda, Sarah Seiler, Marc G. Vervloet, Gunnar H. Heinic;2 Martin H. De Borst,1 Nephrology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia;1Nephrology, The Univ of Melbourne, Melbourne, Victoria, Australia;2Nephrology, Saarland Univ Medical Center, Homburg, Germany;2Nephrology, VU Medical Center, for NGrAm, Amsterdam, Netherlands.

Background: Fibroblast growth factor 23 (FGF23) is known to regulate the sodium transporters thereby inhibiting tubular phosphate reabsorption. Chronic kidney disease (CKD) leads to FGF23 excess and deficiency of sKlotho but not FGF23 levels. The effect of excess sodium on volume status. FGF23 putatively induces sodium retention which significantly increases LOS. Further to consensus between renal and surgical teams we have increased the preloading dose of one-alfacalcidol to 5 mcg for 5 days pre operatively. A follow up study is planned in 12 months to observe the outcome of this change.

Funding: Private Foundation Support

PB536

Hypocalcaemia Management Post Parathyroidectomy in Renal Patients – Our Experience and Change in Practice
Rajkumar Chinnadurai, Maharan Raman, Constantina Chrysoucho, Smeeta Sinha. Dept of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom.

Background: Hypocalcaemia is common post parathyroidectomy in renal patients with secondary hyperparathyroidism due to hungry bone syndrome with an incidence as high as 51%. Hypocalcaemia can be prevented by effectively preloading patient with Vitamin D supplements and close monitoring of calcium levels post operatively. Currently there is no clear guidance on the preloading dose of one-alfacalcidol in literature. Our current practice is to preload all patients with 2 mcg one-alfacalcidol for 5 days pre operatively. Our aim was to study the management of hypocalcaemia post parathyroidectomy in renal patients and factors influencing length of hospital stay (LOS). To identify if any changes in current practice could improve outcome.

Methods: Retrospective observational study of all renal patients who underwent parathyroidectomy under a single surgeon over 6 years (April 2008 to September 2014). Data was collected from the Electronic Patient Record. Data were analysed using Stats direct and Fisher Exact test was used for testing statistical significance.

Results: 72% of our sample (n = 25) were male with a mean age of 54. Of the 25 there were 13 transplant, 9 haemodialysis and 3 CKD patients. The mean hospital stay was 5 days shorter than quoted in the literature (5.6 Days). 3 of 25 patients were not preload and 71% of our patients needed intravenous calcium replacements which was the main cause for increased LOS (p=0.0002). Haemodialysis patients had longer LOS than CKD and Transplant patients (p=0.0002), this group were more likely to not have received pre-loading. These undergoing total parathyroidectomy had increased LOS compared to subtotal parathyroidectomy (p=0.0009). There were no surgical complications contributing to a delay in discharge.

Conclusions: Insufficient preloading was identified as a major risk factor for hypocalcaemia, which significantly increased LOS. Further to consensus between renal and surgical teams we have increased the preloading dose of one-alfacalcidol to 5 mcg for 5 days pre operatively. A follow up study is planned in 12 months to observe the outcome of this change.

Kath: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
PUB538

Fibroblast Growth Factor 23 Can Predict the Progress of Aortic Artery Calcification in Dialysis Patients
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Background: To investigate the factors associated with progress of aortic artery calcification in maintenance haemodialysis (MHD) patients and to determine whether plasma FGF23 level is related to progress of aortic artery calcification.

Methods: MHD patients from Ruijin Hospital from July 1st 2011 to July 31st 2011 were involved in our study. Follow up 36 months. Aortic artery calcification (AAC) was detected by a lateral lumbar X-ray plain and read by two radiologists.

Results: 120 MHD patients were enrolled and followed up for 36 months. To July 2014, a total of 67 MHD patients finished the study. Among 67 patients, 32 were male, mean age 53.9±13.1 years old, mean dialysis vintage 44.1±38.1 months, median FGF23 level 48052 (11372-35750.4)Ru/ml, LgFGF23 3.79±0.83. In July 2011, 53.7% of patients had visible calcification in the abdominal aorta and mean involved segment was 1.42 with mean AACS (ACAS). 3.96. In July 2014, 73.1% had AAC and mean involved segment was 2.34 with mean AACS 10.7. There are significant differences between two AAC involved segments and AACS (both P<0.001). Age, dialysis vintage and FGF23 level had significant difference between AAC progress group and no AAC progress group (P = 0.007, <0.001 and 0.020, separately). Logistic analysis showed that the independent parameters associated with AAC progress were age (OR=1.114, CI:1.045-1.186) and LgFGF23 level 48052 (11372-35750.4)Ru/ml, LgFGF23 3.79

Conclusions: The severity of vascular calcification progress yearly in maintain haemodialysis patients. Age and FGF23 are independently associated with the progress of AAC. FGF23 level could predict the progress of AAC in MHD patients.

Funding: Government Support - Non-U.S.

PUB539


Background: Hepcidin is a 25-amino-acid protein synthesized in hepatocytes and macrophages that acts as a post-translational inhibitor of ferroportin, the only receptor known to export iron from intracellular compartments to systemic circulation. Thus, higher hepcidin levels are associated with greater intracellular sequestration of iron, and increased risk of anemia. Vitamin D is an inhibitor of hepcidin expression; the working hypothesis is that FGF23 could be an ‘inverse’ regulator of iron metabolism in comparison to vitamin D, with a stimulation of hepcidin expression, an increase of intracellular ferritin and an inhibition of ferroportin expression in the cell membrane, leading to a further intracellular sequestration of iron.

Methods: Three different types of liver cells were used: HepG2, HepaRG and primary human hepatocytes (PHH). Cells were exposed to FGF23 (1, 10 or 100ng/mL) at different time points (6h, 24h, 48h). Cultures were performed in triplicates, and QRT-PCR in duplicates (StepOne Plus Real-Time PCR). Western Blots were also performed (Erk and Akt phosphorylation pathways, FGRF1, FGRF3, ferritin).

Results: In HepG2, even though FGF2R1 expression was found by Western blot analysis, FGF23 did not modify hepcidin expression by QRT-PCR, and Erk/Akt pathways were not activated by FGF23. In HepaRG cells, hepcidin expression was modified with FGF23 by QRT-PCR, i.e. increased at 6 hours and decreased at 24 hours.

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

Underline represents presenting author.

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PUB540

Prevalence of Hyperparathyroidism and Its Correlates in a Large Cohort of Hemodialysis Patients Pasquale Esposito,1 Fabio Malberti,2 Elena Caramella, Marta Calatroni,1 Edoardo La Porta,1 Marina Foramitt2, Rosanna Coppo,1 Antonio Dal Canton.1 Nephrology, Fondazione IRCCS, Pavia, Italy; 2 Nephrology, Istituti Ospitalieri di Cremona, Cremona, Italy; 3 Nephrology, Regina Margherita Children’s Hospital, Turin, Italy.

Background: Beyond experimental setting of randomized trials, little is known about the occurrence of mineral bone disorders (MBD) in the real-life clinical practice of hemodialysis (HD). This is the reason why we designed this observational study to define the prevalence of hyperparathyroidism (HPT) and its correlates in a large cohort of HD patients.

Methods: We enrolled HD prevalent patients from 38 Dialysis Units collecting data on: clinical information, dialysis parameters, biochemical and instrumental evaluations and pharmacological therapy. According to the KDIGO guidelines we divided the patients in: patients affected by HPT (i.e. PTH > 9 the upper reference limit of each laboratory) vs patients on target.

Results: Out of 495 patients, 34 (6.8%- 59.9% in 15.5 years, 53%M) presented HPT with mean PTH of 1064±536 pg/ml, while 461 patients resulted OHT (93.2%- 66.9;±13.7 years, 66%M), mean PTH 242±151 pg/ml (p<0.001). HPTs were younger than OHT (59.9±15 vs 69.9±13.7 years, p=0.008), with a longer HD history (126.2±125 vs 64.3±69 months, p=0.003). There were not significant differences in both clinical and dialysis parameters. Similarly, there were not differences in laboratory examination except from serum ALP that resulted higher in HPTs (194.8±142 vs 144.1±108 U/l OT, p<0.01). Moreover, there were not differences in the use of phosphate binders, whereas a significantly higher percentage of HPTs was taking paracalcitol and calcimetics and the prescribed vitamin D doses (both as calcitriol and paracalcitrol) were significantly higher in HPT patients.

Conclusions: The prevalence of HPT in our population was surprisingly lower, compared to that reported in previous studies. This finding could be due to the general application of KDIGO guidelines, which recommend more permissive PTH levels compared with the previous K/DOQI guidelines, thus to the availability of effective drugs, probably used more appropriately than in the past.

PUB541

Effect of Vitamin D Receptor Activators on Glomerular Filtration Rate: A Meta-Analysis and Systematic Review Qian Zhang, Jing Chen. Div of Nephrology, Huashan Hospital, Fudan Univ, Shanghai, China.

Background: Vitamin D receptor activators (VDRAs) can protect against mineral bone disease, but they may also elevate serum creatinine and reduce glomerular filtration rate (GFR).

Methods: We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) to evaluate the effect of VDRAs on kidney function and adverse events. MEDLINE, EMBASE, the Cochrane Controlled Trials Register were searched for RCTs that evaluate vitamin D receptor activators (alfacalcidol, calcitriol, doxercalciferol, falcacidinol, maxalcalcitin and paracalcitrol) up to March 2015.

Results: We included 31 studies, all of which were performed between 1976 and 2015, which enrolled 2621 patients. Patients receiving VDRAs had lower eGFR (weighted mean difference WMD=-1.29 mL/min/1.73 m², 95% CI -2.42– -0.17) and elevated serum creatinine (WMD 7.03 µmol/L, 95% CI 0.61–13.46) in sensitivity analysis excluding studies with dropout rate more than 30%. The VDRAs and control groups had no significant differences in all-cause mortality (relative risk RR 1.41, 95% CI 0.58–3.80), cardiovascular disease (RR 0.84, 95% CI 0.42–1.71), and severe adverse events (RR 1.15, 95% CI 0.75–1.77). Episodes of hypercalcemia (RR 3.29, 95% CI 2.02–5.38) were more common in the VDRAs group than in the control group.

Conclusions: Although administration of VDRAs slightly reduced the eGFR, all-cause mortality and severe adverse events were comparable between the groups. Future RCTs with larger sample sizes are needed to assess whether the mild reduction of eGFR is of clinical significance.
Low Dose Cholecalciferol Supplementation on Serum Inflammatory Markers in Hemodialysis Patients with Hypovitaminosis D

Vitamin D deficiency is common in hemodialysis (HD) patients and has been reported to be associated with mortality due to cardiovascular disease and an inflammatory response. The aim of this study was to investigate the hypothesis that low dose cholecalciferol supplementation improves serum 25(OH)D and 1,25(OH)D levels, and reduces inflammatory markers. Moreover, it was to analyze the association of FGF-23 and 25(OH)D levels.

Methods: This study was an one-year intervention study for hemodialysis patients with hypovitaminosis D (25(OH)D<30 ng/mL). During the first six months, the patients received 3,000 IU of cholecalciferol after each hemodialysis (9,000 IU/week), thereafter, they stopped taking supplements. Serum levels of 25(OH)D, 1,25(OH)D, and other biological variables were measured every 3 months for one year. We investigated the effects of cholecalciferol supplementation on the biological variables and inflammatory markers. In addition, the effective factors on the levels of 25(OH)D and 1,25(OH)D after cholecalciferol supplementation were assessed by multivariate regression analysis.

Results: Twenty-nine patients with hypovitaminosis D participated in our study. During cholecalciferol supplementation, the 25(OH)D and 1,25(OH)D concentration significantly increased from baseline to six months [9.9 to 34.3 ng/mL (p<0.001) and 19.7 to 22.9 pg/mL (p<0.05), respectively]. At 6 months, 65.5% of the patients had 25(OH)D levels within the target range [30 ng/mL] with a low dose of cholecalciferol supplementation. Also serum calcium and phosphorus levels did not increase above the normal range. However, the inflammation markers, hsCRP, e-selectin, VEGF-A, were not shown significant improvement after taking cholecalciferol supplements. The effective factors on serum 25(OH)D levels were BMI, baseline 1,25(OH)D and 6 months FGF-23 concentration by multivariate regression analysis.

Conclusions: The low dose cholecalciferol supplementation was effective in correcting serum vitamin D deficiency or insufficiency and safe for hemodialysis patients. However, 6 months of low dose cholecalciferol supplementation in these patients did not improve serum vitamin D deficiency or insufficiency and safe for hemodialysis patients. However, the inflammation markers, hsCRP, e-selectin, VEGF-A, were not shown significant improvement after taking cholecalciferol supplements. The effective factors on serum 25(OH)D levels were BMI, baseline 1,25(OH)D and 6 months FGF-23 concentration by multivariate regression analysis.

Effect of Intravenous Saccharated Ferric Oxide on FGF23 Metabolism in Dialysis Patients

Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone, secreted from the bone. It has been well known that the reduction in serum phosphate occurs following intravenous administration of saccharated ferric oxide. A recent clinical study showed that both production and degradation of FGF23 is enhanced in the setting of iron deficiency (M Wolf. J Bone Miner Res 2013). These findings suggest that iron may be a key regulator of FGF23. However, its precise mechanism remains to be elucidated.

Methods: We previously reported that intravenous saccharated ferric oxide further increase in elevated serum FGF23 levels in hemodialysis patients with iron deficiency anaemia, using the intact FGF23 assay which only detects the full-length protein (Am J Nephrol 2011). In this study, we additionally examined the FGF23 levels by the C-terminal FGF23 assay which detects both the full-length protein and C-terminal fragments, and compared the results of these two assays (N = 27).

Results: We previously reported that intravenous saccharated ferric oxide further increase in elevated serum FGF23 levels in hemodialysis patients with iron deficiency anaemia, using the intact FGF23 assay that only detects the full-length protein (Am J Nephrol 2011). In this study, we additionally examined the FGF23 levels by the C-terminal FGF23 assay which detects both the full-length protein and C-terminal fragments, and compared the results of these two assays (N = 27).

Conclusions: Collectively, in hemodialysis patients with iron deficiency anaemia, substantial amounts of C-terminal fragments of FGF23 accumulate by increase in both the production and degradation. The administration of saccharated ferric oxide suppresses both the production and degradation, leading to increase in values of intact FGF23 assay and decrease in those by C-terminal assay. Specific preparations of iron for intravenous use may regulate both the production and degradation of FGF23.

Serum Levels of Sclerostin (SOST) in Renal Transplantation (Tx)

Sclerostin is a negative regulator of bone metabolism. In CKD patients SOST serum levels are higher than in the general population and in HD patients SOST correlate negatively with bone turnover. Little is known about serum levels of SOST in Tx. Aim of our study was to evaluate serum SOST levels in Tx in whom few data are available.
Methods: We performed a cross sectional study in 80 Tx (55:10 y.o.:49M/31W) with CKD stage 2-4 (eGFR 47±16 ml/min). 30 healthy subjects (34:12 y.o.:eGFR59±19 ml/min) were the control group. We evaluated in all patients SOST, Ca, Pi, PTH, FGF23 and Alkaline Phosphate (AP).

Results: SOST was not different between Tx and controls (27.6±10.2 vs 23.6±8; p<0.05). The table shows the mean values of the parameters evaluated With mild vitamin D insufficiency (25D<26.1±11ng/ml), TX had normal 1,25D values, mild increment of PTH and Ca, and normal values of Pi.

Serum levels of FGF23 were increased compared to controls (47.3±13.6 vs 30.1±19,0 pg/ml; p<0.05). SOST showed a negative correlation with AP (r=-0.37; p<0.05) and a positive correlation with FGF23 (r=0.56; p<0.05) and 25D (r=0.28; p<0.05). No correlation existed with other parameters

Conclusions: eGFR does not affect serum levels of SOST in Tx. The negative correlation with AP indicates that SOST maintains its modulatory role of osteoblastic activity in this population. The correlation with FGF23, which is in agreement with low FGF23 in SOST null mice, suggests modulatory effects of both proteins on osteoblastic direct, through Wnt inhibition, for SOST; indirect, through effects on 1,25D levels, for FGF23. Serum SOST may be an additional marker of bone metabolism, useful to understand metabolic pathways in normal subjects and in CRF.

PUB547

Comparison of Cholecalciferol Supplementation Dosing with a Bolus Dose Versus Daily Administration in Chronic Hemodialysis Patients 
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Background: The aim of this study was to assess the safety profile of bolus cholecalciferol supplementation and compare its effectiveness to daily oral administration in hemodialysis (HD) patients

Methods: This 6-month prospective, intervention study enrolled 60 stable HD patients with 25-hydroxyvitamin D (25(OH)D) levels <30 ng/ml, who received cholecalciferol (25,000 IU/week or monthly oral cholecalciferol levels >70 IU daily (n=30). Differences in biochemical parameters, including 25(OH)D, calcium, phosphorus, parathyroid hormone (PTH), alkaline phosphatase and C-reactive protein levels, were analyzed monthly. Primary outcome was 25(OH)D level at 6 months. For safety purposes, in the subgroup of patients receiving the bolus regimen, biochemical parameters were also assessed on days 2,4 and 7 after the first bolus dose.

Results: At baseline, patient and biochemical characteristics were similar in both groups. No changes were observed in calcium, phosphorus and 25(OH)D levels in the first week after the first bolus dose. Throughout the 6-month follow-up similar responses in 25(OH)D levels and other biochemical parameters were observed in both groups.

Conclusions: Supplementation of 25,000 IU fortnightly or monthly oral cholecalciferol seems to be safe, being equally effective for raising 25(OH)D levels than 700 IU daily cholecalciferol administration.

PUB548

The Prevalence of Vitamin D Deficiency Among IgA Nephropathy: A Cross-Section Study from One Center  
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Background: Low serum vitamin D concentrations have been reported in chronic kidney disease (CKD). Very few studies concerns vitamin D deficiency of IgA nephropathy (IgAN) in Chinese patients. Our aim is to assess the deficiency of serum 25(OH)D concentrations in patients with IgAN, and to explore the possible correlated factors contributing to Vitamin D deficiency.

Methods: 283 patients who come from north China and were not receiving vitamin D supplementation were included in this study from February 2013 and April 2014. We collected blood samples to determine levels of Scr, BUN, UA, serum phosphate (P) and calcium (Ca), iPTH, albumin, as well as urinary excretion of creatinine, protein, P and Ca within 24h. Electrochemiluminescence immunoassays measured total 25-hydroxyvitamin D. Vitamin D deficiency should be defined as a 25(OH)D of < 15 ng/ml

Results: All of the 283 patients, 25(OH)D concentration was 10.25±6.94 ng/ml. Only 18.82% of the patients had a circulating 25(OH)D level greater than 15ng/ml. The prevalence of deficiency (<15ng/ml) were 87.2%, 72.9%, 75.0%, 85.4%, 93.1%(P<0.000) at different CKD stages.All the 120 IgAN patients were divided into 4 groups according to eGFR. The prevalence of vitamin D deficiency were higher in CKD stage 1 and 4 (p<0.001), but there is no difference of average 25(OH) D concentration according to eGFR (P>0.05). The 25(OH)D concentration was higher in IgAN than MN and DN patients. But, 24UPR in IgAN patients was lower than MN and DN patients. In different age, gender, season, BMI or iPTH group, 25(OH)D levels were not affected, but 25(OH)D level was lower in '3.5±24h group.

Conclusions: For the IgAN patients in north China, kidney function might be related to vitamin D deficiency, and 24UPR may play a very important role in maintaining 25(OH) D serum concentrations.

PUB549

Utility of Whole Exome Sequencing in the Diagnosis of a Family with Apparent Mineralocorticoid Excess  
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Background: Apparent Mineralocorticoid Excess (AME) is a rare familial disorder with hypertension, hypokalemia, metabolic alkalosis and low plasma renin and aldosterone due to mutations in the 11-β-hydroxysteroid dehydrogenase-2 (HSD11B2) gene. Five siblings of a third degree consanguous family with unaffected parents were evaluated for hypertension of juvenile onset. They had varying degrees of hypokalemia, medullary nephrocalcinosis, concentric left ventricular hypertrophy and renal dysfunction. Plasma renin and aldosterone levels were low. Given the clinical picture and autosomal recessive inheritance pattern, a provisional diagnosis of AME was made. 24 hour urinary cortisol and cortisone estimation was unavailable. We decided to confirm the diagnosis using next generation gene sequencing.

Methods: Whole blood was collected from the parents and the affected members after informed consent. 30 ng of the isolated high quality DNA was used to prepare library and sequencing. Sequencing was performed using v3 reagents to generate over 49.48 million paired end reads of 101bp. The reads were aligned to the Human genome (hg19 build, UCSC) and was further filtered for read duplicates, recalibrated and realignment was performed around well-annotated Indels from the 1000 genome project using GATK and Picard tools. Variations were called using the GATK Unified Genotyper and analysed using ANNOVAR and annotated ClinVar.

Results: Analysis revealed the presence of homozygous variation p.R337C in HSD11B2 gene annotated to be pathogenic in ClinVar and predicted to be deleterious using PROVEAN in the affected siblings. The variant was further validated using Sanger sequencing of the amplicons, confirming the diagnosis. Both parents were heterozygous for the variation. This variation has been reported to be associated with the similar phenotype in two independent studies on native American populations.

Conclusions: A homozygous mutation (p.R337C variation) in the 11HSD2 gene was demonstrated in the family using whole-exome sequencing. This is the first genetically demonstrated Syndrome in the family with whole-exome sequencing. This is the first genetically characterized report of AME from Indian population. Our study underscores the utility of using next generation sequencing in the diagnosis of rare inherited diseases.

Funding: Government Support - Non-U.S.

PUB550

Genetics of Thrombotic Microangiopathies – The Viennese TMA Cohort  
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Background: Thrombotic microangiopathies (TMA) classified as hemolytic uremic syndrome (HUS) are characterized by acute kidney injury (AKI), mechanical hemolysis and thrombocytopenia, caused by an excessively activated alternative pathway of the
publication

complement system. This is a result of either genetic alterations within complement factors and regulatory proteins or secondary causes. The aim of this study was to symptomatically investigate our cohort of patients with TMA regarding genotype and triggers of disease episodes.

Methods: Data were analyzed by means of patient records: Demographic and laboratory data, results of kidney biopsies, results of genetic sequencing of complement regulatory proteins, CFH, thrombomodulin (THBD) and C3, and medical history for triggering factors were analyzed.

Results: Out of 92 patients with TMA we classified 30 as atypical HUS (aHUS), 1 as classic HUS, 21 as secondary HUS. At onset of disease patients with aHUS had a mean age of 25 years (range: 1-47), 20 were female (67%), and 13 (43%) were kidney transplant recipients. First presentation of 24 patients was AKI, 3 showed hemolysis, 2 had pre-eclampsia and 1 HELLP-syndrome. Distinct triggering factors in 20 patients were: infection (n=10), pregnancy (n=2), surgery, diarrhea and renal transplantation (each n=1). Thirteen and 3 showed a CFH-H3 and a MCPggaac risk haplotype, respectively; potentially disease-causing mutations were identified in 22 patients (7 CFH, 6 CD46, 5 CFI, 4 C3, 2 CFB, 1 THBD; 4 of them with more than 1 mutation); 7 showed wild-types and no data existed for 1 patient.

Conclusions: In our cohort of TMA patients we identified 30 cases of aHUS. In 22 patients (74%) we identified a mutation within genes of the complement regulatory proteins or C3, whereas 7 subjects showed wild-type sequences despite presenting with a classic phenotype of aHUS.
without IgG or C3. Metabolic analyses showed an elevation of plasma homocysteine, methylmalonic acid, and propionylcarnitine concentrations. Genetic analyses found a compound heterozygosity in MMACHC gene, with c.271dupA and c.82-9delTTTC mutations. The patient’s brother died at the age of 17. Autopsy revealed pulmonary capillary hemangiomatosis, while the kidney histology showed similar lesions to those of his brother.

Conclusions: This is the first report of late-onset rTMA, atypical glomerulopathy, and PAH associated with cblC deficiency. We suggest that the association of rTMA and/or glomerular proteinuria with PAH in children and young adults should prompt metabolic investigations to identify cblC deficiency, and provide early specific management including hydroxycoenzyme A, folinic acid, and betaine.

PUB555

The DS3 Scores and Quality of Life in Japanese Patients with Fabry Disease

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Background: Fabry disease (FD) is the lysosomal storage disorder, caused by the deficiency of lysosomal hydrolase α-galactosidase A activity. Various symptoms associated with renal disease, heart lesion and cerebrovascular disease occur in Fabry disease patients. Thus, the quality of life (QoL) would be altered with the disease progressed. We evaluated the clinical severity and the QoL in a sample of Japanese patients with Fabry (FD) disease using the Disease Severity Scoring System (DS3) and the SF-36 survey in male and in female.

Methods: Observational cross-sectional study. The DS3 and SF-36 survey was administered to the patients of the hospitals, which belong to the research group of Kanagawa enzyme replacement therapy. Participants were treated with agalsidase-alpha or agalsidase-beta. Disease activity was assessed by the Disease Severity Scoring System (DS3). The QoL was measured by Short form-36 (SF-36) and the Kidney Disease Qol. Short form version 1.3 (KDQol).

Results: Fifteen patients were included in the study. Mean age was 45 years (M/ F=10/5), and all patients were receiving ERT. The mean serum Cr was 2.9 mg/dl. The DS3 scores were follows; mean assessment score: 26.5 +/- 10.1, average domains: 10.5 +/- 9. The renal domain and the cardiac domain showed relatively high score compared to PNS and CNS scores. The QoL scores of the FD patients were lower than those of general population, but the scores were better than the previous reports of FD from U.S. or EU. The mental component summaries of women were similar to those of the general population. The physical component summaries of QoL were negatively associated with the KDQol (-0.554; p=0.001).

Conclusions: Japanese patients with FD receiving ERT had a relatively good QoL beyond anticipation. DS3 score is useful for assessing disease severity, and may predict some components of QoL.

PUB556

Two Cases of Fabry Disease in Women with Proteinuria Diagnosed by Molecular Analysis of α-Galactosidase A Gene and Kidney Biopsy

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Background: Fabry disease is a X-linked lysosomal storage disorder caused by deficiency of α-galactosidase A. This abnormality in enzyme results intracellular accumulation of globotriaosylceramide and leads to severe neuropathy with progressive renal, cardiovascular, and cerebrovascular dysfunction and early death. We report 52 and 55 year-old women with proteinuria and hematuria, which were proven to be due to Fabry disease.

Methods: A 52 and 55 year-old women was admitted to the hospital due to proteinuria. They denied previous histories of hypertension, diabetes mellitus, pulmonary tuberculosis, and nephritis. Their sister and cousin diagnosed fabry disease. Physical examination revealed nonspecific findings. On admission, blood pressure 110/60 mmHg, heart rate 64/min, respiratory rate 16/min, body temperature 36.5°C. Lungs were clear and heart was normal. The extremities showed no edema, cyanosis or skin rashs. The laboratory data showed the WBC 3560/mm³, HB 13.2 g/dl, Platelet 212,000/mm³, BUN 10.2 mg/dl, serum creatinine 0.7 mg/dl. Urinalysis showed pH 5.0 SG 1.023 protein + RBC 5-9/HPF WBC 5-9/HPF. 24-hour urine protein was 533 mg. Abdomen & Pelvic CT and echocardiography were normal. The senologic study was normal. The kidney biopsy showed expansion of mesangial matrix and glomerular hypertrophy. The cytoplasm of podocytes was vacuolated, which consisted of multiple, variable-sized, concentric electron-dense lamellated structures, by electron microscopy.

The enzyme activity for α-galactosidase in serum was 0.59 nmol/min/mg protein.

Conclusions: The patients received enzyme replacement therapy every other week. They had reduction in proteinuria and normal renal function.

PUB557

Intradaylisis Partial Parenteral Nutrition (IDPN) in Hemodialysis Patients (HDP) with Protein Caloric Malnutrition (PCM): Preliminary Results

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Background: PCD is higly prevalence in HDP and predicts morbi-mortality. NPID is according Esben Guidelines (march2012) and the SMOFF formula(uoja,TG,olive oil and fish oil), improve inflammation and lipid status.Our goal is to define the evolution of nutritional parameters in HDP and characterize them for future interventions. OBJETIVE: To evaluate if severe PCD in HDP, improve malnutrition and inflammation markers such as albumin(Ab),cholesterol (Ch), reactive C protein(RCP).

Methods: Prospective and observational study that included 14 patients up this time,both sexes,age27-80 years old, in maintenance HD from a University Hospital and Army Hospital.Patients signed informed consent. Patients received each HD session and during six months,SMOF lipids 4 gr/kg/dy IV continuous infusion. We analyzed weight, Hematorcrit,Alb,Ch,TG,creatinine,RCP and Global Subjetive Valorization(GSV) in pre HD blood samples at the beginnig,three and six months.Cuantitative demographic variables(age,sex,biochemic parameters)were expressed as medium,SD and applied Student Wilcoxon Test and Chi Test (p<0.01).

Results: fourteen patients improved weight(63,1+/-3,3vs64,9+/-3,5,p:0,311),albumin(g/dl)(33,3+/-1,27/6.94vs33.7+/-1.3,p:0.856),CH(mg/dl)(28,9+/-6,7vs10,1+/-2,5,p:0.009),there were not statical significance inHto(gr/dl)(13,3+/-1.9vs33,7+/-1.7,p:0.856),creatinine(g/dl)(7.7+/-0.7vs7.4+/-0.5,p:0.233). In proteinuria there was not statical significace in RCP(mg)(28,9+/-6.710,1+/-2,5,p:0,009).there were not statical significance in fat(g)(163,9+/-12.9vs165+/-13.9,p:0.846)

Conclusions: 1- NPID is a successful tool as partial suplementation in HDP with oral dietary intake.2-In spite of our sample is small, the improvement of Nutritional and inflammatory status, applying Internatmeal Guidelines was observed after three months of treatment.3- Medical awareness about nutritional risks in HDP, is the best tool to prevent alteration of nutritional status 4-We`ll expand the sample.

PUB558

Association of Protein Energy Wasting with Income in Chronic Kidney Disease Stage 3 Patients

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Background: Protein energy wasting (PEW) is a major challenge in CKD. Purpose: Assessment of PEW in predialysis patients at first visit to a nephrologist.

Methods: Three day dietary intake of 484 CKD stage 3 patients. Patients were divided in to groups based on appetite and BMI.

Results: Male and female parameters: Serum albumin 3.70±0.84/3.68±0.81g/dl;total protein 7.02±1.27/6.94±1.26 g/dl;creatinine 4.68±4.19/3.74±3.36 mg% creatinine clearance 33.22±30.48/37.55±33.87 ml/minute, BMI 22.60±4.29/23.43±4.77 kg/m² energy/kg 16.97±0.65/16.8±0.64, protein g/kg 6.65±0.28/6.46±0.30, carbohydrate g/kg 2.98±1.54/2.88±1.36, fat g/kg 2.96±0.23/2.79±0.22, respectively. As appetite decreased dietary protein and energy intake decreased significantly.
Appetite was average 14.46% (± 1.23) poor 9.7% (± 1.18), anorexic 33.2% (± 4.7) in males and females. Income correlated with BMI (p < 0.001), dietary protein (p < 0.001) energy (p < 0.001), and carbohydrate (p < 0.001). Appetite correlated with creatinine (p < 0.019), dietary energy, protein, carbohydrate, and fat intake (p < 0.001). BMI correlated with protein, fat, carbohydrate, energy and creatinine intake. Anova showed significant difference among groups in energy, protein, fat, carbohydrate, creatinine intake (p < 0.001) and serum creatinine (p < 0.001) and serum creatinine intake (p < 0.001) between groups. Based on income there was significant difference between groups in BMI (0.001), energy intake (p < 0.019), protein (p < 0.01), albumin (0.001).

Conclusions: With decline in renal function, appetite worsened and nutritional intake decreased. Energy intake was significantly deficient. 84% patients had reduced appetite and 69.2% had PEW. Low income is a risk factor for PEW in CKD.

PUB589
Study on Correlation Between Serum Creatinine, Cystatin-C, Urinary Albumin
Cystatin Ratio and Body Composition
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Background: Based on an epidemiological survey in Peking, China, to study the correlation between serum creatinine, Cystatin-C and urinary albumin cystatin ratio (ACR) and body composition.

Methods: Residetns over the age of 35 of the Beijing Pinggu District by random sampling method. Laboratory test: take morning ACR, blood samples were taken for blood routine, kidney function test. Body composition analysis after emptying the bladder by using INBODY-720 machine.Use SPSS 17.0 software for data statistical analysis, count data were analysed by using multivariable linear regression.

Results: A total of 9283 people participated in the survey, which 4324 males, age 54.71±10.7 years, 4599 females, age 53.1±11.2 years. Male: 1) Human body cell mass (BCM) and ACR, Cystatin-C, no correlation, was positively correlated with height (B=0.43, P<0.01), and serum creatinine was that positive correlation (B=0.01, P<0.01). 2) Lean body mass (FFM) and ACR, serum creatinine, Cystatin-C, no correlation. 3) Skeletal muscle content and ACR, serum creatinine, Cystatin-C, no correlation. 4) Body fat mass and ACR, no correlation, and Cystatin-C was positively correlated with (B=0.79, P<0.01). Female: 1) Human body cell mass (BCM) with height and cystatin-c, no correlation, but positively correlated with serum creatinine (B=0.035, P<0.01), and ACR was negative correlation (B<0.005, P<0.05). 2) Lean body mass (FFM) and ACR, Cystatin-C, no correlation, and serum creatinine were positively related (B=0.035, P<0.01). 3) Skeletal muscle content and ACR, Cystatin-C, no correlation, and was positively correlated with height (B=0.031, P<0.01), and serum creatinine were positively related (B=0.035, P<0.01). 4) Body fat mass and ACR was negative correlation (B=0.01, P<0.05) Cystatin-C was positively correlated (B=12.3, P<0.01), and age were negatively correlated (B=0.13, P<0.01), and serum creatinine was negative correlation (B=0.092, P<0.01).

Conclusions: There was a positive correlation between serum creatinine and the human body cell mass (BCM), lean body mass (FFM) in men, and skeletal muscle content, body fat weight in women, but the correlation is not strong. The blood cystatin-C and body fat weight was positively correlated.

PUB560
Worsening Nutritional Status Assessed Is an Independent Predictor of All-Cause Mortality in Incident Dialysis Patients
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Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.

Background: Malnutrition is closely associated with mortality in end-stage renal disease (ESRD) patients. However, little is known whether improvement or deterioration of nutritional status after dialysis initiation affects clinical outcome. This study was aimed to elucidate the association between the changes of subjective global assessment (SGA) after dialysis initiation and mortality in ESRD patients.

Methods: Data were collected from the Clinical Research Center for ESRD cohort. SGA score was measured by trained investigators at the time of dialysis initiation and after 12 months. Nutritional status was defined as well-nourished (SGA 6-7), A, mildly to moderately malnourished (SGA 3-5, B), or severely malnourished (SGA 1-2, C). Severely malnourished patients (SGA C) were excluded due to small sample size. The patients were divided into four groups according to the change of SGA: group 1, b) group 2, A to B; group 3, A to B; and, group 4, B to B. Results: A total of 911 patients were enrolled. The mean age was 54.6±14.1 years, 554 patients (60.9%) were male. During a median follow-up duration of 30 months, 109 patients (12.0%) died. Survival rate of group 1 was the highest, and that of group 4 was the lowest (group 1, 77%; group 2, 72%; group 3, 64%; P<0.001). Worsening nutritional status was a significant risk factor for mortality (group 3 vs. 1, HR=3.15, CI=1.51-6.54, P<0.002), while baseline nutritional status at dialysis initiation was not (group 1 vs. 2, P=0.063; group 3 vs 4, P=0.107).

Conclusions: Improvement of nutritional status after dialysis initiation could be beneficial for patient outcomes regardless of baseline status, suggesting that intervention to improve nutritional status after dialysis initiation might be a strategy to reduce mortality in ESRD patients.

PUB561
Prophylactic Effect of Erythropoietin Injection to Prevent Acute Mountain
Sickness: An Open-Label Randomized Controlled Trial
Hyun Jhee, Soon Bae Kim
Div of Nephrology, Dept of Internal Medicine, Univ of Ulsan, College of Medicine, Asan Medical Center, Seoul, Republic of Korea.

Background: This study was performed to evaluate whether increasing hemoglobin before ascent by prophylactic erythropoietin injections prevents acute mountain sickness (AMS).

Methods: This open-label, randomized, controlled trial involved 39 healthy volunteers with hemoglobin $15.5g/dL, who were divided randomly into erythropoietin (n=20) and control (n=19) groups. Epoetin alpha 10,000 IU injections were given weekly for four consecutive weeks. On day 1, and 7 days after the last injection (day 29), oxygen saturation (SatO2), and hemoglobin were measured. The subjects departed Seoul on day 30 and arrived at ANNAPURA base camp (ABC, 4,130 m) on day 34. AMS was diagnosed when headache and Lake Louise score (LLS) of ≥ 3 were present. Immediate descent criteria followed US Army recommendations.

Results: Two groups differ in hemoglobin levels on day 29 (15.4 ± 1.1 vs 14.2 ± 1.0 g/dL, P<0.001). At ABC, erythropoietin group had a significantly lower mean LLS, AMS incidence, and number of subjects who met immediate descent criteria. Multiple logistic regression analysis showed that SatO2 < 87% and control group, but no hemoglobin < 15.0 g/dL, independently predicted satisfaction of immediate descent criteria.

Erythropoietin-related adverse effects were not observed.

Conclusions: Erythropoietin-related adverse effects were not observed. In conclusion, erythropoietin may be an effective prophylaxis for AMS.

Funding: Pharmaceutical Company Support - CJ pharmaceutical

PUB562
Nutritional Assessment for the Chronic Dialysis Patients with/without Sarcopenia
Miiho Suzuki, Yuya Sakai, Ikuto Masakane. Tabuki Hospital.

Background: A recent arising problem of chronic dialysis patients is sarcopenia closely related to malnutrition. Muscle loss deteriorates daily activities of dialysis patients and ultimately worsens the QOL and prognosis of the patients. The aim of this study was to clarify the relationship between the nutritional status and sarcopenia and to analyze the status of nutrient intake in these patients.

Methods: 90 chronic hemodialysis patients were enrolled to the current study. (age 62.8±5.4 years. Men were 76%, DM 41%).Skeletal muscle mass (SMM) was estimated by bioelectrical impedance analysis and a low muscle mass was defined by the SMM index (SMM [kg] / height [m]² > 7.0kg/m², women: 5.7kg).Muscle function was estimated by grip strength and walking speed as the Timed up and go test (TUG).A low grip strength was defined as less than 26 kg (men) or 18 kg (women). TUG less than 11 second was diagnosed as a low walking speed.Malnutrition was defined as by the Nutrition-Inflammation-Inflammation Score(MIS)(≥6point), GNRI(<92) and the criteria of protein energy wasting (PEW).The dietary assessment was performed by the food frequency questionnaire.

Results: Sarcopenia was identified in 22% of the subjects. The sensitivity to detect sarcopenia was not sufficient as 35% in MIS, 50% in GNRI and 10% in PEW. In the patients with sarcopenia, the average of total energy intake and protein was significantly lower than those in non-sarcopenia, 1618±122kcal vs 2041±65kcal in energy, 52±4g vs 68±2g in protein. The intake of fish and meats (110±15g vs 153±8g),beans (31±11g vs 61±6g),confectionery, beverages and sugar (126±77g vs 306±41g ) were significantly lower in sarcopenia than non-sarcopenia.

Conclusions: Malnutrition-related sarcopenia was only 10-50% among sarcopenia. It is important to measure muscle mass and muscle function regularly for dialysis patients because it is not enough to screen sarcopenia only by nutritional measurements. Sufficient protein and energy intake are essential for the prevention of sarcopenia. If patients don’t have appetite,confectionery or a beverage or sugar may be acceptable for the prevention of muscle loss.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Stomach Acid Reducers May Predict Nutritional Deficiency in Dialysis Patients

Klaia Bertes, Mihaly B. Tapolyai, Maria Faludi, Melinda Forro, Ákos Géza Pethő. Dialysis, Fresnes Medical Care Semmelweis Univ, Budapest, Hungary.

Background: Malnutrition is a major predictor of mortality among dialysis patients. Malnutrition markers are thus regularly monitored in order to intervene when the nutritional status may decline. We investigated whether taking stomach acid reducing medications may indicate future nutritional risk.

Methods: This is a cross sectional study of 103 patients undergoing chronic hemodialysis in Budapest, Hungary at a university hospital based dialysis unit. The patients’ nutritional indicators such as serum albumin, phosphorus, nPCR and whether they were on diet counseling were assessed. Information on medication were collected among those who did not take an acid reducing agent, such as a proton pump inhibitor (PPI) or H2 blocker.

Results: Six patients were excluded because data were incomplete or the patients had not been on dialysis for more than 2 months. Of the 96 patients 44% took an acid reducer on a regular basis. The serum albumin (3.7±0.02 mg/dL vs. 3.56±0.01 p<0.008), phosphating (1.88±0.49 mmol/L vs. 1.64±0.54 p<0.04) and nPCR (1.00±0.20 vs. 0.91±0.25: p=0.06) were lower among PPI takers. PPI takers were much more likely to be taking cholecalciferol for measured 25-OH-vitamin-D deficiency (1.8% vs. 18.1% p=0.01). While PPI takers were older (59.7±16.2 years vs. 65.7±13.3 p<0.04), there was no difference in the two populations in the presence of an AV Fistula, delivered Kt/V, calcium or serum bicarbonate.

Conclusions: We conclude that taking PPI’s or H2 Blockers in dialysis patients may be an indicator of being at risk for malnutrition.

Impact of the Potassium Additives on the Total Content of This Element in Processed Foods

Margareth Lage L. de Fornasari,1,2 Maria raquel Manhani,1 Yvoty As Sens.1,2
1 Post Graduation, Santa Casa de Sao Paulo School of Medical Sciences, Sao Paulo, SP, Brazil; 2 Nutrition, Sao Judas Tadeu Univ, Sao Paulo, SP, Brazil.

Background: The additives of potassium salts are allowed in processed foods to preserve, to inhibit mold, to emulsify products. Patients with chronic kidney disease need to control the intake of potassium, and are advised for doctors and dietitians to restrict potassium, mainly in patients with renal disease. Therefore, we aimed at this study to determine the actual potassium content of a number of products often consumed in the presence of an AV Fistula, delivered Kt/V, calcium or serum bicarbonate.

Methods: We collected two dialysis days (DD) and two on non-dialysis days (NDD) using the USDA 5-pass method. Dietary information was entered and analyzed using diet analysis software

Results: All products had potassium-containing additives listed among their ingredients. The medium values of potassium (mg for 100 g or mL) for the different foods were: milk beverages, yogurt, a type of cream cheese, margarine, tomato sauce, salad dressing, milk beverages, yogurt, a type of cream cheese, margarine, tomato sauce, salad dressing, powder, powdered juices, and had potassium sorbate or other potassium salts. The concentration of potassium (mg K/100 g of food) was determined by flame photometry according to the Adolfo Lutz Institute methodology, and in triplicate. The comparison of the potassium obtained with the expected potassium was based on two national reference tables.

Conclusions: Processed foods with potassium additives contain higher levels of potassium than those listed in reference tables.

Differences in Eating Patterns Between Maintenance Hemodialysis Patients from the U.S. and the UK

Anabel Birute,1 Brandon Kistler,1,2 Kristin P. Wiens,1,2 Peter J. Fitschen,1 Alice C. Smith,1 Ken Wilund1
1 Univ of Illinois; 2 Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; 3 Univ of Delaware.

Background: Maintenance hemodialysis (HD) patients in the United States (US) have poorer nutritional status than their European counterparts. The characteristics and clinical practices are hypothesized to contribute to these differences. Therefore, our aim was to compare eating patterns between HD patients from the US and the United Kingdom (UK).

Methods: HD patients (US=86,UK=29) were recruited. Four 24-hour diet recalls were collected, two dialysis days (DD) and two on non-dialysis days (NDD) using the USDA 5-pass method. Dietary information was entered and analyzed using diet analysis software and then grouped into eight food categories according to NHANES. Food security was measured 25-OH-vitamin-D deficiency (1.8% vs. 18.1% p=0.01). While PPI takers were older (59.7±16.2 years vs. 65.7±13.3 p<0.04), there was no difference in the two populations in the presence of an AV Fistula, delivered Kt/V, calcium or serum bicarbonate.

Conclusions: Processed foods with potassium additives contain higher levels of potassium than those listed in reference tables.

Is Reverse Epidemiology in BMI of Maintenance Hemodialysis Patients Adaptable to the Patients without PEW?

Yuya Sakai, Miho Suzuki, Ikuto Masakane. Yabuaki Hospital.

Background: Reverse epidemiology has been addressed in Body mass index (BMI) of chronic hemodialysis patients; the lowest mortality rate in BMI 24-26 as reported by the Japanese Society for Dialysis Therapy. The higher BMI the lower mortality as stated by the Dialysis Outcomes and Practice Patterns Study. However, because these survey subjects included lower BMI patients with malnutrition and chronic inflammation, the high BMI patients’ mortality risk might have been relatively low. The optimal BMI derived from these epidemiological analysis may not be well indicated for the patients who do not have malnutrition and inflammation. So, we aim to study the optimal BMI of maintenance hemodialysis patients without Protein Energy Wasting (PEW).

Methods: 183 patients on maintenance hemodialysis patients were enrolled in the current study. All subjects have over 2 years of dialysis diagnosis and are not applicable to PEW and don’t have inflammation which was defined as CRP less than 0.3 mg/dL as of December 2009. The observation period is from December 2009 to December 2014. The subjects were classified into 4 groups on BMI scale (<18.5, 18.5≤22.8, 22.8≤25, 25≤27.5). The 5-year cumulative survival rate, the death risk factor, and each BMI groups’ relative mortality risk for BMI 22≤25 group were examined.

Results: During the observation period, clinical deaths resulted in 19 patients, changing hospital or accidental death resulted in 22 patients. There was no significant difference in cumulative survival rate of BMI groups. Age, diabetes mellitus, albumin were dependent risk factors for death. When the mortality risks were adjusted by these 3 parameters, the mortality risk of BMI ≤18.5 was significantly higher than each of the 3 BMI groups (HR 6.97, P=0.0017). The mortality risk of BMI <25 was relatively higher than BMI 22<25 group but not significant.

Conclusions: In the maintenance hemodialysis patient without PEW syndrome and inflammation, the patients of BMI <18.5 have a higher risk of death so they require nutritional management to maintain and/or achieve a BMI ≥18.5. Reverse epidemiology in BMI was not applicable to the Japanese dialysis patients without PEW and inflammation.

Body Weight and Proteinuria Determine Plasma Triglycerides via Hepatic Syndecan-1/Heparan Sulfate in Experimental Nephrosis

Santia Aden,1 Harry Van Goor,2 Gerjan Navis,3 Stephan J.L. Bakker,1 Jacob van den Born.1,2 Nephrology, Univ Med Center Groningen, Netherlands; Pathology, Univ Med Center Groningen, Netherlands.

Background: Dyslipidemia contributes to a high cardiovascular risk profile of proteinuric patients. Via its hepatic uptake receptor (HS) side chain, syndecan-1 (syn-1) is a major uptake receptor of remnant lipoproteins. We hypothesized that proteinuria induces changes in hepatic syn-1/HS metabolism leading to dyslipidemia, which is reversed by caloric restriction (CR).

Methods: We used the hypertensive rat MWF proteinuria model. Male rats (22 wks) were nephrectomized and fed ad libitum (AL) food (MWF-AL; n=14), or CR (MWF-CR; n=13, 60% of MWF-AL food intake). Wistar rats matched for sex, age, nephrectomy on AL food intake served as controls (W-AL; n=6). Sacrification is at 48 wks. Wistar control rats were sacrificed at 22 wks (Young W-AL; n=6). Body weight, blood pressure, plasma creatinine, cholesterol, triglycerides, and proteinuria were measured at 22 and 48 wks. Livers were used for qRT-PCR and immunostaining. Correlation analysis was done by linear regression analysis.

Results: Renal aging (W-AL vs Young W-AL) was associated by mild proteinuria and dyslipidemia (both p<0.05). Compared to W-AL rats, at 48 wks MWF-AL rats developed hypertension, proteinuria, reduced creatinine clearance (all p<0.05) and comparable dyslipidemia. CR reversed all these parameters in MWF-CR compared to W-AL rats (p<0.05). Hepatic syn-1/HS side chain remodeling was associated by increased HS sulfation in proteinuric W-AL and MWF-CR. CR normalized syn-1 protein levels and increased HS sulfation. Syn-1 appeared positively (r=0.366, p<0.02) and HS sulfation inversely (r=-0.450, p<0.005) associated with plasma triglyceride concentrations. Both associations were lost after adjustment for body weight or proteinuria.

Conclusions: CR normalized hypertension, renal function, proteinuria, dyslipidemia and syn-1/HS in MWF rats. Regression analysis suggests that body weight and proteinuria reduce hepatic HS sulfation, leading to hampered TRL binding and uptake and increased TG values.

Funding: Government Support - Non-U.S.
PUB568

Obese Donors: The Multidisciplinary Approach in Improving Outcomes

Giselle Guerra,1 Ian Thomas,1 Panagiotis Tryphonopoulos,2 Linda J. Chen,2 Gaetano Ciancio.2 1Dept of Medicine, Miami Transplant Inst, Miami, FL; 2Dept of Surgery, Miami Transplant Inst, Miami, FL.

Background: Living donation appears safe over the years but concerns still exists long term. Analyses similar of unilateral nephrectomy have included patient compliance issues, changes to doses in response to serum drug levels closely monitored. Patients are satisfied with the new homecare service and clinicians value the use of Pharmacist Independent Prescribers has insured the whole pathway is efficient and the nephrologist for clarification and interventions.

Methods: A single center retrospective analysis was performed at out transplant center. Study period: January 1, 2013 – November 30, 2014. LDK ages 18-65 were assessed: 1. Study Arm (SA): obese LDK with BMI>30 who were enrolled into a nutritional program. 2. Control arm (CA): non-obese living donor candidates at the time of referral. Weight loss prior to surgery and afterwards, surgical complications, loss of kidney function (eGFR), and proteinuria (spot urine protein/spot urine creatinine ratio) after 6 months from donation were reviewed.

Results: Patient demographics - SA:15 African Americans (AA), 13 Hispanics (H), 7 White, 1 Other, 3 Unknown versus CA: 55 H; 49 Whites; 20 AA; 5 Other [figure1]. In the SA: 24/40 had BMI>35 at time of referral and placed in nutritional program; 8/24 dropped BMI to less than 35 prior to surgery and 3/24 pending surgery now; 4/24 ruled out due to medical issues & (9/24) were non-compliant. Surgical complications 1/8: Parasthesia. After donation in SA, blood pressure remained stable, 2/8 gained weight, kidney function at 6 months: 47% of obese donors had a decrease in eGFR at 6 months of 40% or greater. The mean decrease in eGFR was 33.9% in the study arm. In the control arm: 55Hispanics; 49 Whites; 20 AA; 5 Other. 15% had a decrease in eGFR at 6 months 40% or greater and the mean decrease in eGFR was 28.9.

Conclusions: Obese living donors needs careful analysis especially in minority populations since there is a trend to have a greater loss in kidney function after donation. Donation is possible but strict nutritional and guidelines and medical evaluation need to persist for the wellbeing of these patients long-term.

PUB569

The Role of Renal Pharmacist in Prescribing Immunosuppressant Medication for Renal Transplant Patients to Improve Safety

Jrrt Baig, Preetham Boddanna. Pharmacy Dept, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, Gloucestershire, United Kingdom.

Background: This paper describes the safe and efficient repatriation of renal immunosuppressant prescribing from General Practitioners (GPs) to secondary care using hospital Pharmacist Independent Prescribers (PIPs).

Methods: From March 2015 the UK commissioner NHS England required all renal immunosuppressant medication, which was traditionally prescribed by GPs following nephrologists’ advice, to be prescribed by hospital renal prescribers. Gloucestershire hospitals NHS Foundation Trust decided to use Pharmacist Independent Prescribers to implement this change and provide the ongoing service using commercial Homecare Companies. All Patients were initially sent detailed information about the changes and asked to consent. On receipt of the completed consent form the PIP wrote the initial homecare prescription which was then processed by the pharmacy homecare team. Patients continued to be reviewed at regular intervals by their nephrologists. Details of these consultations were documented using a central renal database which included graft function, drug levels to be reviewed at regular intervals by their nephrologists. Details of these consultations were documented using a central renal database which included graft function, drug levels and communications with GPs. The Pharmacist Prescribers subsequently reviewed the renal database prior to generating new homecare prescriptions and, when necessary, contacted the nephrologist for clarification and interventions.

Results: This service reconfiguration has resulted in safe and robust pathway. The use of Pharmacist Independent Prescribers has insured the whole pathway is efficient and closely monitored. Patients are satisfied with the new homecare service and clinicians value the pharmacists’ input. Pharmacist prescribers have made a number of interventions which have included patient compliance issues, changes to doses in response to serum drug levels and appropriate brand changes to improve cost effectiveness.

Conclusions: The use of Pharmacist Independent Prescribers to prescribe and manage the renal immunosuppressant homecare service at Gloucestershire Hospitals NHS Foundation Trust has been shown to be safe and efficient.

PUB570

Tools for Adverse Events Prevention in a Hemodialysis Facility: A Local Experience

Cinthia Sobral Vieira,1 Cassiana G. Prates,2 1Nephrology Service, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil; 2Hospital Epidemiology and Manager Risks Service, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.

Background: After the publication “To err is human” there has been a new approach to prevent risks in health system. According to the International Patient Safety Goals there are six steps to be followed like patient identification, proper communication, right surgery in the right patient, right side, fall prevention, high alert medication and infection prevention. The goal is to show how a hemodialysis unit, for ambulatory and hospitalized patients leads with adverse event prevention.

Methods: This experience happens in a hemodialysis unit with 101 patients, 3 shifts of 4 hours. It is located in a general hospital in Porto Alegre, south Brazil.

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

PUB571

Zinc Deficiency Correction and Phosphaturia in Children with CKD – A Pilot Study

Vladimir Belostotsky,1 Stephanie A. Atkinson,1 Michelle N. Rasiah,1 Steven Arora,1 Ji Cheng,1 Joanne Grimmier,2 Guido Filler.1 1Pediatrics, McMaster Children’s Hospital, Hamilton, ON, Canada; 2Pediatrics, Children's Hospital, London Health Sciences Centre, London, ON, Canada.

Background: There are no guidelines for correction of Zinc (Zn) deficiency in Chronic Kidney Disease (CKD). Experimental data (Morshita 2001) suggests that Zn modulates the phosphaturic response to PTH and may increase phosphaturia. Aim: To identify Zn deficiency and determine whether 3 months of oral Zn therapy normalizes Zn status in children with CKD. To assess feasibility of conducting a clinical trial similar to Morshita’s in mice and gather information on clinical outcomes and relationship between Zn status and correction of Zn deficiency and phosphate (P) excretion.

Methods: 40 patients (pt) 4-18 yr with primary CKD and CKD due to declining graft function were enrolled from 2 tertiary pediatric nephrology centers. Plasma Zn was measured by High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry at baseline and 3 months with routine blood and urine parameters. Pt with Zn<11.5 mmol/L were treated for 3 months with Zn citrate tablets (10mg Zn/day for 4-8 yr and 20 mg/day for 9-18 yr). Statistical analysis was done using nonparametric methods and relative risk ratio.

Results: Of 21 pt (M:13, F:8) with completed data, Zn deficiency was found in 10. Stages of CKD were: 2-11 pt, 3-5 pt, 4-5 pt. One pt was hyperphosphatemic. 2 Zn deficient pt had abdominal discomfort whilst taking Zn. Plasma Zn improved in 8 out of the 10 treatment pt (4.4 times more frequently than in control pt) after 3 months of Zn therapy. Zn therapy over 3 months did not change serum P (median 1.23 mmol/L to 1.25 mmol/L) or its fractional excretion (median 24.08% and 21.71%).

Conclusions: Zn deficiency occurred in about 50% of CKD pt. Preliminary analysis indicates that 3 months of oral Zn supplementation is likely beneficial in Zn deficient pt but a larger sample size is required to evaluate the impact of correction of Zn deficiency on other metabolic parameters. Correction of Zn deficiency does not alter P excretion in pt with normal blood P. Similar studies are feasible to perform in hyperphosphatemic pt.

Funding: Private Foundation Support

PUB572

Proteinuria as a Marker of Severe Unilateral Ureteral Obstruction in Infants

Mariselas Rosa-Sanchez, Jayanthi Chandar, Wacharee Seehurongv, Chryso P. Katsoufis, George N. Sfakianakis, Rafael Gosaulbez, Andrew Labbie, Gaston E. Zilleruelo, Carolyn L. Abitbol. Pediatric Nephrology, Nuclear Medicine, Pediatric Urology, Holtz Children's Hospital/Uof Miami, Miami, FL.

Background: Unilateral ureteral obstruction (UO) is a common congenital anomaly in infants. Controversies remain regarding clinical indications for timely surgery. The objective was to compare the radiologic and laboratory parameters of a cohort presenting with significant unilateral hydronephrosis that were managed either conservatively or surgically.

Methods: This retrospective analysis included 81 infants during a 10 year period with high grade hydronephrosis designated by renal ultrasound. Further assessment included renal function by nuclear scintigraphy and proteinuria. Proteinuria was determined by random urine total protein to creatinine ratio (Upr/cr) and albuminuria by random urine albumin to creatinine ratio (Ualb/cr). Receiver operator characteristic (ROC) area under the curve (AUC) statistics were applied to Upr/cr and Ualb/cr ratios with determination of likelihood ratios (LR) for requiring surgery.

Results: In this cohort, 22/81 (27%) were operated, including 21 pyeloplasties and 1 nephrectomy for severe UUO. Initial proteinuria was significantly greater in UUO patients who underwent surgery compared to those without surgery (p=0.02). ROC-AUC demonstrated that both Upr/cr and Ualb/cr predicted the presence of severe UUO requiring surgery (Upr/cr: AUC=0.71, p=0.01 and Ualb/cr: AUC=0.75, p=0.02). Upr/cr and Ualb/cr was similar in normal control infants and those with non-surgical UO.
Corpus Christi, TX.

nourani, Samhar I. Al-Akash.

Although both were sensitive markers of renal injury, albuminuria was superior in predicting who required surgery compared to normal term infants and those with non-surgical UUO.

measure SCr. We defined GHF as GFR > 150 ml/min/1.73m² using the original Schwartz formula (OSF) to calculate GFR as our lab uses the Jaffe method to determine SCr. We defined GHF as GFR > 150 ml/min/1.73m² using the original Schwartz formula (OSF) to calculate GFR as our lab uses the Jaffe method to

Background: Glomerular hyperfiltration (GHF) has been described in diabetic and obese (O) adults, and usually precedes proteinuria or clinical disease, and may indicate underlying renal damage and chronic kidney disease (CKD). GHF is poorly studied in adolescent children (AC). We hypothesized that GHF is present in AC and that GFR correlates with the BMI.

Methods: We queried the electronic medical records from 6/2010 to 12/2013 to include AC 12-21 years of age with at least one serum creatinine (SCr) and BMI in the same encounter, and excluded pts with CKD, HTN, DM, proteinuria, or renal transplant. Pts were separated into 2 groups; Control (C) - BMI < 30 and O - BMI ≥ 30 kg/m². We used the original Schwartz formula (OSF) to calculate GFR as our lab uses the Jaffe method to measure SCr. We defined GHF as GFR > 150 ml/min/1.73m².

Results: Demographic data and results are shown in table 1.

<table>
<thead>
<tr>
<th>N (encounters)</th>
<th>C (Control) BMI &lt; 30</th>
<th>O (Obese) BMI ≥ 30</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Mean age-years</td>
<td>15.5±0.8</td>
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<td>Male%</td>
<td>48%</td>
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<tr>
<td>Prevalence of GHF (GFR &gt; 150)</td>
<td>3%</td>
<td>16%</td>
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<td>Mean GFR</td>
<td>A 89.6 (85-95)</td>
<td>B 128.2 (114-141)</td>
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<td>Prevalence of GFR &gt; 130</td>
<td>20%</td>
<td>43%</td>
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<tr>
<td>Male%</td>
<td>14%</td>
<td>62%</td>
<td>&lt;0.0001 (OR 19.1)</td>
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<tr>
<td>Female%</td>
<td>12%</td>
<td>25%</td>
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Conclusions: Proteinuria and albuminuria were significantly elevated in UO infants who required surgery compared to normal term infants and those with non-surgical UUO. Although both were sensitive markers of renal injury, albuminuria was superior in predicting the need for surgery in patients with UUO.

High Prevalence of Glomerular Hyperfiltration in Obese Adolescents

Anitha Ezekiel. Jennifer Therese Potonia, Pedro Anis Rahmenaye rabbani nourani, Samhar I. Al-Akash. Driscoll Children's Hospital - Kidney Center; Corpus Christi, TX.

Background: Glomerular hyperfiltration (GHF) has been described in diabetic and obese (O) adults, and usually precedes proteinuria or clinical disease, and may indicate underlying renal damage and chronic kidney disease (CKD). GHF is poorly studied in adolescent children (AC). We hypothesized that GHF is present in AC and that GFR correlates with the BMI.

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<td>Prevalence of GHF (GFR &gt; 150)</td>
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<td>&lt;0.0001 (OR 19.1)</td>
</tr>
<tr>
<td>Female%</td>
<td>12%</td>
<td>25%</td>
<td>&lt;0.029 (OR 2.5)</td>
</tr>
</tbody>
</table>

Conclusions: Proteinuria and albuminuria were significantly elevated in UO infants who required surgery compared to normal term infants and those with non-surgical UUO. Although both were sensitive markers of renal injury, albuminuria was superior in predicting the need for surgery in patients with UUO.

PUB574

Familial Lecithin-Cholesterol Acetytransferase Deficiency Masquerading as Membranous Nephropathy in Childhood

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Background: Familial Lecithin-cholesterol acetyltransferase deficiency (LCAT) deficiency is a rare autosomal recessive disorder of lipid metabolism characterised by severely reduced HDL concentrations and impaired esterification of cholesterol. It is characterised clinically by glomerulopathy and mild haemolytic anaemia presenting in adulthood leading to ESRD by the fourth decade of life through the deposition of abnormal lipoproteins in the renal stroma. Paediatric cases are rarely described.

Methods: 2 siblings aged 8 and 11 years presented with asymptomatic non-nephrotic range proteinuria detected on routine testing. There was no family history of renal disease, although parents were consanguineous. Initial screens revealed normal renal function and normal serum albumin. Other investigations demonstrated raised lipid profiles but in keeping with nephritic syndrome. A renal biopsy was performed in view of escalating protein and albumin creatinine ratios.

Results: Renal biopsy initially demonstrated light microscopic features of membranous nephropathy. However, electron microscopy demonstrated inclusions that were not typical of the adult form of the disease but clearly lipid filled (Figure 1). Confirmation of the diagnosis was by demonstration of significantly reduced HDL-cholesterol, and detection of a novel LCAT gene missense mutation G54V as well as reduced LCAT enzyme activity on assay.

PUB575

Umbilical Artery Histomorphometry: Linking the Intrauterine Environment and Nephrogenesis

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Background: An adverse intrauterine environment is linked to the developmental origins of aortic stiffness, nephron deficit, and adult onset cardiovascular and renal disease. We hypothesized that umbilical artery histomorphometry(UAH), a direct extension of the central vascular tree, would provide insight into nephrogenesis across gestational age (GA) groups.

Methods: From 156 newborns enrolled in the Gerber Infant Kidney Study, a subcohort of 32 had umbilical cord specimens evaluated (7 term(T-S), 15 preterm singletons(PT-S) and 10 preterm twins(PT-T)). The umbilical cord was sectioned, stained with Trichrome and digitalized.Muscular(MA) and collagenous areas(CA) of the umbilical arteries were measured in pixels using the ImageJ 48q software and converted to mm². The combined total kidney volume(TKV) was measured by ultrasound and factored by the infants' ponderal indices and BSAs.

Results: TKV/PI of T-S (6.9±1.8) and PT-S (7.5±1.9) were similar; while TKV/PI of PT-T was significantly less than either of the singleton groups (4.5±0.8;p<0.001). Among PT-S, 6(40%) were from pre-eclamptic (PE) mothers. When paired by GA to other PT-S not from PE mothers, they demonstrated stunted TKV/BSA (93±28 versus 122±19µm²/ m²;p=0.02). Among twin pairs, there was also a discordance in TKV/BSA (68±10 versus 8±1±15 µm²/m²;p=0.04). UAH demonstrated a positive correlation with increasing %MA and a negative correlation with increasing %CA.

Conclusions: LCAT deficiency may present with mild symptomatic proteinuria in childhood. Although rare, it should be considered in a differential in paediatric membranous nephropathy. The diagnosis was made on characteristic EM appearances, genetics and reduced enzyme activity. A trial of enzyme replacement is planned. Interestingly, the older sibling has higher lipids yet the younger worse renal disease opening up new hypotheses for how LCAT deficiency might cause renal pathology.
Insulin-Like Growth Factor/Growth Hormone and Insulin-Like Growth Factor Binding Proteins in Normal Heighted and Short Children with CKD

**Background:**Earlier reports indicated that children with chronic kidney disease (CKD) have ‘normal’ Growth Hormone (GH) and Insulin-Like Growth Factor-I (IGF-I) levels, suggesting that intracellular resistance and increased IGF-1 Binding Proteins (BPs) account for the poor growth seen in 35% of these children. We explored key growth mediators in subjects with CKD enrolled in the Chronic Kidney Disease in Children (CKiD) study with either normal height or short stature to explore potential explanatory differences in these two subsets.

**Methods:** 232 children in CKD (206 normal height: 26 short stature; none on GH therapy) were matched by gender, age and GFR. Short stature = Height Standard Deviation Score (SDS) < -1.88. GH, IGF-1, and IGFBP-1 and 3 were determined by chemiluminometer and ELISA.

**Results:** Normal height CKD children had higher serum IGF-1/GH, higher IGF-1/IGF-1 BP1 and similar IGF-1/IGF-1 BP3 compared to short CKD children.

**Conclusions:** Height SDS correlated with IGFBP-1 in normal height children (r = 0.323), but not well in short children not on GH RX (r = 0.046).

**Differences:** Comparisons in IGF-1, IGF-1/GH, and IGF-1/IGFBP-1 may explain some variance in growth in CKD children. Height is more highly correlated to IGF-1 in normal height than short children. Analyses in paired subjects may provide further insights in children naïve to and those on GH to allow detection of critical thresholds that explain and predict growth in children with CKD.

**Funding:** NIDDK Support, Private Foundation Support

**PUB577**

Assessment of Cochlear Sensitivity of the Pediatric Chronic Kidney Disease and Hemodialysis Patients

**Background:** Abnormalities in auditory system are frequent in patients with chronic renal disease and are not only related to hearing loss, but also to the development of renal disease. The aim of this study was to throw light on the relationship between cochlear sensitivity and chronic kidney disease with or without hemodialysis.

**Methods:** Children aged 6-18 years were evaluated in three groups; 36 nondialytic patients with chronic kidney disease, 16 end stage renal disease patients undergoing hemodialysis, and 30 age and sex-matched control subjects. Hearing outcomes were obtained by pure-tone audiometry and distortion product otoacoustic emissions measurements.

**Results:** No significant difference was found except in the both ears at 500 Hz frequencies between the study group and the control group. The signal/noise ratio levels and distortion product levels were significantly lower in the nondialytic and dialytic group at all frequencies. Patients with normal hearing were found to have significantly lower signal/noise ratios and distortion product levels than those observed in the healthy controls.

**Conclusions:** These results showed lower cochlear functions in their younger and/or nondialytic group regardless of hearing loss than in the control group. Patients with chronic renal disease with or without hemodialysis should be monitored periodically even if the hearing thresholds seem to be within normal limits.

**Funding:** Government Support - Non-U.S.
Moality of Treatment of Pediatric Patients with Diarrheal HUS in Acute Renal Failure Does Not Affect Long Term Outcome and Survival

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Background: Diarrheal HUS is a disease process usually resulting from infection by E. coli H7:O157 and leading to the development of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Acute renal failure typically follows in five days from infection, with a majority of the mortality from PD catheter associated complications. Studies have demonstrated that these patients are at risk for long term renal insufficiency and end-stage renal disease. Indications to start dialysis and the mode of dialysis vary from institution to institution. There is no current study comparing which mode of dialysis, hemodialysis or peritoneal dialysis, has better benefit and less complications. The main purpose of this study is to compare dialysis modalities and determine whether one modality will result in less complications and better outcomes.

Methods: This is single center, retrospective review. We studied a total of 102 patients from 1/2009 to 12/2014. We divided patients with HUS into two groups (HD and PD). We compared the number of complications and the types of complications from each modality. Long term outcomes were measured by each patient’s CKD staging at least one year after diagnosis. EGFR was calculated using the Schwartz formula. Fisher’s exact statistical test was used to assess statistical significance.

Results: No statistical significance was found between the mode of dialysis and associated complications (p>0.4). There was also no statistical significance between mode of dialysis and long term outcome (p>0.9). Complications of PD were catheter malfunction (p=6%), peritonitis (p=5%), and the need to switch to HD or CVVHDF (p=3%). Complications of HD included central line infections (p=1%).

Conclusions: PD and HD are equally effective in treating patients with HUS in renal failure and have comparable long term outcome and risks for complications. An important complication to consider for patients on PD the potential need to switch to HD or CVVHDF; this exposes the patient to an additional surgical procedure that may result in further complications.

Self-Reported Health Care Transition Readiness Among Mexican Adolescents with Chronic or End-Stage Kidney Disease

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Background: 90% of pediatric patients with chronic disease live more than 20 years after being diagnosed. When pediatric patients are transferred to adult-focused health services, generally they do not have the skills and abilities to manage their disease. Adolescents tend to have poor adherence to treatment, and there is a period when there may be complications and increased morbidity-mortality. Performance on self-reported health care transition readiness (HCTR) needs to be assessed in patients with chronic or end-stage kidney disease. The aim of the study was to measure self-reported HCTR using the STARS (Self-management and Transition to Adulthood with Rx=Treatment) Questionnaire, among adolescents in the Nephrology Service at Hospital Infantil de Mexico Federico Gomez.

Methods: The Spanish version of the STAR Questionnaire was translated and back translated to collect self-reported health care transition readiness among end-stage kidney disease, adolescents in the outpatient nephrology department over a 9-month period. The 18-question tool diagnoses management and Transition to Adulthood with Rx=Treatment (STAR) Questionnaire, among adolescents in the Nephrology Service at Hospital Infantil de Mexico Federico Gomez.

Results: We enrolled 68 adolescents (53% males) who had a mean age of 15.75 years (± 1.87). Patients who received hemodialysis in the past 2 were 22 (34%). Females had significantly greater scores than males in the “action” category. Those who received hemodialysis in the past had greater knowledge about the disease (p=0.013).

Conclusions: The self-reported HCTR among Mexican adolescents with chronic or end-stage kidney disease differs by sex and treatment modality.

Funding: Government Support - Non-U.S.

Italian Survey on Patients on Peritoneal Dialysis Treatment: ATENA

Alessandro Possidoni, Sara Di Fiona, Flavia Caputo, Carlo Crepaldi, Roberto Dell’Aquila, Emilio Giulio Galli, Anna Maria Costanzo, Umberto Di Luzio, Roberto Russo, AbbVie Italy; H. Cívico de Palermo; H. Civile San Bartolo; Bussano del Grappa; H. di Treviso; H. di Bari.

Background: in Italy, there are few epidemiological data concerning the clinical management of patients on peritoneal dialysis (PD) and the impact of PD on clinical outcomes. The aim of the study was to evaluate PD patients in Italy.

Methods: epidemiological, multicenter study with a retrospective phase (12 months) and a prospective phase (6 months) of patients on PD. Primary objective: evaluate anemia, hypertension and mineral metabolism compared to K-DIGO and K-DOQI guidelines. Secondary objective: assess ESRD stage, complications, hospitalizations, therapeutic strategies, mortality and quality of life (QoL).

Results: 377 consecutive pt. were enrolled at baseline, CAPD 50.4% / APD 49.6%; Male 59%; mean age 67 years, dialysis duration 39.7 months. The most frequent complications were: hypertension (88%) and cardiovascular diseases (46%), hyperparathyroidism (25%), dyslipidemia (25%) and diabetes (20%). The cause of hospitalization was peritonitis (27%); no death associated, followed by CVD (20%). At 6 months, anaemia not corrected or inadequately corrected (Hb 11 g/dL) occurred in 30% of pt. 73% received ESA. Systolic value ≤ 130 mmHg and diastolic value ≤ 80 mmHg occurred in 50% and 30% of pt, respectively. Left ventricular hypertrophy was observed in about 60% of echocardiograms. 25% (HD) vs 10% (PD) in 30% of patients. Secondary hyperparathyroidism (SHPT) occurred in 30% of pt. The drugs used to manage SHPT were calcitriol (36%), paricalcitol (29%), cacoletic (23%), and cinacalcet (21%). Considering a group of patient under therapy for a year with similar basalPTH levels, a significant reduction of iPTH occurred with paricalcitol (1.05 mcg/day), but not with cinacalcet (39.4 mcg/day; p<0.003 vs p=0.626). No effect on Ca and P occurred in the paricalcitol group. At the end of the study, PD didn’t modify the QoL significantly.

Conclusions: Hypertension and CVD are the most common comorbidities of PD. Peritonitis is the main cause of hospitalization. Anaemia and SHPT are frequent and have to be treated and monitored carefully. There are significant differences in efficacy between different treatment options to treat SHPT.

Advancements in Automated Peritoneal Dialysis: What Is the Future in improved Quality of Care?

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Background: Evaluations to APD technology directed at greater ease of use and health care professionals’ (HCP’s) oversight of patient status may help overcome barriers to home dialysis. Use of connectivity to enable remote patient monitoring (RPM) and communication may facilitate patient management, increase HCP and patient communication, and improve outcomes. Advancements in design may also help simplify and improve training. Objective is to understand and qualify importance of enhanced graphical user interfaces (GUI), voice-guided instruction, and RMM embedded into APD cycler for HCPS and patients.

Methods: Forty-minute telephone interviews and web-based surveys, including cycler videos, were conducted with 214 nephrologists, 138 renal nurses, and 193 CKD patients from US and HCPS included those in practice for 3 years, spending > 75% of their time treating patients, and experience with use of conventional cyclers. Patients included those considered candidates for PD or those currently on dialysis, including incented HD, home HD or PD. In double-blinded study, participants compared 2 conventional cycler and a cycler with new technology with information screen, enhanced GUI and clinic connectivity.

Results: On a scale of 1-7 (the most important), cycler features rated most important to nephrologists, nurses, and patients include size and portability, GUI with voice-guided instructions, and data connectivity/RPM. When rating each cycler on favorability of attributes, the cycler with new technology scored highest. Attributes of 1st conventional cycler scored an average of 0.5 (on a scale of 3-3), while attributes of the cycler with new technology from the same manufacturer scored an average of 2.6 (p<0.0005). The attributes of the 2nd conventional cycler compared to the cycler with new technology scored on average 1.15 and 2.3 (p<0.0005), respectively.

Conclusions: HCPS and patients identified enhanced GUI, voice guidance, and data connectivity allowing RPM as favorable attributes to cycler usability and patient management. Technological enhancements that facilitate ease of cycler use and connectivity may increase PD acceptance by patients and HCPS.

A Single Center Ten-Year Experience in PD Catheter Placement

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Background: In our early implantation practice, cut-off tip catheters had better function and less migration when compared with straight catheters and as such, we for the past 10 years have implanted almost exclusively the cut-off tip catheters. This is in disagreement with some current literature that favors straight catheters. Due to this discrepancy, we decided to review our single center experience with PD catheters over the past 10 years.

Methods: PD catheters placed over the period of 2004-2014 at our hospital were reviewed. Demographics, comorbidities, operative note, type of catheter, surgical approach, complications and overall survival were collected.

Results: 170 PD catheters were inserted during 10 years (49.7% men, mean age 54.7 years, 167 cut-off tip catheters vs 1 straight intra-peritoneal, 63% placed by open surgical technique vs 37% by Y-Tek peritoneoscopy). Diabetes mellitus was the most common cause of ESRD. 60 peritonitis cases occurred during the period of observation (24 lost their catheter), 30 had a leak out of which 4 lost their catheter; 3 (6%) patients had primary non-function of their catheter, 4 had hernias (1 taken off PD). There was no difference in hazard ratios in catheter survival after adjusting for demographics; diabetes status and number of previous catheter placement for overall follow up. But, looking at 2-year catheter survival, open placement of catheters had a higher adjusted hazard ratio for catheter loss compared to peritoneoscopy placement (AHP 2.61; 95% CI 1.02-6.71; p=0.04).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
**Background:** This study evaluated the real world effectiveness of sucroferric oxyhydroxide (SO) use among peritoneal dialysis (PD) patients (pts) who self-reported race as Black or African American (AA).

**Methods:** A retrospective database analysis was conducted on a cohort of AA PD pts who were prescribed SO as part of standard care at FMCNA clinics. Pts had 1 serum phosphorus (sPhos) measured while using SO and had been on sevelamer, calcium-based phosphate binders or had no phosphate binder specified prior to SO treatment. Differences in sPhos, pill burden(PB), serum calcium(Ca), ferritin, transferrin saturation(TSAT), and intact parathyroid hormone(iPTH) were noted between baseline (BL; 3 months prior to SO) and follow-up (SO-TX; 3 months during SO). 

**Results:** 117 AA PD pts (mean age=50 years, dialysis vintage=4-2 years) were included. At BL, 37% were on sevelamer, 31% on calcium-based phosphate binders, 2% on dual therapy and 31% had no phosphate binder specified. Figure shows increase in pts who have in-range sPhos (20% to 31.6%; 58% increase). Mean sPhos decreased from 6.55-6.38 mg/dl (p=0.06). A significant decrease in PB was observed (4.5 pills/day, p<0.001) between BL(8.8 pills) and SO-TX(4.3 pills). No significant differences were observed between BL and SO-TX for sCa (BL=9.1 mg/dl, SO-TX=9.1 mg/dl), ferritin (BL=861.9 ng/ml, SO-TX=870 ng/ml), TSATs (BL=34.7%, SO-TX=36.8%) and iPTH (BL=729.5 pg/ml, SO-TX=696.4 pg/ml).

**Conclusions:** In a cohort of African American peritoneal dialysis patients who were prescribed sucroferric oxyhydroxide as part of routine clinical care, there was a 58% increase in the number of patients with serum phosphorus levels in-range (p<0.006). Furthermore, there was a significant reduction in pill burden (4.5 fewer pills, p<0.001).

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America.
associated morbidity. Larger controlled trials are warranted to explore the potential impact of PD on the mortality of patients with RHF and to define those subgroups most likely to benefit from this therapy.

PUB888
Procalcitonin: Is it a Useful Biomarker for Peritoneal Dialysis Peritonitis? Shishan Song, Hyeon-Cheol Park, Jae Seok Kim, Jae Won Yang, Byoung Geun Han, Seung-Ok Choi. Internal Medicine, Yonsei Wonju College of Medicine, Wonju, Korea.

Background: Peritonitis is a common complication in peritoneal dialysis (PD). Procalcitonin is a peptide hormone which has been used as a biomarker for the diagnosis of bacterial infection. We aimed to investigate the usefulness of procalcitonin in the patients with PD peritonitis.

Methods: This study included 33 episodes of peritonitis in 27 patients for follow-up period of 450 days. In addition, we collected samples of PD effuents from 7 PD patients without peritonitis to compare with those of peritonitis. We investigated clinical characteristics, serum and PD effluent levels of procalcitonin at the time of initial visit and discharge.

Results: The mean value of dialysis vintage of patients with peritonitis was 1774 days, incidence of total peritonitis for period of PD maintenance; 4.3 times, interval from symptom onset to visit; 13.6 hours, duration of intraperitoneal antibiotic treatment; 8.2 days, and interval from clinical improvement to recurrence; 80.7 days. Initial serum procalcitonin increased to 0.97 ± 3.67 ng/mL (mean ± standard deviation) compared with reference values (healthy <0.05, PD patients <0.30, PD peritonitis >0.50 ng/mL), and PD effluent procalcitonin increased to 0.97 ± 3.67 ng/mL. The serum procalcitonin decreased to 0.33 ± 0.54 ng/mL with clinical improvement but not significantly (p=0.308), and the PD effluent procalcitonin also showed the decreased level of 0.03 ± 0.08 ng/mL but not the statistical significance (p=0.360). Pearson’s correlation analysis showed that the serum and PD effluent procalcitonin did not have relationships with existing inflammatory markers such as ESR, CRP. Lastly, procalcitonin could not predict recurrence and mortality of peritonitis.

Conclusions: Collectively, procalcitonin showed the tendencies corresponding to the clinical course of PD peritonitis, but not statistical significance. We believe that procalcitonin is not superior biomarker in PD peritonitis compared with other existing markers.

PUB889
Epidemiological Survey of Maintenance Peritoneal Dialysis in China Xiang-Mei Chen, Xueying Cao, Delong Zhao, Guangyan Cai. Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases.

Background: To analysis epidemiology and trend of peritoneal dialysis during 2011-2014 in China.

Methods: Patient-reported outcome data from the peritoneal dialysis centers were collected online during the study.

Results: (1) By the end of 2014, there were 5573 cases of maintenance peritoneal dialysis patients in China, had increased by 17% per year over this time period. The average incidence rate was 5.81/100 million people. The prevalence was 34.3/100 million. (2) The average age was 53 years. Male to female ratio was 1:2.1. The average age at initiation of dialysis was about 30 years old. The average residual renal function was 3ml/min. The average dialysis time was 2 years. The primary causes were primary glomerular disease 54%, diabetic nephropathy 16%, hypertensive renal damage 14%. (3) In 2014, DOH fell to 6.6%. TOT was 27.2 months. The death patients accounted for about 51.3% of exit patients. The average death age was 64.8 years. The average therapy time was more than 28.6 months. The cause of death was the cardiovascular and cerebrovascular events. (4) Peritoneal dialysis access was the two cuffs, no gooseneck, straight. 78% patients were the continuous ambulatory peritoneal dialysis patients. The therapeutic dose was 6L to 8L. High peritoneal transport type was the largest. (5) PD patients with hemoglobin 100g/L ratio was raised every year. The albumin level in plasma was greater than or equal to 35g/L with more than 50% patients. Serum calcium, phosphorus, parathyroid hormone level was improved year by year. The average Kt/V was maintained at 2.1/ weeks. Ccr could reach 2.1/ weeks.

Conclusions: Collectively, there was a 17% annual increase in peritoneal dialysis patients. The therapeutic dose was 6L to 8L. High peritoneal transport type was the largest. There is a 17% annual increase in peritoneal dialysis patients. The cause of death was the cardiovascular and cerebrovascular events. The average death age was 64.8 years. The average therapy time was more than 28.6 months. The cause of death was the cardiovascular and cerebrovascular events.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
The UK Peritoneal Dialysis Catheter Study (UK Cath): An Ancillary Study to the Peritoneal Dialysis Outcomes and Practice Patterns Study

Background: Delivering high quality peritoneal dialysis (PD) access placement and outcomes is limited by lack of standardization of PD access definitions and events, variable reporting of outcomes, and a paucity of robust evidence regarding optimal PD catheter insertion pathways. The UK Renal Registry PD access audit (2013) demonstrated 82% catheter survival at 1 year, with considerable variation between centres. Moreover, catheter function at 3 months was poor for a medical (percutaneous) compared to a surgical (open) insertion pathway.

Methods: UK-Cath, a multi-centre prospective cohort study (1350 patients, 45 dialysis centres, 18 month recruitment window) will assess the outcomes associated with different pathways of catheter insertion, dialysis unit-level policy associated with pathway use, and patient-level factors (e.g. case-mix, urgent start). Health economic benefits of these pathways will be determined using the cohort data, enriched by additional information obtained from more long-term follow-up study in a subset of patients using Hospital Episode Summary (HES) data linkage. The study has received funding from the UK NHRI Research for Patient Benefit Programme, NIHR PB-PG-0613-31028. A subset of study 20 centres will contribute to International Peritoneal Dialysis Outcomes & Practice Patterns Study (PDOPPS) with the primary objective of understanding variations in PD technique failure.

Results: We will present information on study design, instrument development, governance mechanisms, and recruitment plan. We will discuss the impact of patient engagement on study design.

Conclusions: The UK Peritoneal Dialysis Catheter Study will inform dialysis units’ decision to either focus their efforts on improving a single surgical pathway or to practise a mixture of surgical and medical insertions, with the ultimate goal to improve catheter survival, patient experience and optimise health economic efficiency.

Funding: Government Support - Non-U.S.

Preparedness for Telemedicine in Outpatient Peritoneal Dialysis

Background: Peritoneal dialysis (PD) is generally performed daily by patients at home, where questions may arise. Telemedicine has the potential to improve the delivery of healthcare services and outcomes for PD patients. We studied the preparedness of a PD clinic run by a large dialysis organization (LDO) serving an urban undersourced population.

Methods: Adult PD patients cared for by the clinic were asked about their interest and ability to use VSEE® (HIPPA-compliant tool for video calls) to remotely manage clinical concerns about PD. We compared patient characteristics between interested and non-interested groups. We also assessed the clinic’s ability to implement VSEE®.

Results: Initial barriers encountered were with the LDO. These included a firewall that prevented video products from being loaded onto clinic computers, consent issues, concerns regarding unequal care potentially being provided to patients with and without internet access, and lack of video equipment for on-call nurses. All of these barriers were overcome. We then assessed interest in 56 patients. Their age (mean/standard deviation) was 54.0 ± 13.5 years and 54.0% were male. English was the primary language for 66%, and they had been on PD for 3.0 ± 3.2 years. 34 patients (61%) showed some interest in telemedicine, 16 (29%) downloaded the software to their laptop, tablet, or cell phone, and downloading in process for the remaining 18 (32%). The most common reason for not being interested was “no device” or “no internet access at home”, which was reported by 15 patients (27%). The only additional difference in characteristics between the interested and non-interested groups was that those interested lived further away from the clinic (12.9 vs 9.3 miles, p<0.03).

Conclusions: Multiple barriers to delivering telemedicine to PD patients exist, both on the medical and patient side. 61% of patients were telemedicine-ready. Future evaluations will determine the impact on clinically significant outcome, patient satisfaction, and clinic workflow in this population.

When to Remove the Peritoneal Dialysis (PD) Catheter After Renal Transplantation? (RT)

Background: There seems to be consensus that the time of removal of the peritoneal catheter after RT may be delayed until renal function and the patient is stabilized, but there are few publications about...

Methods: We analyzed retrospectively patients on Peritoneal Dialysis Unit (PDU) who have received a RT between May 1995 and March 2015 gathering medical history data relating to the peritoneal catheter removal and complications.

Results: 108 patients transplanted from PD, 32 women/76 men with a mean age at the time of transplantation (58.0 ± 13.7 years) were analyzed. Two patients received RT of living donor and 106 of cadaver. The catheter used in all was a straight Tenckhoff with two cuffs. If renal therapy substitution was needed posttransplantation all patients were treated with hemodialysis. The catheter was removed during surgery in nine patients (8%) due to exit tunnel infection by Staphylococcus aureus or Pseudomonas aeruginosa. The withdrawal was delayed in 91 patients (84%) and 8 has not yet been removed. The average withdrawal time was 4.1 ± 2.7 months. The indication of withdrawn was: stable renal function in 85 (93%), stable pancreatic and renal function and 4 exit site infection in 2 (2%). The median time at the withdrawal was 2.1 (mg±1.8) months. Two patients were removed surgically under local anesthesia. The mean duration of hospitalization was 2.1 ± 1.8 days (0-12). Four patients (3.7%) had complications during withdrawal (one hemaatoma, two hemorrhagic shock and one surgical wound infection). 15 (18%) patients showed complications before withdrawal: 13 exit site infection, one peritonitis associated with urinary fistula and one spontaneous peritonitis.

Conclusions: In our experience the removal of the peritoneal catheter may be delayed until renal graft function were stabilize since the rate of complication is low compared with another studies.

Funding: Other NIH Support - Spanish Public Health Service

Clinical Outcomes by Differences in Therapy Among Peritoneal Dialysis Patients

Background: Studies evaluating the outcomes of peritoneal dialysis (PD) technique and patient survival, including those among patients who switch from PD to hemodialysis (HD), are scarce.

Methods: This retrospective study screened 120 patients in whom PD was initiated between January 1998 and December 2012 at our hospital. Of these, patients who were transferred to HD before completing one year were excluded. We compared the outcomes in patients who had complete follow-up data were excluded. Fifty-two patients (mean ± SD: 69.2 ± 12.6 years) were included to investigate the time of survival based on PD technique and overall survival, including those patients who switched to HD, and to evaluate the correlation between survival time and pharmacotherapy at the initiation of PD.

Results: Time (in months) on PD, HD, and overall survival were 34.3 ± 30.0, 18.5 ± 43.4, and 52.6 ± 53.2, respectively. Compared between the APD (n = 20) and non-APD patients (n = 28) showed that time on PD was 45.3 ± 34.4 vs. 31.3 ± 26.0 months, time on HD was 59.0 ± 40.6 (n = 8) vs. 91.8 ± 72.5 (n = 8) months, and overall survival time was 60.9 ± 49.9 vs. 54.7 ± 55.4 months, respectively. Comparison between groups with (n = 41) and without use of icodextrin (n = 7) showed time on PD was 10.8 ± 6.0 vs. 41.4 ± 30.1 months, time on HD was 49.6 ± 45.0 (n = 3) vs. 62.9 ± 65.3 (n = 13) months, and the survival time was 32.1 ± 41.7 vs. 61.6 ± 53.6 months. When analyzed by age groups of <60, 61–70, 71–80, and >81 years: time on PD (months) was 47.2 ± 38.4 (n = 14), 45.2 ± 23.4 (n = 15), 19.8 ± 27.0 (n = 10), and 21.2 ± 19.2 (n = 13), respectively. Time on HD was 22.8 ± 44.2 (n = 6), 14.6 ± 36.3 (n = 5), 8.7 ± 28.2 (n = 1), 26.3 ± 60.1 (n = 4), respectively, and survival time was 70.1 ± 52.8, 59.2 ± 41.9, 28.5 ± 39.7, and 46.7 ± 67.2 months.

Conclusions: The time on dialysis and survival time may be underestimated because of the exclusion of patients who are currently on dialysis. Compared with non-APD patients, APD patients had longer time on PD and overall survival time. Patients who needed icodextrin when commencing PD had shorter time on PD and overall survival time.

Combined Markers of Protein-Energy Wasting and Inflammation Predict Clinical Outcomes in Incident Peritoneal Dialysis Patients

Background: Protein-energy wasting (PEW) and chronic inflammation are not only common but are known as predictors of adverse clinical outcomes in end stage renal disease (ESRD) patients. Whether the combined values of serum albumin, high sensitivity C-reactive protein (hs-CRP), and body mass index (BMI) have an additive impact on clinical outcomes compared to each variable by itself in incident peritoneal dialysis (PD) patients is to be evaluated.

Methods: A prospective cohort of 565 incident PD patients from the Clinical Research Center for ESRD in Korea was selected. Patients were divided into two groups based on the baseline levels of albumin (≥ 3.5 g/dl), hs-CRP (≥ 0.45 mg/dl), and BMI (≥ +/− 23 kg/m²). Primary endpoint was the occurrence of all-cause mortality and unplanned hospitalization.

Results: The mean age was 51.4 years and 60.0% were male. During a median follow-up duration of 27 months, 50 patients (8.8%) died and unplanned hospitalization events occurred in 123 patients (21.8%). Univariate analysis revealed an increase in primary outcome risk with lower albumin and elevated hs-CRP compared to higher albumin and lower hs-CRP, respectively. A similar tendency was observed with lower BMI and primary outcome, although without statistical significance. Regarding the combination of these factors, Cox proportional hazards revealed that patients with any two risk factors and all three risk factors exhibited significantly higher hazard ratios for primary outcome compared to patients without any single risk factor. The combination of these factors retained a significantly higher HR for predicting primary outcome, even after adjusting for other confounders.

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

1026A
PUB597

Single Center Experience with a Peritoneal Dialysis Cycler with Advanced Patient Interactive Screen: Impact on Patient Training

**Background:** Learning proper device use and clinical concepts of care must be internalized by patients to successfully perform PD at home. With increasingly diverse patients going on PD and increasing adoption of urgent start PD, there is a need for simpler devices. Enhancing the patient education environment with methods including visual, graphical and voice will improve the educational experience leaving the patient with better understanding of the procedure.

**Methods:** Automated PD training was undertaken at a university based home dialysis program using a novel APD device (AMIA). 5 patients were trained on the device in a 1:1 nurse to patient ratio. The cycler provided on screen instructions using a touch screen interface with voice guidance, text instructions and animation. Each patient was trained according to standardized outlines and sequential training progression from CAPD to APD techniques. Training included RN demonstration followed by patient direct interaction with the device. Instructions were displayed on a touch screen.

**Results:** Patient training completion required consistency of error free setup. Patients going on PD and increasing adoption of urgent start PD, there is a need for simpler devices. Enhanced patient education environment with methods including visual, graphical and voice will improve the educational experience leaving the patient with better understanding of the procedure.

**PUB598**

Peritoneal Dialysis-Related Peritonitis in a Single Center: 10 Years Experience

**Background:** Peritonitis remains the main Peritoneal Dialysis (PD)-related complication. It is estimated that it contributes directly to 20% of dropout and is related to 16% of all deaths. This study proposes to evaluate episodes of PD-related peritonitis and describe its incidence, causative organisms and possible predictors in patients belonging to a PD program from a reference center at Araçatuba-São Paulo-Brazil.

**Methods:** Retrospective cohort study that evaluated 565 patients who stayed for at least 30 days in routine start patients. Device training ranged from 2-3 days for urgent start patients and 4-5 days for urgent start patients.

**Results:** From our experience, training times were similar or reduced using the AMIA cycler and allowed the ability to efficiently train urgent start patients. Observations of the new cycler included: 1) less need for memorization 2) distinction of a beginner vs advanced mode 3) online alarm troubleshooting 4) presence of an air detector in the device. Instructions were displayed on a screen.

**Conclusions:** The combination of serum albumin, hs-CRP, and BMI at the time of PD commencement was a significant independent risk factor for the composite outcome of all-cause death and unplanned hospitalization in incident PD patients. Funded: Government Support - Non-U.S.

**PUB599**

Placement of Peritoneal Dialysis Catheters: Not Limited to Operating Rooms

**Background:** As of December 2012, only 7% of ESRD patients in the USA utilize Peritoneal Dialysis (PD) for renal replacement therapy, despite many advantages of PD over hemodialysis (HD). One factor leading to low PD utilization is the lack of experienced surgeons available to place PD catheters in a timely manner. Interventional Radiologists (IR) can help with catheter placement. As of December 2014, Kaiser Permanente achieved a 25% PD rate among its ESRD population. One factor that contributed to the high percentage of PD utilization is a skilled IR service in the Greater Southern Alameda Area (GSA) that facilitates the placement of PD catheters in a timely manner. We report a large number of PD catheters placed by GSAA IR physicians from January, 2011 to December, 2013 and compare to PD catheters placed by laparoscopic surgeons in the nearby East Bay Area (EBA) and Diablo Service Area (DSA) during the same time period.

**Methods:** We retrospectively analyzed KPNC electronic data base from 1/1/2011 – 12/31/2013. We extracted data from GSA where IR placed PD catheters using an Advanced Image guided Percutaneous (AIP) technique. We also extracted data from the EBA and DSA where surgeons placed PD catheters using the Advanced Laparoscopic Surgical (ALS) technique.

**Results:** We identified 203 PD catheters placed by GSAA IR with the AIP technique and 316 PD catheters placed by EBA/DSA surgeons using the ALS technique. Overall, GSAA IR placed 39% of all PD catheters across the 3 areas during the study time period.

**Conclusions:** IR placed a significant percentage of overall PD catheters in 3 areas of our integrated health care system. In doing so, we overcame one of the barriers to high PD penetration in ESRD patients. In areas where there is a shortage of skilled surgeons, one can consider utilizing IR to solve this problem. Currently we are studying the outcomes of these two approaches.

Funding: Private Foundation Support

**PUB600**

Body Composition and Cardiovascular Outcomes Using Continuous Automated Peritoneal Dialysis – A Prospective Cohort Study

**Background:** Fluid overload (FO) due to compliance in Continuous Ambulatory Peritoneal Dialysis (CAPD) is common. Efforts to achieve dry weight and avoid cardiovascular outcomes (CO) are less from inaccurate body composition (BC) estimations despite best clinical assessment.

**Methods:** We’ll follow BC, multiple frequency bioelectrical impedance (InBody SI0, InBody CO), standard laboratories and CO, in all new patients to continuous Automated Peritoneal Dialysis (APD) previously in a CAPD. Measurements at baseline (CAPD), 1 month and every visit to the dialysis clinic thereafter (APD) for a 5 year period.

**Results:** These are the first data of BODY cohort study. Initial 10 subjects are described, 4 men and 6 women, median age 27 years (17-46), height 159.5cm (146-166), baseline and first follow up variables are in Table 1. Wilcoxon rank test for related samples was performed. We found that PD modality switch to APD, at 1 month, reflected a body composition transition with statistical significance (P <0.05), within the EW/BTW ratio at expense of trunk compartment. Most likely from improved dialysis adherence

**Conclusions:**

**Variables**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Etiology of renal disease</th>
<th>Incident (%)</th>
<th>Urgent (%)</th>
<th>Training Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>F</td>
<td>Hypertension/NSAID</td>
<td>U</td>
<td>U</td>
<td>2</td>
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<tr>
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<td>47</td>
<td>F</td>
<td>FSGS</td>
<td>U</td>
<td>U</td>
<td>3</td>
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<tr>
<td>3</td>
<td>49</td>
<td>F</td>
<td>Calcineurin</td>
<td>P-HD</td>
<td>R</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>FSGS</td>
<td>F-HD</td>
<td>R</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>F</td>
<td>Lupus Nephritis</td>
<td>P-APD</td>
<td>R</td>
<td>4</td>
</tr>
</tbody>
</table>

5 patients aged 30-68 yrs (mean 47), 80% female with a minimum of HS education completed training. Device training ranged from 2-3 days for urgent start patients and 4-5 days for urgent start patients.

**Conclusions:** From our experience, training times were similar or reduced using the AMIA cycler and allowed the ability to efficiently train urgent start patients. Observations of the new cycler included: 1) less need for memorization 2) distinction of a beginner vs advanced mode 3) online alarm troubleshooting 4) presence of an air detector in the device. Instructions were displayed on a screen.

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

Underline represents presenting author.

1027A
Conclusions: We consider that APD, on the ground of increased, uninterrupted and rigorously performed therapy, is a appropriate therapy to optimize FO and aim for dry weight in PD. Further recruitment of patients and follow up of the BODY Cohort study is expected to confirm this hypothesis.

Funding: Pharmaceutical Company Support - HiTec Medical

PUB601

The Changes in Bicarbonate Level and Ionized Ca/ Corrected Ca Ratio of Patients Receiving Peritoneal Dialysis Using Bicarbonate/Lactate-Buffered Solution

Emi Kimoto, Nanae Matsu, Masamitsu Morishita, Mami Nakamura, Yukio Murayama, Yatsuaki Nakada, Masatsugu Nakao, Yudo Tanno, Ichiro Ohkido, Hiroyasu Yamamoto, Keitaro Yokoyama, Takashi Yoko. Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.

Background: Recently, PD solution which contains 25mEq/l bicarbonate and 10mEq/l lactate (Bicarbonate/Lactate-buffered peritoneal dialysis solution; B/L solution) is developed in Japan. Because of high concentration of lactate (40mEq/l) of conventional peritoneal dialysis (PD) solution, patients have generally higher serum bicarbonate level than those of patients receiving hemodialysis (HD). The new B/L solution is expected not only its biocompatibility but also improving excess correction of acidosis. Under the metabolic alkalosis environment, we reported that PD patients have lower levels of ionized Ca (iCa) at the same corrected Ca (cCa) levels. Thus, we hypothesized that iCa / cCa ratio increased after switching PD solution from Lactate-buffered to B/L solution.

Methods: We recruited 28 patients (55 ± 13 years, male 82%, PD duration 42 ± 21 months) who switched from Lactate-buffered to B/L solution, and investigated changes in serum bicarbonate, iCa, and cCa levels.

Results: After switching solution, serum bicarbonate decreased (26.7 ± 3.2 vs 24.8 ± 2.5, P<0.01), and cCa did not change (9.3 ± 0.5 vs 9.3 ± 0.5, P=0.63). Neither iCa nor iCa/cCa ratio increased significantly (1.12 ± 0.09 vs 1.11 ± 0.09, P=0.48; 0.120 ± 0.007 vs 0.119 ± 0.0006, P=0.54, respectively).

Conclusions: Conversion to B/L solution from lactate solution was associated with lower serum bicarbonate. Unfortunately, iCa did not change. Further investigations are needed to confirm the utility of the monitoring of iCa for the management of chronic kidney disease - mineral and bone disorder (CKD-MBD) in PD patients.

PUB602

Road to Success: One Academic Medical Center’s Experience Building a Peritoneal Dialysis Clinic

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Background: Peritoneal Dialysis (PD) is an option for renal replacement therapy. The US Renal Data System 2012 Annual Report states that the annual per-patient HD cost is approximately $87,500 whereas for PD it is $66,750. In addition, studies have demonstrated that some aspects of quality of life are improved in PD patients compared with HD patients. Despite this, PD is underutilized in the US. Northwestern Medicine’s PD Program was initiated in 01/2014 with 4 nephrologists and 10 patients who transferred from a neighboring PD Unit. From 02/2014 to 04/2015, Northwestern’s Peritoneal Dialysis Clinic grew to 50 peritoneal dialysis patients.

Methods: We included all patients who started on PD (or transferred to PD) in PD Clinic between the periods of 2/14 and 4/15. Patients excluded from this analysis stopped PD within this period for the following reasons: switched to HD, expired, recovered kidney function, or underwent transplantation.

Results: From January 2014 to April 2015, PD Clinic grew to 50 patients. The age range was 22-86 years and mean age was 54.4 years. Thirty-one (62%) were men. Twenty-four (42%) are African American, 13 (26%) are Caucasian, 11 (22%) are Hispanic, and 5 are of Asian descent.

Conclusions: We describe a single, academic medical center experience on growth of PD Clinic from 0 to 50 patients within 14 months. Obstacles to PD Clinic growth included lack of availability of dialysate in mid 2014 and lack of experience with Urgent Start PD. However, with time, both nephrologist and surgeons and medical staff grew comfortable with this method of dialysis initiation. Features that facilitated successful and timely growth are: 1- Minimizing options training, 2- Surgeon cooperation, 3- Physical proximity to CKD Clinic and to inpatient floors, 4- Continuity of care for patient-physician from outpatient CKD Clinic to inpatient setting to outpatient Home Dialysis Clinic.

PUB603

Peritoneal Membrane Transport Evaluation in Peritoneal Dialysis Using Traditional PET, Modified PET and Mini-PET

Miguel C. Riella, Jacke Waniweski, Bengt Lindholm, Marcelo Nascimento, Umberto B. Gori, Marcela de Carvalho, Danila Colacim, Rui F. Araujo, George C. Kaelin, Antonio B. Bento, David K. Stein, Silvia C. Knackstedt, Daniel C. Knackstedt, Pro-Renal Foundation, Curitiba, Parana, Brazil; 2- Inst Biocybernetics and Biomedical Engineering, Warsaw, Poland; 3- Baxter Novum and Renal Medicine, Karolinska Inst, Stockholm, Sweden; 4- Pro-Renal Foundation, Curitiba, Parana, Brazil.

Background: Peritoneal equilibration test (PET) is widely used for evaluating peritoneal transport; however, additional methods have been described to facilitate and improve this evaluation. Here, we compared traditional PET (PET) with two newer methods, mini-PET and modified PET (mod-PET), which are increasingly used to investigate ultrafiltration capacity and peritoneal membrane characteristics in patients undergoing peritoneal dialysis.

Methods: Twenty-one non-diabetic adult patients on peritoneal dialysis (PD) for >3 months underwent: PET (2.27%; h), mini-PET (3.86%; h); and mod-PET (3.86%; h). Results of dialysate to plasma concentration ratios for creatinine (D/P Cr) and sodium (D/P Na), and dialysate to initial glucose concentration (D/D0 glucose) at the end of each test were compared by analysis of variance (ANOVA), Pearson correlation and Bland-Altman test.

Results: Whereas D/P Cr was not significantly different between PET and mod-PET (p=0.746) there were significant differences between mini-PET and both PET (p=0.001) and mod-PET (p<0.001). D/P Cr for PET correlated with D/P Cr for mod-PET (r=0.387; p=0.009) but not with D/P Cr for mini-PET (r=0.088; p=0.241). Bland Altman test showed no significant bias of D/P Cr for PET vs mod-PET (-0.029; p=0.201) but a systematic difference (0.206; p<0.001) of D/P Cr PET vs mini-PET. Whereas measurements of D/D0 glucose and D/P Na were in general not comparable nor significantly correlated, ultrafiltration during PET and mini-PET were weakly correlated (r=0.260; p=0.009).

Conclusions: These results confirm that characterization of transport status based on D/P Cr may not necessarily differ between conventional PET and mod-PET.

Funding: Government Support - Non-U.S.

PUB604

Low Level of Albumin Is a Risk Factor for Short-Term Mortality of PD Patients

Kenji Harada, Kokura Memorial Hospital; Kokura Memorial Hospital.

Background: Mortality of HD(hemodialysis) patients are reported, but few reports about PD(peritoneal dialysis) patients. This study aims to investigate clinical features of PD patients, their short-term mortality(1-2 years).

Methods: We investigated the mortality about PD patients(n=269, age:65 year old:13.7, male/female 173/96, PD vintage within 2 years, DM:121), and the influence of several parameters from 2009 to 2012. The dead and the transferred HD were excluded within 90 days. Finally 241 patients are remained. The survival rates for one year and two years were 91 % and 72 %. Infection was the most causes of death(33%). We investigated between death and several parameters(age, sex, blood pressure, albumin, hemoglobin, Ca, P, whole PTH, TC) by univariate analysis with JMP12, SAS. Those physical and laboratory data were measured at one month after PD started. Age and level of albumin were correlated with death. We hypothesized that low albuminumia and malnutrition influenced the rate of death. We divided three categories, from group A(albumin<3.3, n=82) and group B(2.8<albumin<3.3, n=89), group C(albumin<2.7, n=73). Cox proportional hazards regression model was used to analyse prognostic risk factors and establish prognostic model.
Results: There were significant differences between group B and A (Hazard Ratio: 2.61, p = 0.016, 95% CI: 1.232-6.09), group B and C (Hazard Ratio: 6.031, p = 0.001, 95% CI: 2.975-13.53), group C and A (Hazard Ratio: 2.309, p = 0.0029, 95% CI: 1.33-4.09). In addition these groups were analysed by adjustment factor such as age, sex, blood pressure, hemoglobin, Ca, P, whole PTH, TC with multivariable analysis. The results proved that there were tended to be correlation between group B and A (Hazard Ratio: 1.963, p = 0.09, 95% CI: 0.901-4.61). There were significant differences between group B and C (Hazard Ratio: 4.00, p = 0.003, 95% CI: 1.866-9.35), group C and A (Hazard Ratio: 2.037, p = 0.0029, 95% CI: 1.165-3.63).

Conclusions: Low level of albumin increases the mortality of PD patients gradually. Therefore we may decrease mortality of PD patients by improving nutritional condition and infection control when PD patients are introduced.

PUB607

Peritoneal Dialysis: A Decade Experience at a Reference Centre in Brazil
Patricia O. Costa, Carla M.V. Melo, Flavia A. Nobrega, Jordiano P. Oliveira, Jandson P. Oliveira, Kleyton Andrade Bastos, Dept of Medicine, Federal Univ of Sergipe, Aracaju, Sergipe, Brazil.

Background: Peritoneal Dialysis (PD) is underutilized in most countries. The Brazilian prevalence is around 9%. This study aims to describe the ten years experience on PD in a dialysis center in Northeast of Brazil (Aracaju-Sergipe). Unlike other national programs, negative selection for DP is not an attribute of this dialysis unit.

Methods: Retrospective cohort study that evaluated the sociodemographic and clinical profiles, comorbidities, peritonitis, hospitalizations and death causes of 565 patients who remained in PD for at least 30 days from 01/01/2003 to 12/31/2012.

Results: Patients were mostly men (55%), living outside Sergipe's capital (56%), had a mean age of 54 ± 19 years old when started on dialysis, were illiterate or had less than 4 school years (62%) and had a family income less than 5 national minimum wages per month (88%). The etiology of nephropathy was identified in 54% of cases, diabetic nephropathy (46%) and hypertensive nephrosclerosis (22%) were the most prevalent. Hypertension was the most common comorbidity (76%). D/Pcre was the initial dialysis modality for 53% of patients, namely as an emergency (58%), and only 9% of patients had undergone predialysis care for at least six months. Patients remained in PD by an average of 710.5 (± 714.2) days, and 61% of them also underwent hemodialysis (HD) at some point during their dialysis treatment. 676 peritoneal catheters were implanted (1.19 patient), 75% by trocar, by nephrolith, mostly Tenckhoff (58%). The main cause of dropout was infectious complications related to therapy (17%). The peritonitis index was 1 episode every 27.03 months, and S. aureus was the most prevalent etiological agent (22%). There were 1045 hospitalizations during follow up, most frequently due to infections (48%). The cause of death was identified in 64% of cases, mostly from cardiovascular diseases (50%).

Conclusions: In this study, patients had predominantly low socioeconomic status and did not have access to predialysis treatment, however, peritonitis rates and catheter complications are similar to those reported in other international series. HD and PD are shown as complementary techniques.

PUB608

Implementation of Clinical Practice Guidelines on Antimicrobial Prophylaxis in Peritoneal Dialysis Patients
Denise Campbell, Fiona Brown, John F. Collins, Jonathan C. Craig, Martin P. Gallagher, David W. Johnson, Geoffrey S. Kirkland, Subramanian K. Kumar, Wai Hon Lim, Dwarakanathan Ranganathan, Walaa W. Saweire, Germaine Wong, David Mudge, School of Public Health, Univ of Sydney, Sydney, New South Wales, Australia; Nephrology, Monash Univ, Clayton, Victoria, Australia; Renal Medicine, Auckland City Hospital, Auckland, New Zealand; Renal and Metabolic Div, George Inst for Global Health, Sydney, New South Wales, Australia; Nephrology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; Nephrology, Royal Hobart Hospital, Hobart, Tasmania, Australia; Renal Unit, Gosford Hospital, Gosford, New South Wales, Australia; Renal Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; Nephrology, Royal Brisbane & Women's Hospital, Herston, Queensland, Australia; Renal Unit, Whangarei Hospital, Whangarei, New Zealand.

Background: Despite the existence of international guidelines, peritoneal dialysis (PD)-related infections vary widely across Australian and New Zealand units, with multiple units reporting suboptimal rates and variable practice.

Methods: The current practice and barriers to guideline uptake were evaluated in eight PD units located in Australia and New Zealand in 2011. A multifaceted intervention was developed which included case report forms, a patient diary, a ‘Preventing Peritonitis Checklist’, an Emergency Department flyer, a letter to the patient’s general practitioner, a medical card, and a poster summarizing ISPD and KHA-CARI guidelines.

Results: At baseline (1 Jan-31 Dec 2011), exit-site infection (ESI) rates ranged from 0.06-0.53 episodes/patient-year; peritonitis from 0.31-0.86 episodes/patient-year; and fungal peritonitis from 0.00-0.08 episodes/patient-year. After implementation (9 Dec 2013-8 Dec 2014), the ESI rates were 0.00-0.22 episodes/patient-year; peritonitis was 0.29-0.49 episodes/patient-year; and fungal peritonitis was 0.00-0.14 episodes/patient-year.

Conclusions: Implementing the various tools resulted in improvement in the ESI and peritonitis rates but the difference was not statistically significant (P=0.15 and P=0.08). There was no statistically significant difference in the fungal peritonitis rate (P=0.64).

Funding: Government Support - Non-U.S.
Factors Influence the Baseline Peritoneal Transport Status

Hao Zhang, Bin Yi, Cuiling Hou. The Third Xiangya Hospital, Central South University, Changsha, Hunan, China.

Background: Baseline peritoneal solute transport rate (PSTR) is an independent risk factor for total cardiovascular (CV) mortality in the PD (peritoneal dialysis) population. The determinants of PSTR in incident PD patients are still under debate. Our objective was to explore the influence factors of baseline PSTR.

Methods: (1) 205 incident PD patients who had a standard peritoneal equilibration test (PET) within 1-3 months after commencing PD and without peritonitis history were enrolled. Pre-PET clinical parameters and biochemical indexes were assessed. 205 individuals were divided into two groups according to the baseline PSTR. High transport group: PET > 0.65. Low transport group: PET ≤ 0.65. (2) Pre-PET serum advanced oxidation protein products (AOPP) and dialysate AOPP: GPx, hsCRP, IL-1beta, TG-beta 1 of 59 patients among the enrolled 205 individuals were detected.

Results: (1) High baseline PSTR are more likely to be malefemal: 77.3% vs 52.5%, p = 0.001, had lower serum albumin (34.0 ± 4.40 g/L vs 35.9 ± 4.55 g/L, p = 0.005) and TG levels (1.11 ± 0.62 mmol/L vs 1.28 ± 0.57 mmol/L, p = 0.047) compared to the low baseline PSTR. Gender (r = 0.299, p = 0.299), serum albumin (r = 0.199, p = 0.199) and TG level (r = 0.140, p = 0.140) are correlated with the baseline PSTR respectively. Multiple stepwise linear regression analysis showed that gender (β = 0.085), serum albumin (β = 0.005, p = 0.005) are associated with baseline PSTR independently. Multivariate Logistic analysis showed that men (OR = 3.314, p = 0.001), hypoalbuminemia (OR = 2.552, p = 2.552) are independent risk factors for high baseline PSTR. ROC curve display that when serum albumin < 35.8 g/L, it is likely to have a high baseline PSTR. (2) High baseline PSTR had a relatively high level of dialysate TGF-beta1 (1.58 ± 0.35 mg/mL vs 1.75 ± 0.30 mg/mL, p = 0.049) than the low transport status. No statistical differences were found in serum AOPP and dialysate AOPP: GPx, hsCRP, IL-1beta between groups. Dialysate TGF-beta1 (r = 0.135, p = 0.001) contributed to the baseline PSTR independently.

Conclusions: (1) Male, hypoalbuminemia, high dialysate TGF-beta1 level are independent predictors of fast baseline PSTR. (2) When serum albumin < 35.8 g/L, it is likely to have a high baseline PSTR.
follow up and dialysis start. PD patients (p=0.02) received more modality information than HD (92% vs. 78%) and were mainly under 50 years (p = 0.001). Incidence varied according with different studied groups

<table>
<thead>
<tr>
<th>Studyed groups</th>
<th>n (%)</th>
<th>HD</th>
<th>PD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER + P</td>
<td>168 (31)</td>
<td>133 (27)</td>
<td>35 (59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Late referral + P</td>
<td>63 (12)</td>
<td>58 (12)</td>
<td>9 (9)</td>
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<tr>
<td>ER + Unplanned Start</td>
<td>113 (20)</td>
<td>104 (21)</td>
<td>9 (15)</td>
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<tr>
<td>Late referral + Unplanned Start</td>
<td>203 (37)</td>
<td>193 (40)</td>
<td>10 (17)</td>
<td></td>
</tr>
<tr>
<td>Optimal care: ER + modality informed</td>
<td>121 (22)</td>
<td>96 (20)</td>
<td>25 (42)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Despite commitment to offer PD/HD as complementary treatments, PD incidence is still low. Optimal care provision is important to improve outcomes but also to involve patients in their therapy choice.

PUB615

The Adsorption Kinetics Profile of Aminoglycoside Antibiotics During Lixelle S-35 Cartridge Hemoperfusion
Marco Sartori, 1, 2 Angela Casas, 3 Silvia De Rosa, 1 Mirella Zancato, 2 Leopolda Zampieri, 1 Davide Giavarina, 1 Claudio Ronco. 1
*International Renal Research Inst of Vicenza, St. Bortolo Hospital, Vicenza, Italy; 1Dept of Pharmaceutical and Pharmacological Sciences, Univ of Padua, Padua, Italy.

Background: The bacterial activity against Gram(-)ino of Tobramycin(TOB)and Gentamicin(GEN)is concentration-dependent. It is therefore fundamental achieving the maximum antibiotic plasma levels. Lixelle S-35 is a new sorbent for dialysis-related amyloidosis which can modify the drug plasma levels. The aim of in vitro study was to evaluate the TOB and GEN adsorption removal by Lixelle S-35.

Methods: We performed mock direct hemoperfusion (DHP;Q=100ml/min;Bellco prototype dialysis machine)for 120 min using Lixelle S-35 cartridge. Human blood was diluted with fresh frozen plasma in order to achieve appropriate rheological characteristics(Hct 30%;650ml each bag;n=6).Blood was separately spiked with TOB(1.00±0.42 mg/L;n=3) and GEN(12.80±1.00mg/L;n=3).In 30 min it was circulated into the system. Samples were taken from arterial(Cpin)and venous(Cout)lines at 5,10,60 and 120 min. Sample levels were measured by TOBR and GENT Flex methods(Siemens prototype dialysis machine)for 120 min using Lixelle S-35 cartridge. Human blood was diluted with fresh frozen plasma in order to achieve appropriate rheological characteristics(Hct 30%;650ml each bag;n=6).Blood was separately spiked with TOB(1.00±0.42 mg/L;n=3) and GEN(12.80±1.00mg/L;n=3).In 30 min it was circulated into the system. Samples were taken from arterial(Cpin)and venous(Cout)lines at 5,10,60 and 120 min. Sample levels were measured by TOBR and GENT Flex methods(Siemens Healthcare,Newark,NJ,USA)for TOB and GEN,respectively. The adsorption kinetics profiles were calculated.

Results: At the of DHP TOB and GEN levels were 7.13±0.18 and 7.20±0.90mg/L. Ratio Cout/Cpin rose rapidly during the first 5 min then reach plateau for both antibiotics as shown Fig. On mass balance analysis, the total mass of antibiotics introduced into the system decreased from 5.12±0.25 to 3.22±0.50 and from 6.16±0.51 to 3.52±0.41mg for TOB and GEN, respectively. The TOB mass adsorption was 37.20% whereas GEN was 46.20% in human serum by capillary HPLC/mass spectrometry(MS). Although this method works well for identification of the drug, it is semi-quantitative unless a suitable isotopic internal standard is used.

Methods: A simple, rapid, sensitive and quantitative method is presented for the analysis of six AG AMBs (streptomycin, ribostamycin, kanamycin, amikacin, dibekacin, arbekacin) in human plasma samples. Hydrophilic interaction liquid chromatography tandem mass spectrometry (HILIC-MS/MS) is a small volume (50µL) of plasma spiked with six drugs was diluted with 350µL of acetonitrile containing 0.1% formic acid. After centrifugation, 100µL of the clear supernatant extract was directly injected into the HILIC-MS/MS, without any solvent evaporation and reconstitution steps. The chromatographic separation of the AG AMBs was achieved on Unison UK-Amino HILIC column (50mm x 3mm i.d.; particle size 3µm) with a linear gradient elution system composed of 0.1% formic acid and acetonitrile.

Results: All drugs showed base peaks due to [M+H]+ ions with HILIC-MS with positive ion electrospray ionization, and the product ions were produced from each drug by the following collision-induced dissociation (CID) experiments. TOBR and GENT product ions were identified using the standard method of selected reaction monitoring (SRM) and the product ion spectra of all drugs were consistent with the literature. The method was validated for six AG AMBs in human plasma by HILIC-MS/MS. The sensitivity of the method was 0.1 µg/mL for TOB and GEN, and 0.001 µg/mL for all other AG AMBs. The accuracy of the method was 99.6% for TOB and GEN, and 97.5% for all other AG AMBs. The precision of the method was 1.2% for TOB and GEN, and 1.5% for all other AG AMBs. The method was applied to the analysis of six AG AMBs in human plasma samples from healthy volunteers and patients. The results showed that the method was accurate and precise for the analysis of six AG AMBs in human plasma samples.

Conclusions: The method would seem to be useful in clinical and forensic medicine because of its ability to both identification and quantification of the drugs.

PUB616

Prevalence of Chronic Musculoskeletal Pain Among Hemodialysis Patients
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Background: Chronic musculoskeletal pain (MS pain) is common in patients with end stage renal disease (ESRD) undergoing hemodialysis; however information regarding its frequency and prevalence is relatively scarce.

Methods: A cross-sectional study was conducted on 100 ESRD patients on maintenance hemodialysis 3 times per week for at least 3 months. Chronic musculoskeletal pain was defined as pain that the VON KROFF questionnaire for grade 3. Chronic musculoskeletal pain correlation was done between chronic MS pain and serum parathormone (PTH), serum corrected calcium, serum phosphorus, serum alkaline phosphatase, serum albumin & hemoglobin level.

Results: Mean age was 57.46 years. Mean dialysis duration was 3.80 years. 42% were females and 58% males. In our study, 37% of the patients had low disability low intensity of pain i.e. little affection on the daily, social & work activity (grade 1).37% of the patients had low disability high intensity of pain (grade 2) while 26% of them had high disability high intensity of pain i.e. moderate limitation of the daily, social, recreational & work activities (grade 3). Chronic musculoskeletal pain showed positive correlation with muscle state, tenderness and power (r=0.001, p<0.001, r=0.001 respectively). Grade 3 disability patients had the highest level of serum Ca and i-PTH which were significantly different from grade 1 and 2 patients (p<0.001, p=0.013 respectively) While albumin serum level was lowest in grade 3 patients (p=0.025).

Conclusions: Chronic MS pain is common in ESRD patients. Disturbed mineral metabolism is strongly associated with chronic MS pain in long-term HD patients. Musculoskeletal system involvement remains a common problem that limits the physical function of patients with ESRD.

PUB618

Practice Patterns of United States Nephrologists in Blood Pressure Medication Use when Transferring Patients to Dialysis
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Background: As there is no standard approach to transition a patient in chronic kidney disease (CKD)-5 to CKD5-Dialysis in regards to adjustment of diuretics, BP medication, optimal frequency of medication reconciliation (MR) and determination of dry weight (DW) we conducted a survey to determine how US nephrologists transition a patient from CKD5 to CKD5-D in these aspects.

Methods: We designed an anonymous electronic survey with 39 questions and sent it to practicing nephrologists in the US after IRB approval.

Results: 120 US Nephrologists replied to the survey; 60% were in Nephrology for more than 10 years. Most (79%) used furosemide in CKD 5, (66%) used a combination of furosemide and metolazone. The first choice of diuretics in CKD5 was furosemide (79%), then hydrochlorothiazide (12%) and torsemide (8%) (p=0.005). In CKD5, 45% used diuretics daily, 29% on non-dialysis days and 26% discontinued them(p=0.002). In CKD 5, 63% would continue ACEI or ARB. In CKD5D, 84% of respondents had at least 30% of patients on ACEI/ARB and most (64%) would not stop these medications despite hyperkalemia. The majority (79%) did not change ACEI to those that were not dialyzed out. The perceived most effective BP medication in CKD5-Dialysis in decreasing order: Nifedipine/amlodipine (36%), ACEI/ARB (32%), beta blockers (17%), diuretics (13%) and others (4%) (p<0.0005). Most responders (79%) prescribed BP medication on non-dialysis days only and 88% thought that BP should be controlled with ultralow sodium. The furosemide dose in the first month was on average 1.00 mg/day. In the first month of dialysis, CKD5 was monthly (78%), weekly (12%) and as needed only (8%). DW was determined in the first week(31%) and the first month(52%). Of those surveved, 59% felt HTN in CKD5D had multiple causes.

Conclusions: Transitioning patients from CKD5 to CKD5 continues to remain challenging in terms of adjustment of BP medication. Variations in practice regarding the frequency of medication use may benefit from guidelines.
First Dialysis Prescription and Access Use: A Survey of United States Nephrologists

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Background: As there is no standard approach to initiate renal replacement therapy in CKD patients in regard to location of first treatment, access and dialysis prescription were evaluated in a survey of US nephrologists to better identify current practice patterns.

Methods: We created an anonymous electronic survey with 39 questions that was validated then approved by the IRB. Aggregate data was analyzed using descriptive statistics, avoiding duplicate responses.

Results: 120 US nephrologists replied to the survey, 60% were in nephrology practice for more than 10 years. The first hemodialysis (HD) treatment was at inpatient (22%), outpatient (29%) or either (47%). At the first HD, most nephrologists (92%) used a blood flow (BF) of 300 mL/min; 65% would use lower than usual dialysate flow rates (DFR) and 47% would use a smaller dialyzer. Ninety percent prescribed less time less than usual, even with blood area nitrogen less than 100 mg/dL. About 45% replied that only 10-50% of patients meeting criteria for peritoneal dialysis were actually started on this modality (p<0.005). Of the participants 47% noted that only 10-50% of patients who were eligible for transplant were listed, and the majority of responders (83%) noted that less than 10% of their patients got a preemptive transplant (p<0.0005). A patient educator was available to 64% of the patients. First dialysis with a permanent access was noted among 30-60% of patients by 43% of responders and in more than 60% of patients by 22% of responders. Of the participants 73% replied that the majority (>60%) of their patients got vein mapping before access creation. The time between vein mapping and access creation was one week to one month (61%) and more than one month (26%), (p<0.005). The number of angioplasties that were acceptable prior to primary access failure was noted as 2, (25%) 3 to (25%) or more than (4/24%).

Conclusions: There is variation in practice in several areas in regard to the initial dialysis session in CKD5D which may benefit from guidelines.

How to Dialyze a Patient with Left Ventricular Assist Device in a Chronic Dialysis Unit? A Practical Protocol

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Background: To provide chronic HD treatments to ESRD patients with LVAD in a chronic unit in the community is a challenge and a relatively new experience for nephrologists. As LVADs have revolutionized the treatment of advance heart failure there are rising numbers of these patients developing ESRD with need for HD in the community. Development of a practical, simple and safe protocol is needed to dialyze these patients in the chronic units.

Methods: This protocol and safety check list is developed to provide routine HD treatment for patients with LVAD and successfully implemented in a chronic dialysis unit in the community setting. The special policy and procedure relevant to this protocol, safety check list and standing orders for the dialysis nurses were approved by the governing body before dialysis staffs were trained. The VAD coordinator is present during first training.

Results: This protocol is a step by step guidance for the dialysis staff. The whole process has 3 components. A supplemental informed consent signed by the patient to cover for any adverse reactions and/or side effects potentially related to Lixelle S-35. Presence of support person who waits in lobby after power base is connected. LVAD check list

Conclusions: This protocol to provide incenter HD to patients with LVAD in a chronic unit is simple & safe. It can be implemented in a chronic HD unit.
**PUB625**

More Nephrologist Visits Are Associated with Lower Cost of Care for Dialysis Patients  


**Fresenius Medical Care North America, Waltham, MA.**

**Background:** Medicare patients with end stage renal disease (ESRD) are treated by nephrologists, primary care providers (PCPs), cardiologists and other specialists on a regular basis. We investigated the relationship of visits to these providers and total costs of care.

**Methods:** Medicare 100% ESRD data for patients with evidence of dialysis at any time during January 1, 2010 through December 31, 2011 were analyzed. Nephrologist, PCP and cardiologist visits were determined by specialty codes of Part B claims (including both in- and out-patient patients). All data was aggregated at the Metropolitan Statistical Area level (MSA). We computed a ratio of nephrologist visits to PCP visits per MSA as well as nephrologist visits to cardiologist visits per MSA during the above period (visits were calculated on a per patient per month basis). Total costs of care (per member per month [PMPM]) were determined by aggregating Medicare Part A and B costs. Comparisons of ratios were performed using t-tests for quartiles of PMPM for two specialty visit ratios.

**Results:** Claims for 368,711 patients were analyzed. Patients in the lower quartiles of total cost had significantly more nephrology visits relative to PCPs and cardiologists.

**Conclusions:** These results indicate that higher ratios of nephrologist visits to cardiologist/PCP visits are significantly associated with decreased cost on a MSA level. Taken that nephrologist visits tend to be constant (due to the monthly capitated payment), these results may be revealing a “sicker” and therefore more expensive population of patients on a MSA level that require more medical attention from a cardiologist or PCP, likely due to hospitalizations. Adjustments for underlying disease should be considered.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

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**PUB626**

Prediction of Non-Adherence to Hemodialysis Treatment Regimens  

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**Background:** Non-adherence with hemodialysis (HD) treatment regimens is known to be associated with increased morbidity and mortality. The aim of this project was to develop a predictive model (PM) to identify HD patients who will likely have unexcused no shows to routine dialysis treatments within the next week.

**Methods:** Using data between 1/1/2014 and 12/31/2014 from the Fresenius Medical Care Knowledge Center and 2014 weather data from the National Oceanic and Atmospheric Administration National Centers for Environmental Information, PMs were designed and developed for prediction of unexcused no shows in patients not residing in a nursing home. Various PMs were investigated and included the generalized linear model, partitioning and regression trees, artificial neural networks, and generalized additive model (GAM). In all, 1,554,833 records stratified in weekly intervals on 60 variables from 172,854 patients were utilized. Variables included data on the patient’s history of unexcused no shows, demographics, comorbidities, laboratories, holidays, sporting events, and weather. A multi-tier prediction process was performed with respect to the availability of data. The area under the curve (AUC), sensitivities and specificities were investigated to determine the model with the highest performance.

**Results:** Best performing model had AUC of 0.87 for the multi-tier PMs utilizing a 30% test dataset. A small pilot test on 860 patients for three weeks utilizing optimal Yoden index as the cutoff value to predict the high probability of the unexcused no show events achieved an average sensitivity of 0.57 and specificity of 0.95.

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

Underline represents presenting author.

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Conclusions: This pilot test of the developed modeling demonstrates that PM can assist in identifying patients with a high probability for unexposed missed HEV cases. Additional studies are needed to further analyze the potential of predictions forand interventions associated with reducing unexposed no show events.

**Funding:** Pharmaceutical Company Support - Fresenius Medical Care North America

**PUB627**

Factors Influencing Residual Renal Function Decrease in Hemodialysis Treated Patients

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**Background:** We have shown in previous studies that maintenance of residual renal function in hemodialysis treated patients is conditioned by the number of weekly sessions, and is better in patients who start treatment with a twice weekly schedule. The aim of this study is to analyse the influence of other variables in the preservation of residual renal function.

**Methods:** Of the 174 consecutive patients who started hemodialysis treatment in the hospital, 98 began with 2-weekly sessions (2HD group), and 76 with 3-weekly sessions (3HD group). Residual renal function was measured every two months (mean urea and creatinine clearance).

**Results:** Decrease in residual renal function was lower in the 2HD group (median 0.19 ± 0.46 ml/min/month, p=0.005). In both groups the residual renal function decrease was higher in the patients from the transplant program than in those from predialysis: 2HD group: median 0.93 ± 0.17 ml/min/month, p=0.003; 3HD group: median 0.76 ± 0.32 ml/min/month, p=0.005. Neither the initial schedule, sex or etiology of the renal disease influenced the decrease in residual renal function in either of the two groups of patients. Moreover we found no correlation between the decrease in residual renal function with age, the residual function at the start of dialysis or with the Charlson comorbidity index. Of the 98 patients who began with the 2HD schedule, 45 went on to dialysis three times a week when the residual renal function was less than 3 ml/min/these patients had a mean of 10.8 months on the 2HD schedule. The length of time on this model was not influenced either by age, sex, etiology of the nephropathy, comorbidity index, scheduled start or basal renal function.

**Conclusions:** The decrease in residual renal function in the patient treated with hemodialysis depends basically on the number of weekly sessions with which the dialysis treatment was started. Of all the variables analysed only the return to dialysis due to graft loss conditioned a higher decrease in residual renal function in both groups of patients.

**PUB628**

Circadian Blood Pressure Behaviour in Hemodialysis Patients

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**Background:** Blood pressure (BP) evaluation and management in haemodialysis (HD) patients is often a matter of debate. During HD hypotension as well as a paradoxical rise in BP can be observed. Ambulatory BP monitoring in ESRD patients is a promising non invasive technique to assess the presence of this phenomenon.

**Methods:** We included 38 patients with ESRD (68% men, mean age 62.19 years, 52% hypertensive) that underwent HD three times a week in the HD unit of our hospital and were on their ideal dry weight. Ambulatory BP monitoring was applied one hour before an HD session and was set to measure BP every 30 minutes and until arrival for the next HD session, for a total of two subsequent 24-hour periods. Blood pressure dipping was defined as [(daytime systolic BP – nighttime systolic BP)/ daytime systolic BP]. Patients were defined as dippers if BP dipping was >10% and risers if BP dipping <0%.

**Results:** Body weight before and after the HD session was 72±2kg and 77±2mg Hg respectively. Ambulatory systolic/diastolic BP increased not significantly from 127±23/70±13mmHg to 130±19/71±11mmHg (p=0.05) from the first to the second 24-hour period. Mean dipping was 1.5±7.8% in the first day and further decreased to -0.94±6.8% in the second day. Accordingly, in the first 24-hour period, only 6 patients (16%) were dippers and reduced to 2 patient in the following day (5%). Sixteen patients (42%) and 18 patients (47%) were risers at the first and second 24-hour period respectively.

**Conclusions:** Daytime systolic BP does not substantially change during the 48-hour period extending from HD to HD session. Yet, prevalence of the non-dippers as well as the riser pattern is high and further increases during the interdialytic period. Patients with this BP pattern are at high risk for coronary artery disease, especially if other comorbidities coexist. Ambulatory BP monitoring in ESRD patients is a promising non invasive technique for the recognition of future heart disease.

**PUB629**

In Vitro Dialysability of SNF472, a Novel Inhibitor of Vascular Calcification, Using Conventional Hemodialysis and Hemodiafiltration

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**Background:** SNF472 is being developed for the treatment of calciphylaxis and cardiovascular calcification in end stage renal disease patients on hemodialysis. The intended use of SNF472 is intravenous infusion during dialysis; therefore our aim was to assess its possible dialyzability and its effects on calcium (Ca) chelation.

**Methods:** Dialysability of SNF472 was assessed using online hemodiafiltration (OL-HDF) and conventional hemodialysis (HD) systems. The interaction of SNF472 with the system was assessed under bypass conditions (dialysis in off-mode). One liter of heparinized fresh blood spiked with 8 mg/dl creatinine was introduced in a container maintained at 37°C and a one hour dialysis session was simulated. 66.6, 30 and 10 ml/min SNF472 were infused during the first 20 minutes of dialysis. Samples were obtained at different time points and creatinine, total and ionized Ca and SNF472 levels were quantified.

**Results:** No dialyzation of SNF472 was detected at 30 and 66.6 mg/mL neither in OL-HDF nor in HD systems. Dialyzation was measured at 10 ml/min SNF472 both in OL-HDF and in HD, with an estimated clearance (CI) of 39 and 18 ml/min, respectively. Creatinine showed a CI of 231 and 220 ml/min, respectively. In bypass conditions, blood Ca was chelated during the 20 minutes of SNF472 infusion when added at 66.6 mg/mL. However, when the system was switched to the dialysis mode, the Ca in the dialysis bath compensated the chelating effect of SNF472 and Ca levels remained unaltered.

**Conclusions:** SNF472 dialyses with a low CI. SNF472 levels increase in blood during infusion and dialysis and does not prevent from attaining potentially therapeutic levels. As SNF472 will be infused during the whole dialysis session, this low CI is not expected to affect systemic exposure.

A Simple and Cost Effective Approach to Ultra-Pure Dialysate

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**Background:** Ultrapure dialysate has been shown to reduce inflammation and improve nutritional and anemia parameters in patients on chronic maintenance hemodialysis. The Nephros® DSU (Dual Stage Ultrafilter, Nephros Inc, River Edge, NJ) has been shown to reduce bacterial counts and endotoxin levels by at least a 5-log order of magnitude.

**Methods:** We performed an observational trial of this filter in a hospital-based acute dialysis facility in the USA.

**Results:** There were 23 chronic stable hemodialysis outpatients treated during the 6 months before and after the installation of the Nephros® filters. The mean age was 51 (range 29-91), 61% male, predominantly Hispanic (70% Hispanic, 17% African-American, 9% Caucasian, 4% Asian) and 30% diabetic. Comparing data from the 6 month period after the installation of the filters to the preceding 6 months, there was an increase in the mean hemoglobin level of 0.5 g/dl (p=0.010) with a reduction in the mean weekly darbopentin dose of 14.6 mg or 40% (P<0.001) translating to a reduction in the ESA resistance index (weekly ESA dose/hemoglobin level) of 1.52 (P<0.001). During this time period, indirect inflammatory markers showed a reduction in the mean WBC count from 7,000 to 6,600 x 10³/L (p=0.008) and an increase in serum albumin from 3.6 to 3.7 (p=0.024). The mean spKt/V was unchanged during the 2 time periods (from 1.690 to 1.607, p>0.30).

**Conclusions:** In conclusion, the use of the Nephros® DSU filter to further reduce endotoxin exposure in chronic hemodialysis patients can result in improved ESA responsiveness and a lower ESA dose.
Care Delivery Models for End Stage Renal Disease: A Systematic Review

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Background: Reimbursement for dialysis care has led the way for the broader transition to a value-based payment model. As payment policy for dialysis evolves, a better understanding of the evidence around care delivery models that optimize outcomes and increase the value of care for dialysis patients is essential. Limited evidence exists about which care delivery models are most effective.

Methods: Multiple databases were searched for comparative studies of care delivery models for ESRD published between 2000 and 2014. The intervention had to include >5 dialysis patients over age 18 years and receiving treatment. >6 months follow up, and reported patient important outcomes i.e. mortality, important clinical outcomes, hospitalizations and quality of life. Data was abstracted by reviewer pairs; study quality was assessed using Canadian and Newcastle Ottawa tools.

Results: 1841 abstracts were screened, 59 full-text articles were reviewed, and 23 studies with 87,281 patients were included for final analysis. The interventions included nutritional (n=4), multidisciplinary care (n=6), satellite programs (n=3), home dialysis (n=3), access monitoring (n=2), physician contact (n=4), and nocturnal dialysis (n=1). Most were observational studies of decent quality with representativeness and incomplete follow up being the main potential sources of bias. Two randomized studies on home dialysis and pharmacist care, had attention as the main risk of bias. Most interventions showed positive effect raising concern of publication bias. Overall, hospitalizations were significantly lower in the intervention group despite large heterogeneity: 0.824, 95% CI 0.781, 0.868, p=0.001, 12.95-65.9%.

Conclusions: Multiple interventions have the potential to improve the outcomes of dialysis patients but have not been compared in terms of safety and effectiveness. Limited evidence is available to inform dialysis practice redesign to adapt to new payment structures. Further studies are needed to define best delivery models for dialysis care.

Syntemet Dimethylarginine (SDMA) Is Poorly Cleared by Standard Hemodialysis

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Background: High SDMA levels have been associated with an increased risk for cardiovascular disease in patients with normal or reduced renal function. The effect of hemodialysis on SDMA has not been thoroughly studied.

Methods: We measured SDMA levels and its handling by hemodialysis and by the normal kidney in subjects with ESRD on chronic hemodialysis (n = 7) and in normal controls (n=6).

Results: The mean (SD) SDMA levels in ESRD were six times higher than in normal controls, 3.350 (0.65) vs 0.530 (0.25) μM, p<0.001. For comparison pre-dialysis BUN levels was 44.12±1.31mg/dl in ESRD, and 14.9±3.2mg/dl in controls. The fractional reduction in SDMA was significantly lower than that of urea, 47.4(15.1)% vs 76.7(4.7)% p<0.001; and the volume of distribution was much higher 58.5(14.5) l vs 35.10(4.4) l. For urea also the urinary clearance of SDMA was 78.2(m3.5) ml/min in normal controls was higher than that of urea 55.2(13.7) ml/min. SDMA production rates were similar 46.7(9.4) vs 52.3(13.9) mmol/day, ESRD vs normals, p>0.05.

Conclusions: In summary, SDMA circulates at high levels in hemodialysis patients due at least in part to its relatively high clearance by the kidney, relative to urea, and its larger volume of distribution. The latter suggests that SDMA is likely to be localized in the intracellular compartment, and therefore less available for clearance by standard hemodialysis.

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On-Line Hemodiafiltration Is Efficient for Inflammation and Phosphorus Control

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Background: High efficiency on-line hemodiafiltration is efficient to remove uremic toxins and phosphorus. Many studies had demonstrated the impact of this modality in mortality. The main objective of this study was to analyze the high efficiency on-line hemodiafiltration ability to remove phosphorus and reactive C protein.

Methods: This is a prospective study with end stage chronic kidney disease patients undergoing dialysis with high levels of phosphorus. High efficiency on-line hemodiafiltration was used as a separation dialyzer with a surface area of 2200, was used for a period of at least one year of follow-up. Beta-2 microglobulin, pre dialysis urea, post dialysis urea, reactive C protein, hemoglobin and phosphorus were collect from patients before starting on-line hemodiafiltration treatment and every month.

Results: Patients included in this study were 375 years old; they were on hemodialysis for at least for one year. 58% had hypertension or coronaryopathy. Hemodialysis dose as single pool Kt/V were significantly higher (12.1±0.20 vs 1.36±0.16; p<0.001) and this difference was kept for all follow-up. In six months of high efficiency hemodiafiltration we also found a decrease on phosphorus levels (7.9±2.4 vs 7.3±2.01; p<0.001) in one year follow up, phosphorus levels were still significantly lower than in the conventional hemodialysis (7.3±2.01 vs 5.6±2.05; p<0.001). We also observed a decline in the need for phosphorus doses in six months (p=0.04) associated with a higher hemoglobin levels (p<0.001). Reactive C protein showed significantly lower levels after six months of online hemodiafiltration (p=0.004).

Conclusions: High efficiency on-line hemodiafiltration is an efficient method of reduction of reactive C protein and may reduce costs due to reduced doses of erythropoietin analogus.

On-Line Hemodiafiltration Filters a Comparative Study

Nadia Guimaraes-Souza, Adriano Luiz Ammiriti, Thais Nenmotu Matsui, Maria C.C. Andreoli, Fabiana Dias Carneiro, Ana C M S Ramos, Bento C. Santos. Dialysis Center, Hospital Israelita Albert Einstein, Brazil.

Background: High efficiency on-line hemodiafiltration is the best method for middle molecules and phosphorus removal. Many studies had demonstrated the efficiency of this method in mortality reduction. The main objective of this study was to compare the three filters available for on-line HDF comparing the ability to remove urea, phosphorus and beta-2-microglobulin.

Methods: Prospective cross-over study including four patients and three available filters for hemodiafiltration. All section of on-line hemodiafiltration was made with high efficiency (23-25Hz). Filters HDF 100, FX100 e HDF90COR were compared. Urea, phosphorus and beta-2 microglobulin were collected before and after first use of each filter A reduction of >33% was related to comparison.

Results: 76% of patients were male, the middle age (61±3.5); 76% of patients were diabetics and had peripheral neuropathy and 34% had coronaryopathy. FX100 filter showed significantly higher dialysis compared to FX80COR (p<0.05); the same was observed for urea reduction ratio(p<0.04). Beta-2-microglobulin and phosphorus reduction ratio were similar between all filters.

Conclusions: FX100 and HDF100 filter were similar for urea remotion ratio. There were no differences for other molecules.

Satisfaction of Patients on Dialysis Unit

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Background: The asessment of the satisfaction of patients in Dialysis, is a useful tool to meet patient needs; axis on which the care service is based.In turn it allows to identify the deficient areas.

Methods: Objektive 1) To know the views of patients about the service that is offered in each of the areas of focus. 2) To analyze the profile of satisfaction of patients they expressed their overall dissatisfaction. Prospective, descriptive study conducted at the Dialysis Unit of the Military Hospital Córdoba, conducted between 15/11/2014 to 15/12/2014. Inclusion: All Patients attending the service, wich received some form of dialysis (hemodialysis-DPD) in the period. Exclusion criteria: a) diagnostis of cognitive dementia, b) Carrying less than three months of treatment c) not be psychological and physical conditions to answer the survey. A qualitative survey, structured ajar, applied voluntary and anonymous.

Results: We measured SDMA levels and its handling by hemodialysis and by the normal kidney in subjects with ESRD on chronic hemodialysis (n = 7) and in normal controls (n=6).

Conclusions: As a management tool, it should be rated as positive aspects stimulate and work on correcting the negative aspects. 2. The level of dissatisfaction is directly related to dialysis treatment time of the patient, the longer, higher degree of dissatisfaction. 3. It is advisable conduct regular surveys on the degree of patient satisfaction Dialysis, and that will help improve their quality of life.

Correlation Between Calcium Phosphorus Product and Hypertension in ESRD Patients on Maintenance Hemodialysis

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Background: Increased levels of serum calcium, phosphorus and product of serum calcium and phosphorus (Ca x P) in end stage renal disease (ESRD) patients has been shown to be associated with increased mean arterial blood pressure (MAP). The available data is limited and no study has been done in Pakistan. We conducted a cross sectional study to determine the correlation between mean arterial blood pressure (MAP) and serum calcium-phosphorus product in our ESRD patients on hemodialysis.

Methods: Blood Pressure of all the prevalent ESRD patients in a single dialysis center was recorded and mean arterial blood pressure (MAP) was calculated pre and post dialysis. All patients were clinically euvelonic. Serum calcium and phosphorus levels were measured and Calcium-phosphorus product (Ca x P) was calculated. The product above 50 and the MAP above 93 were taken as high.
Results: Of the 60 ESRD patients, 35 (58.3%) were males with mean age was 39.5±5 years. The ABI protocol as previously reported could be performed in 18 (30%) patients with high pre-diagnosis MAP in 8 (44%) and high post-diagnosis MAP in 4 (22%) patients respectively. Of 42 (70%) patients with Ca×P product below 50 high pre-diagnosis MAP was seen in 31 (73%) and high post-diagnosis MAP was seen in 29 (69%) patients.

Conclusions: The Ca×P product was too low and cannot be considered with high pre and post-diagnosis MAP. The results are not consistent with earlier studies done in developed countries. Larger studies are needed to re-evaluate these findings.

PUB637

Behaviour of Ankle-Brachial Index During Hemodialysis: Effect of Calcium Dialysate Concentration Zaida Noemí Cabrera Jiménez, Rosa M. A. Moyes, Bruno C. Silva, Luciene dos Reis, Wagner Dominguez, Fabiana Gracioli, Rosieli M. Elias. 1 Nephrology, Univ of Sao Paulo, Sao Paulo, SP, Brazil; 2 Unive Nofe de Julho- UNINOVE, Sao Paulo, SP, Brazil.

Background: Ankle-brachial index (ABI) is a simple way to access cardiovascular risk. Both low (<0.9) and high (>1.3) ABI are associated with increased mortality risk in patients on hemodialysis (HD). However, little is known regarding the acute variation of ABI from pre to post hemodialysis, and also whether the calcium dialysate content [Ca] may interfere with this variability. We aimed to investigate the impact of [Ca] 3.5 vs. 2.5 on the variability of ABI during HD.

Methods: Incident patients on HD for up to 90 days were included. ABI was evaluated pre and post HD in the midnight session of two consecutive weeks with [Ca] 3.5 and 2.5, respectively. Biochemical variables, electrical bioimpedance and non-invasive hemodynamic (Finapress®) were assessed.

Results: 17 patients (10 men) aged 42 ± 17 years were included. ABI pre- and post- HD with [Ca] 3.5 and 2.5 were 1.2 ± 0.1, 1.1 ± 0.1, 1.1 ± 0.2, and 1.2 ± 0.1, respectively. Although the mean ABI values were within normal range, there was a great variability in the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI, such that in 9 patients it increased using [Ca] 3.5, with 5 patients (29%) changing the ABI. We observed a significant expansion of Tr1 cells expressing a memory phenotype ([CD45RO]) and the immunomodulatory receptor PD-L1 in tolerant but not other animals.

Conclusions: Our data show that the surface markers CD409 and CD43- can be used to distinguish Tr1 from “classical” FoxP3+ Tregs in cryopreserved monocytes. Tr1 cells are likely to inhibit T cell responses mediated by PD-1/PD-L1 interactions. The contribution of these activated Tr1 cells to induction and maintenance of organ allograft tolerance in non-primate humans is under investigation.

Funding: NIDDK Support, Veterans Administration Support

PUB640

Urinary MicroRNA-25 as a Potential Biomarker for Detection of Renal Damage in Rats and Renal Transplant Patients Kumiko Nishihara,1 Masayuki Kanki,1 Moto Kajiwara,1 Kei Kurihara,2 Takahisa Yano,1 Hidehito Kitada,3 Satoshi Masuda,4 Akira Unami.1 1Drug Safety Research Laboratories, Astellas Pharma Inc., Osaka, Japan; 2Dept of Pharmacy, Kyushu Univ Hospital, Fukuoka, Japan; 3Dept of Research and Development of Next Generation Medical and Surgical Sciences, Kyushu Univ, Fukuoka, Japan; 4Dept of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.

Background: Circulating microRNAs (miRNAs) were proposed as potential biomarkers of various biological functions and diseases in the kidneys. We have found that some urinary miRNAs were useful for detection of cisplatin-induced proximal tubular injury in rats (Kanki M et al., Toxicology, 324, 158, 2014). In this study, we examined the feasibility of urinary miRNAs for renal damage in Japanese patients receiving kidney transplantation as well as rats.

Methods: Gentamicin (100 mg/kg; model of tubular injury) was daily given for 7 days and puromycin (50 mg/kg; model of glomerular injury) was given as a single injection on day 1. Seven days after the treatment, the urinary levels of 15 miRNAs were determined by real-time PCR. The receiver-operator characteristics (ROC) curve analysis for proximal tubular necrosis was performed including previous cisplatin study. Human urine samples were collected from 30 healthy volunteers and 11 renal transplant patients at days 1, 2, 10, and 11 weeks after surgery. The levels of 4 miRNAs were determined. Results: In gentamicin treated rats, the levels of miR-238, let-7a-1, miR-1839, miR-25, miR-140, and miR-378 were increased more than 2-fold with high values of the area under the ROC curve, which were the same or more than those of BUN and serum creatinine, while they were not changed in rats treated with puromycin. Among these miRNAs, miR-25, miR-140-3p, miR-328 and miR-378 were measured in the human urine samples. In human samples, miR-25 at postoperative day 7 in some patients exhibited higher levels than the highest value of those in the volunteers.

Conclusions: Urinary miRNAs other than miR-25 but not other miRNAs might be available for detecting renal damage in the postoperative course of renal transplant patients as well as that in the rats with proximal tubular injury.

PUB641

Early Activation of Complement in Renal Ischaemia/Reperfusion (I/R) Injury Is Mediated by Pentraxin 3 (PTX3) Synthesized by Peripheral Blood Mononuclear Cells (PBMCs) Giuseppe Castellano,1 Chiara Divella,1 Alessandra Stasi,1 Paola Pontrelli,2 Matteo Accetturo,1 Marco Fiorentino,1 Mattia Rossini,2 Vincenzo Montinaro,1 G. Lucarelli,1 Mattea Battaglia,1 Loreto Gesualdo,1 Giuseppe Grandaldo,2 Dept of Emergency and Organ Transplantation, Univ of Bari, Bari, Italy; 2Dept of Medical and Surgical Sciences, Univ of Foggia, Foggia, Italy.

Background: PTX3 has been recently implicated in the promotion of vascular inflammation in the acute stage and the aim of this work was to investigate the possible involvement of PTX3 in renal I/R injury.

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

Underline represents presenting author.

1036A
Methods: PBMCs were isolated from blood of patients with Delay graft function (DGF, n=10) and Early graft function (EGF, n=10) at T0 and T24h from transplant. Gene expression profiles of PBMCs from both groups were assessed by Affymetrix technologies. Results were evaluated by statistical analysis and functional pathway analysis and validated by confocal analysis on a swine model of IR injury. Renal I was induced in 8 pigs by arterial clamping for 30 min and tissues were analyzed at different time points after R (T15' , 30' , 60' ).

Results: Microarray analysis (FDR<5% and a FC>1.5) revealed that the expression of PTX3 and C3 were downregulated in DGF compared to DGF patients. On the contrary, the gene CR1 was upregulated in DGF. Furthermore, in the pig model, confocal laser microscopy demonstrated deposits already at 0.5, 1, 1.5, 3, 6, and 12 days after T0, localized at peritubular capillary levels. We found a significant increase in infiltrating interstitial leucocytes such as CD16+ /PTX3+ monocyte-macrophages (6.2±1.2;p=0.05) and SWC3α/PTX3+ dendritic cells (3.7±0.5;p=0.05) compared to T0. Finally, we identified tubulo-interstitial FSP1+/PTX3+ myofibroblasts (4.1±1.3;p=0.04) Co-localization between C5b-9/PTX3, PTX3/C1q and PTX3/MBL clearly demonstrated the activation of Classical and Lectin Complement pathways in presence of PTX3 deposits.

Conclusions: Our data would suggest a key role of PTX3 synthesized by peripheral blood mononuclear cells (PBMCs) during DGF leading to an early activation of complement in transplant kidney.

PUB642
The Effect of Combined Treatment of Dipeptidyl Peptidase IV Inhibitor and Metformin in Sildiusin-Induced Diabetes Mellitus
Lim Jin, Jin Sun, Woo Lim, Byung Ha Chung, Chul Woo Yang.

Background: Optimal treatment of post-transplant diabetes mellitus is still controversial. This study was performed to evaluate whether the combined treatment of DPP IV inhibitor with metformin (MET) is effective in sildiusin (SRL)-induced diabetes mellitus.

Methods: SRL-induced diabetes mellitus was made by treating SRL (0.3 mg/kg) for 3 weeks in rats, and then started to treat DPP IV inhibitor (LC15-0444[LC], 5mg/kg), and/or MET (200 mg/kg) for further 3 weeks. The effect of combined treatment of LC and MET on SRL-induced diabetes mellitus was evaluated by IPGTT and islet size. The oxidative stress was evaluated by measuring 4-OHdG, 4-HHE, MnSOD, and catalase in samples. Insulin secretion capacity was evaluated by glucose-stimulated insulin secretion (GSIS) test using normal isolated rat islets treated with SRL, exendin-4 and/or MET.

Results: SRL treatment for 6 weeks decreased body weight and increased water intake and food consumption, and islet volume compared with vehicle group. SRL treatment significantly increased AUCg from the values obtained during the IPGTT, but LC or MET treatment recovered these values compared with the SRL treatment alone. Combined treatment with LC and MET has more significantly decreased blood glucose level than LC or MET treatment alone. Islet size which was significantly decreased in the SRL group was recovered with combined treatment of LC and MET. SRL treatment significantly increased intense nuclear expression and larger positive area for 8HdG and 4-HHE, but combined treatment LC and MET has more significantly decreased blood glucose level than LC or MET treatment alone. The result of GSIS also showed that combined treatment of LC and MET showed higher insulin level than exendin-4 or MET treatment alone.

Conclusions: Combined treatment with LC and MET exerts better glucose control by decreasing oxidative stress compared to SRL, which provides the rationale for the combined use of DPP IV inhibitor and MET in SRL-induced diabetes mellitus.

Funding: Government Support - Non-U.S.

PUB643
Incidence and Outcomes of Hyponatremia Early Post Lung Transplantation
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1Div of Nephrology and Hypertension; 2Pulmonary and Critical Care, Dept of Medicine, Northwestern University Feinberg School of Medicine.

Background: Outcomes of in-hospital hyponatremia in lung transplant recipients are unclear. The aim of this study is to describe the frequency of hyponatremia and outcomes associated with hyponatremia during the early postoperative period.

Methods: We performed a retrospective chart review of all lung transplant recipients at Northwestern Memorial Hospital since the first case performed in July 2014 until May 2015. The severity of hyponatremia was defined as mild, moderate, and severe with serum Na of < 135, < 130, and < 125 mEq/L, respectively.

Results: A total of 13 lung transplant recipients were included. Age at the time of transplantation was 61.5±2.2 (SEM) years and 69% was female. The most common indication for transplantation was severe COPD (54%). Serum creatinine at the time of transplantation and at hospital discharge was 0.8±0.6 and 1.0±0.2 mg/dL, respectively. Seven patients had acute kidney injury (AKI) with Acute kidney injury (AKI) had > 2 times longer length of hospitalization (26.2±4.8 vs. 10.0±1.1 days; p = 0.0046) and were more likely to develop postoperative hyponatremia (100% vs. 71%; p = 0.051). Among 11 patients with postoperative hyponatremia, 7 were readmitted (5 with hyponatremia and 4 with AKI). At the time of transplant, 8% of the patients had hyponatremia, while the incidence was up to 46% at the time of discharge (Table1). Almost half of the patients had persistent hyponatremia during 1 month follow-up.

Conclusions: Lung transplant recipients commonly develop hyponatremia during the immediate post operative period and are more likely to be readmitted with hyponatremia. The incidence of hyponatremia remains high up to 1 month post transplantation, AKI is also a risk for readmission and predicts longer length of hospital stay.

PUB644
Motivations, Challenges, and Attitudes to Self-Management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies
Nathan Jameson,1,2 Camilla Sara Hanson,1,2 Michelle A. Josephson,3 Elisa J. Gordon,4 Jonathan C. Craig,1,2 Fabian Halleck,3 Klemens Budde,4 Allison Tong,1,2 1Centre for Kidney Research; 2The Children’s Hospital at Westmead, Sydney, New South Wales, Australia; 3School of Public Health, Univ of Sydney, Sydney, New South Wales, Australia; 4Dept of Medicine, The Univ of Chicago, Chicago, IL; 2Centre for Healthcare Studies and Comprehensive Transplant Centre, Northwestern Univ Feinberg School of Medicine, Chicago, IL; 3Dept of Nephrology, Charité, Universitätmedizin Berlin, Berlin, Germany.

Background: Kidney transplantation offers superior life expectancy and quality of life outcomes compared to other renal replacement therapy modalities. However, the complex and ongoing medication and self-management regimes impose a treatement burden on patients, and non-adherence remains a leading cause of graft loss.

Methods: MEDLINE, Embase, PsycINFO, and CINAHL were searched from database inception to October 2014. We used thematic synthesis to analyse the findings.

Results: Fifty studies involving 1238 participants aged from 18 to 82 years across 19 countries were included. We identified five themes: empowerment through autonomy (achieving mastery, tracking against tangible targets, developing bodily intuition, routinising and problem-solving, adaptive coping), prevaling fear of consequences (inescapable rejection anxiety, averse to dialysis, minimising future morbidity, trivialisation and denial, defining acceptable risks), burdense treatment and responsibilities (frustrating ambiguities, inadvertent forgetfulness, intrusive side-effects, reversing ingrained behaviours, financial hardship), over-medicalising life (dominating focus, evading patienthood, succumbing to burnout), and social accountability and motivation (demonstrating gratitude towards medical team, indebtedness to donor, peer learning).

Conclusions: Self-efficacy and social accountability are motivators for self-management, but ongoing adherence can be mentally and physically taxing. Multi-component interventions that incorporate education, psychosocial support, decision aids, and self-monitoring tools may foster self-management capacity and improve transplant outcomes.

PUB645
Abstract Withdrawn

PUB646
Characteristics of Patients with Vitamin D Deficiency After Kidney Transplantation in Qatar

Background: Vitamin D deficiency is common among normal people and in patients with chronic kidney disease including dialysis patients. Vitamin D deficiency continues to be prevalent after kidney transplantation (studies showed prevalence of 50-80%) especially with immunosuppression use and sun protection needed for elevated risk of skin cancer.

We studied characteristics of kidney transplant patients with vitamin D deficiency in Qatar.

Methods: We reviewed all available records of kidney transplant patients presented to our clinic at Hamad General Hospital in Doha, Qatar between 1/9/2013 and 1/3/2014 and have vitamin D level less than 30 ng/mL. Background data and laboratory tests of patients were obtained. All patients were receiving vitamin D supplements and prednisone within their immunosuppression per institution protocol.

Results: We studied 83 patients. Mean age was 55.5 ± 16.1 years. There were 55 males (66%) and 28 females (34%). Vitamin D deficiency was severe (level than 10 ng/mL) in 15 patients (18%) and moderate in 38 (46%) and mild in 30 patients (36%). Duration of transplant was 7.9 ± 2.5 years. Glomerular Filtration Rate was 65.5 ± 20.6 ml/min. We found no correlation between vitamin D and PTH levels or between vitamin D and GFR levels. Table 1 summarize bone mineral panel in our patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In a study of kidney transplant patients with vitamin D deficiency in Qatar we found that they were predominantly males, have normal calcium, phosphorus and alkaline phosphatase levels, while they have variable degree of elevated PTH with no correlation to vitamin D level. Most patients have mild to moderate vitamin D deficiency (82%) despite receiving vitamin D supplement although the supplement could have decreased the number of patients with severe vitamin D deficiency (18%). Further study could help to evaluate the role of vitamin D supplement in improving vitamin D level in kidney transplant recipients.

**PUB647**


**Background:** Vitamin D deficiency is common in normal population and in patients with chronic kidney disease including kidney transplant recipients. Elderly patients are vulnerable to vitamin D deficiency with less sun exposure and having multiple medical problems. We compared young versus elderly kidney transplant recipients with vitamin D deficiency in Qatar.

**Methods:** We reviewed all available records of kidney transplant recipients presented to our clinic at Hamad General Hospital in Qatar between 1/9/2013 and 1/3/2014. Background data and laboratory tests of patients were collected. All patients were receiving vitamin D supplements and prednisone per institution protocol.

**Results:** 83 patients were included. 41 patients in the young group (< 60 years old) and 42 in the elderly group (> 60 years old). There were 21 females versus 20 males in the young group and 35 males versus 7 females in the elderly group (pValue<0.05). Time on transplant was 9.1 +/- 4.93 years in the young group versus 8.6 +/- 2.7 in the elderly. Table 1 summarizes laboratory values for kidney transplant patients with vitamin D deficiency.

<table>
<thead>
<tr>
<th></th>
<th>Age over 60 years (n=42)</th>
<th>Age less than 60 years (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>17.7+/-6.4 ng/mL</td>
<td>15.1+/-6.7 ng/mL</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.28+/-0.13 mmol/L</td>
<td>2.29+/-0.15 mmol/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.22+/-0.18 mmol/L</td>
<td>1.16+/-0.3 mmol/L</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
<td>148.7+/-238.3 pg/mL</td>
<td>143.9+/-154.8 pg/mL</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>75.8+/-39 u/L</td>
<td>91.9+/-39.9 u/L</td>
</tr>
<tr>
<td>Glomerular Filtration Rate (GFR)</td>
<td>69.9+/-21.4 ml/min</td>
<td>61.2+/-19.2 ml/min</td>
</tr>
</tbody>
</table>

Conclusions: We compared vitamin D deficiency in young versus elderly kidney transplant recipients in Qatar. Although elderly patients have higher vitamin D levels, it was not statistically significant. This could be due to better compliance with vitamin D supplement in the elderly. Although duration on transplant, calcium, phosphorus and intact parathyroid hormone were similar, Glomerular Filtration Rate (GFR) was higher in the elderly. We explain that it almost all kidney transplants in Qatar are from live donors which lead to a higher GFR in the elderly as they are receiving kidneys from younger donors. There was statistically significant smaller number of females than males in the elderly group.

**PUB648**

Abstract Withdrawn

**PUB649**

The Current Status of Plasmapheresis Before Living Donor Kidney Transplantation in Japan. Norio Hanafusa, 1 Tomoko Usui, 1 Akihiko Matsumoto, 2 Satoko Sakurai, 1 Eisei Noiri, 1 Hideo Yasunaga, 1 Masaoi Nangaku 1 1Dept of Hemodialysis and Apheresis, The Univ of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan; 2Dept of Clinical Epidemiology and Health Economics, School of Public Health, The Univ of Tokyo, Bunkyo-ku, Tokyo, Japan.

**Background:** Plasmapheresis (PP) is utilized to remove alloantibodies before the living donor kidney transplantation (LDKT). The detailed practice patterns of PP before LDKT remains unknown. There also are concerns about the depletion of coagulation factors [Transfus Apher Sci 49: 254, 2013] by PP. We investigated the current status of PP before LDKT with use of the nationwide database.

**Methods:** The Japanese Diagnosis Procedure Combination Database includes all the patients discharged from hospitals participating in this program between July 2010 and March 2013. Those who received LDKT and PP before LDKT were included into this study. The modalities of PP, fresh frozen plasma (FFP) use, and albumin use were examined. We also investigated the relationship between modalities selected and outcomes such as the length and total costs of the hospital stay, or the amount of blood transfusion as the proxy of bleeding.

**Results:** In total 775 patients received PP before LDKT during the period. Among them 209 patients were treated only by simple plasma exchange (PE). Remaining 566 patients received double filtration plasmapheresis (DFPP), or cascade filtration. Interestingly, 274 patients treated by DFPP received also PE before transplantation. FFP was used during PP on 109, 180, and 42 patients treated by PE only, DFPP followed by PE, and DFPP only, respectively. Moreover, FFP was infused before the operation on 161 patients who were not used FFP during PP. As a whole 63.5% of total patients received FFP from the start of PP to the day of operation. DFPP followed by PE groups received less amount of blood transfusion (p<0.047), though the length of stay was longer and total costs were higher, compared to DFPP only (p<0.05).

**Conclusions:** Many of the patients received FFP, which suggests concerns about the depletion of coagulation factors during PP. The practice patterns were quite heterogeneous and the standardization of the practice patterns is needed to maximize the benefits of PP.

**Funding:** Government Support - Non-U.S.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

**1038A**
A DNI value of 2.7% was selected as cut-off value for AGPN, and renal transplant recipients with a DNI ≥ 2.7% were found to be at a higher risk of infection than those with a DNI < 2.7% (odd ratio [OR] 40.50; 95% CI 1.68-189.08; P <0.001). In a multivariate logistic regression analysis, DNI was a significant independent factor for predicting AGPN after adjusting age, sex, log WBC count, log neutrophil count, log lymphocyte count, DNI value, CRP concentration and procalcitonin concentration (OR 4.32; 95% CI 1.81-10.34, P < 0.001).

Conclusions: The present study demonstrated that a DNI value above 2.7% was an independent predictive marker for AGPN and an effective marker to differentiate between AGPN and acute graft rejection. Thus, these finding suggest that DNI may be a useful marker in the management of these patients.

PUB652

Effect of Pre-Transplant Dialysis Modality on Outcomes of Living-Donor Kidney Transplantation Recipients Chiaki Kawabata, General Internal Medicine, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan.

Background: There are few studies on living-donor kidney transplantation that compare the outcomes after pre-transplant dialysis modality. We examined the short-term outcomes of living-donor kidney transplantation recipients after peritoneal dialysis (PD) and hemodialysis (HD), respectively.

Methods: 112 patients have undergone living-donor kidney transplantation procedures in our hospital between January 2001 and May 2014. We studied 40 patients, under 40 years of age, with dialysis durations of less than 5 years. We compared 13 PD patients with 27 HD patients and investigated the short-term outcomes.

Results: These two groups showed no significant differences as regards baseline characteristics including dialysis duration, body mass index, type of calcineurin inhibitor or ABO blood type incompatibility. The PD group was younger than the HD group as regards recipient age and donor age (22.5±8.0 years vs 29.1±6.0 years p=0.005) and, 50.7±8.2 years vs 56.9±7.1 years p=0.02), respectively. There were no differences in early post-transplant complications, such as wound infection, bleeding, thrombosis, delayed graft function, or acute rejection. The PD group was better than the HD group in the estimated glomerular filtration rate (eGFR) at discharge (74.3±27.3 ml/min/1.73 m2 vs 48.3±12.3 ml/min/1.73 m2 p=0.001) and eGFR 1 year post-transplantation (68.4±21.8 ml/min/1.73 m2 vs 45.6±13.2 ml/min/1.73 m2 p=0.003).

Conclusions: In the case of younger and less than 5 years of dialysis duration, PD and HD demonstrated no differences in early post-operative complications. PD is significantly better than HD as regards eGFR up to 1 year post-transplantation.

PUB653

Bright Field Microscopy of the Unstained Urine Sediment: A Basic Tool to Identify Decoy Cells due to Polyomavirus BK on Kidney Allograft Recipients During Routine Urinalysis José A. Poloni,1,2,3 Gabriel Godinho Pinto,1 Maria Giordani,1 Elizete Keitel,1,2 Alessandro C. Pasqualotto,1 Liane Rotta,2 Irmandade da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil; 1Univ Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil; 1Control Lab, Rio de Janeiro, RJ, Brazil.

Background: Polyomavirus BK (BKV) is an important pathogen that can be reactivated in kidney allograft recipients, potentially leading to BKV nephropathy (BKVN), an important cause of graft loss. Decoy cells (DC), urothelial cells or renal tubular epithelial cells modified by the proliferation of BKV, are one of the hallmarks of BKV reactivation and can be identified in the fresh urine sediment.

Methods: A cohort of 102 kidney transplant patients was followed during months 3 and 6 after the transplant procedure. Urine samples were obtained to detect the presence of DC in the fresh and unstained urine sediment under bright field microscopy (BFM) by two experienced analysts, as well as by BKV viruria by qPCR.

Results: DC were found in 15 patients.

Conclusions: Despite its limited sensitivity, fresh and unstained urine sediment analysis under BFM is a method that can be used to identify DC due to BKV reactivation. The analysis procedure is fast, cheap and painless. The information obtained during routine urinalysis can be used to lead to the early diagnosis of BKV reactivation helping on the clinical management of the patients. The ability of less trained observers to perform such diagnosis requires further validation.

PUB654

Intravenous Immunoglobulin in the Management of Pneumocystis Pneumonia: A Case Series Musab Elgaali, Muhammad Inman, Matthew Edey. Hull Royal Infirmary, Hull, United Kingdom.

Background: Pneumocystis pneumonia (PCP) is a well-recognized complication of renal transplantation. We present 2 cases of severe PCP treated successfully with intravenous immunoglobulin (IVIg), trimethoprim-sulfamethoxazole (TMP-SMX) and withdrawal of immunosuppression. Graft function was maintained despite a high baseline immunological risk.

Methods: Case A: A 32 year-old woman presented 2 years post-transplant with acute cellular rejection treated with steroids. 2 months later she was admitted with respiratory failure due to PCP. She required intubation and ultimately oscillatory ventilation. CMV DNA was detected at low levels in bronchoalveolar lavage (BAL) fluid. IVlg 30g on alternate days (10 doses) was added, in addition to withdrawal of immunosuppression and hydrocortisone replacement. She made a full recovery, with preservation of transplant function throughout. Case B: A 47 year-old woman received a second kidney transplant. Early post-transplant she developed acute antibody mediated rejection managed with plasma exchange then maintenance prednisolone, tacrolimus and mycophenolate. 9 months later she was admitted with respiratory failure and Pneumocystis jirovecii in BAL. She required invasive ventilation and inotropic support. She was treated with intravenous TMP-SMX, but her clinical condition deteriorated with acute kidney injury (AKI) requiring hemofiltration and escalating ventilator requirements. She received IVlg 25g/day for 5 days, replacement hydrocortisone and immunosuppression was withdrawn. Her AKI resolved and later she became ventilator-independent. Graft function was at baseline on discharge. Maintenance immunosuppression was recommenced.

Conclusions: It is understood that immunity against Pneumocystis jirovecii is both B- and T-cell mediated. Thus pooled immunoglobulin might be expected to have some anti-Pneumocystis activity. It is also recognized that IVlg has immunomodulatory properties. In both cases the administration of IVlg allowed withdrawal of immunosuppression apart from replacement steroid without graft rejection despite high immunological risk. Both patients survived life-threatening PCP. We suggest adjunctive therapy with IVlg be considered in severe PCP.
**PUB655**

Ethical Issues Related to Kidney Donation/Transplantation: Perspective of Indian Doctors  
Richard S. Fernandes Almeida, 1 Nirmala Almeida, 2 Karen Almeida, 3 Alan F. Almeida, 4 *Lifesupporters Inst of Health Sciences; Human Development, Nirmala Niketan College of Home Science; Psychology, Mumbai Univ; Nephrology, PD Hinduja Hospital, Mumbai, India.

**Background:** Dearth of kidneys for transplantation has provoked the need to evaluate new policies and practices. This spurred the current study which addressed the perspective of doctors regarding emerging ethical issues pertaining to kidney donation/transplantation.

**Methods:** The sample consisted of 140 doctors from Mumbai (Age range: 21–80 years, M=38.1, SD=17.95, MAles=44.3%, Femaless=55.7%). A questionnaire, presenting ethical issues related to kidney donation/transplantation, in an agree/disagree format with supporting reasons was employed. The research design was exploratory; data was analyzed quantitatively and qualitatively.

**Results:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Agree%*</th>
<th>Reasons (%)*</th>
<th>Dis-agree%</th>
<th>Reasons (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated transplants should be promoted by the government</td>
<td>75.7</td>
<td>Saves lives (16.4) Remedies organ donor shortag (16.4)</td>
<td>24.3</td>
<td>Misuse of organs (7.1) Higher chances of mismatch/organ rejection (7.1)</td>
</tr>
<tr>
<td>Kidney selling should be made legal</td>
<td>22.9</td>
<td>Greater donor availability (6.7%) Avoidance of malprac- tice (6.4%)</td>
<td>77.1</td>
<td>May lead to illegal/ unethical practic (41.4)</td>
</tr>
<tr>
<td>Handicapped should not be kidney donors</td>
<td>24.3</td>
<td>Should not burden them as already challenged health- wise (10.7)</td>
<td>75.7</td>
<td>If informed consent given (20) If kidney effectively functioning (41.3)</td>
</tr>
<tr>
<td>Substance abus should not be transplant recipients</td>
<td>50.7</td>
<td>Close to bring deterioration in life(10) Might abuse the transplant (15.7)</td>
<td>49.3</td>
<td>All are entitled to be kidney recipi- ence(22.1)</td>
</tr>
<tr>
<td>Younger indivi- dually should be given transplan- tation preference</td>
<td>60</td>
<td>Longer life expectancy (20) Greater transplantation suc- cess (12.9)</td>
<td>40</td>
<td>Need-based rather than age-based pref- erence (11.4)</td>
</tr>
<tr>
<td>Families of cadaver donors should be given incentives</td>
<td>45.7</td>
<td>Motivates donation (22.9)</td>
<td>54.3</td>
<td>Would lead to commercialization and criminal activi- ties (20.7)</td>
</tr>
<tr>
<td>Kidney donation should be made compulsory after death</td>
<td>44.3</td>
<td>Saves lives(26.4)</td>
<td>55.7</td>
<td>Donation is individu- al’s choice, coercion is unethical (44.4)</td>
</tr>
</tbody>
</table>

*Representative

**Conclusions:** This study is relevant in view of the dearth of Indian research. Educating doctors about medico-ethical issues is the need of the hour.

**PUB656**

Cardiovascular Risk Management of Renal Transplant Patients  
Joseph P. Almeida, Karen Leffondre, 1 INSERM U897, Bordeaux School of Public Health, Bordeaux, France; 2Nephrology and Transplantation, Bordeaux Univ Hospital, Bordeaux, France; 3Agence de la Biomédecine, Paris, France.

**Background:** Kidney transplantation (KT) is the treatment of choice for end-stage renal disease. In France, preemptive kidney transplantation (PKT) should be considered when glomerular filtration rate is under 20 ml/min/1.73m² but European reports on the efficacy of PKT are scarce. Our objective was to evaluate the impact of PKT on graft and patient survival.

**Methods:** We analyzed all first kidney-only transplants performed in adults in France between 2002 and 2012. A Cox multivariable model was used to study the impact of PKT on the hazard of graft failure defined as death, return to dialysis, or retransplant, whichever came first.

**Results:** Between 2002 and 2012, 22 288 patients received a first KT, including 3112 (14%) who had a PKT. Mean recipient age at KT was 50.5 ± 13.4 years, 61.9% were men. Median time of follow-up was 4.7 years. **First**, in living donor recipients for age and sex of recipients, primary kidney disease, donor type (living or deceased donor, expanded criteria donor or standard), HLA mismatches, cold ischemia time, center and year of transplantation, KT was associated with a 43% reduction in the hazard of graft failure when compared with patients who were treated by dialysis before KT (HR 0.57; 95% CI 0.51-0.64). **Second**, in deceased donor recipients (HR in living donor 0.34; 95% CI 0.19-0.55; HR in deceased donor 0.59; 95% CI 0.52-0.66). Among the subgroup of patients registered on the waiting list before the initiation of dialysis, PKT was associated with a 29% reduction in the hazard of graft failure (HR 0.71; 95% CI 0.58-0.87).

**Conclusions:** In France, PKT is associated with better graft survival than KT performed after the initiation of dialysis. Nephrologists should prepare patients to PKT rather than to dialysis.

**Funding:** Private Foundation Support

**PUB658**

Novel Potential Theranostic Targets in Individuals with Kidney Allograft Dysfunction  
Roberto Bassi, 1,2 Monika A. Nieczcza, 2 Stefania Bussolino, 2 Valentina De Zan, 2 Giuseppe Paolo Segoloni, 2 Antonio Secchi, 2 Amil K. Chandraker, 2 Luigi Biancone, 2 Paolo Fiorina. 3, 4 Nephrology, Boston Children’s Hospital, Boston, MA; 5Medicine, San Raffaele Scientiﬁc Inst, Milan, Italy; 6Internal Medicine, Sapienza University of Rome, Rome, Italy; 7Nephrology, PD Hinduja Hospital, Mumbai, India; 8Transplantation Research Center, Brigham and Women’s Hospital, Boston, MA; 9Internal Medicine, San Giovanni Battista Hospital, Turin, Italy; 10Univ of Torino.

**Background:** The lack of early diagnostic and therapeutic targets for chronic allograft dysfunction (CAD) is among the major determinants of poor long-term graft survival. Metabolic abnormalities in serum and kidney graft parenchyma may worsen allograft function, while alterations of urinary metabolites may be used as diagnostic biomarkers. **Objectives:** To explore this hypothesis, we recruited individuals with stable allograft function (n=20), chronic allograft dysfunction (n=20) and healthy controls (n=10), and analyzed their metabolic profile by ex vivo liquid/gas cromatography-mass spectrometry (LC/GS-MS) of serum and urine in vivo two dimensional correlated spectroscopy (2D COSY) of the kidney graft.

**Results:** LC/GS-MS revealed serum and urinary abnormalities of amino acids, biogenic amines and acylcarnitines in individuals with worse allograft function (T3) compared to conserved graft function (T1). Particularly, CAD was associated with reduction of serum choline, creatine and lipids results for the local transplant cohort of 69 patients. Significance of statins, antihypertensives and aspirin were audited against guidelines from the UK Renal Association (RA) and KDIGO. Cardiovascular risk was calculated using the Joint British Societies Guidelines (JBS2).

**Results:** Amongst hypertensive patients, 2/28 (7.1%) were not on antihypertensive therapy. Significant proteinuria (pAUC >50) was not common (6/68 = 8.8%), but of these only 2/6 (33.3%) were receiving an ACE inhibitor or ARB. Glycaemic control of diabetic patients was generally good, with 9/12 (75%) achieving target HbA1c of <48 mmol/mol. For non-diabetic patients, 11/56 (19.6%) were found to have a random glucose ≥7. Of these 4/11 (36.4%) had HbA1c checks, one of which confirmed new diabetes. The remaining 7 patients (63.6%) have not had a follow up HbA1c 20.69 (29.0%) of patients were calculated as >20% cardiovascular risk on the basis of comorbidities or using JBS2. Of these only 12/20 (60%) were on statin therapy. Almost all (67/68 = 85.7%) of patients with vascular disease were taking regular aspirin.

**Conclusions:** We have identified room for improvement in the management of hypertension and proteinuria. Rates of statin prescription suggest that we often underestimate cardiovascular risk clinically, however, further analysis will determine whether valid reasons exist to support decisions to omit statins or renin-angiotensin

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

Underline represents presenting author.

1040A
Background: Compared with non-diabetic subjects, patients with type 2 diabetes and end-stage renal disease (ESRD) have seldom been selected for renal transplantation. The aim of this study is to compare patient and graft outcome in kidney transplant patients with diabetes mellitus.  

Methods: We retrospectively studied 358 patients who underwent kidney transplantation between 1979 and 2014, including 88 with diabetes ESRD (DM group) (type 1, n = 8; type 2, n = 80) and 270 without non-diabetic ESRD (NDM group). Mean follow-up was 92 (10.1-389) months.  

Results: Mean age was higher in the DM group (52.8 vs 44.6 years; P < .0001), and there was no significant difference in recipient gender, donor age or donor source. At the end of follow-up, there were no differences between the groups in terms of blood pressure (DBP: DM 139.3±16.7 vs NDM 138.3±17.6 mmHg; P = 0.83; SBP: DM 83.5±17.8 vs NDM 82.1±18.1 mmHg; P = 0.9). Mean creatinine clearance was 66±24 vs 71±24 ml/min/1.73 m², respectively, (P = 0.9). In total, 26 patients had acute transplant rejections [8 patients with diabetes mellitus].  

Conclusions: Renal transplantation in diabetic ESRD patients yields good results in terms of patient survival and complications, suggesting that renal transplantation can be performed in these patients and should become a more established treatment option.

Impact of Pre-Transplant Peritoneal Dialysis Compared with Hemodialysis on the Incidence of Delayed Graft Function in Kidney Transplant Recipients with Lupus

Background: Delayed graft function (DGF) increases the risk of allograft failure in recipients of kidney transplants.  

Methods: In this study, we assessed the impact of pre-transplant peritoneal dialysis (PD) compared with hemodialysis (HD) on the risk of DGF in patients with lupus using logistic regression models.  

Results: Three-hundred-fifty-three of 2513 (14 %) recipients transplanted between 3/22/1994 and 9/27/2006 with complete records in the United Network for Organ Sharing files had DGF. The incidence of DGF was lower in recipients who used HD (68.6±13.1%) compared with HD (285/1900 = 15%) prior to transplantation (P = 0.013). After adjusting for donor and recipient age, gender and race-ethnicity, type of donor, recipient education and insurance, time of dialysis prior to transplantation, panel reactive antibodies (PRA), human leukocyte antigen (HLA) mismatch, and ABO blood type compatibility, the lower risk for DGF associated with the use of PD compared with HD remained significant ( Odds ratio 0.70 [95% confidence interval 0.53-0.94]; P = 0.015). Donor age (1.01 [1.00-1.02] per 1 year), deceased donor transplantation (1.64 [2.59-5.12] living donor as reference), HLA mismatch (1.08 [1.01-1.15] per 1 antigen mismatch), and PRA (1.01 [1.00-1.01] per 1%) were also independently associated with DGF.  

Conclusions: In lupus recipients of kidney transplants, the use of PD compared with HD is associated with lower risk of DGF after adjusting for important predictors.  

Funding: Other NIH Support - This work was supported in part by Health Resources and Services Administration contract 231-00-0015. The content is the responsibility of the authors alone and does not necessarily reflect the views of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.
**PUB664**

**Successful Treatment of BK Nephropathy with Tacrolimus and mTOR Inhibitors**


*Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.*

**Background:** BK nephropathy (BKN) is a relevant cause of graft dysfunction in kidney transplantation. mTOR inhibitors (mTORi) have been suggested as the best immunosuppression in BKN. However, Tacrolimus-free therapy could increase risk of rejection. Since 2009 in patients with BKN we conducted a protocol discontinuing Mycophenolate and decreasing Tacrolimus (TAC) dose in association with mTORi, both with target levels of 5 ng/mL.

**Methods:** From 2007 to 2013 we diagnosed 22 BKN. Patients diagnosed since 2009 (n=14, group 1) were treated beginning mTORi and decreasing TAC dose. The others 8 patients suffered significant reduction of immunosuppression (group 2). We analyze renal function, plasma quantitative BK PCR, antiHLA antibodies, reactions and dialysis or death at final follow-up.

**Results:** 22 patients were identified. The BKN was diagnosed at 7th month after transplantation (range 2-55). The medium duration of follow-up was 53 months (6-85). Baseline characteristics and evolution are listed in table 1.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=14)</th>
<th>Group 2 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine at baseline (mg/dl)</td>
<td>1.3 ± 0.36</td>
<td>1.68 ± 0.57</td>
</tr>
<tr>
<td>AntiHLA antibodies positive at BKN diagnosis</td>
<td>43% (6)</td>
<td>12.5% (1)</td>
</tr>
<tr>
<td>Serum Creatinine at BKN diagnosis (mg/dl)</td>
<td>1.93 ± 0.37</td>
<td>2.4 ± 0.63</td>
</tr>
<tr>
<td>Serum Creatinine at final follow-up (mg/dl)</td>
<td>1.6 ± 0.7</td>
<td>3.2 ± 2.2</td>
</tr>
<tr>
<td>Dialysis at final follow-up</td>
<td>7.1% (1)</td>
<td>12.5% (1)</td>
</tr>
</tbody>
</table>

Although group 1 had a greater immunologic risk and a higher plasma BK viral load at diagnosis, the renal function during follow-up was more favorable than patients from group 2. No rejection episodes were diagnosis in group 1. Only one patient in each group started chronic dialysis at the end of the follow-up (52 and 85 months after BKN diagnosis).

**Conclusions:** An immunosuppression regimen based in TAC and mTORi is an effective and safety treatment in patients with BKN. This treatment reduces viral load and increases graft survival without increases the rejection risk.

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**PUB665**

**A Rare Case of Guillain-Barré Syndrome Associated with Cytomegalovirus Disease in a Renal Transplant Patient**

Jessica Bian, George P. Bayliss.

*Medicine, Rhode Island Hospital, Providence, RI.*

**Background:** While cytomegalovirus (CMV) infection is associated with Guillain-Barré syndrome (GBS) in the general population, there are few reports of GBS associated with CMV disease in the renal transplant patients. We describe the case of one renal transplant patient who developed GBS after treatment for documented CMV disease.

**Methods:** The patient is a 62-year-old woman with ESRD from polycystic kidney disease status post deceased donor renal transplant (CMV donor positive/recipientseronegative) on tacrolimus and prednisone. She completed 6 months of CMV prophylaxis with valgancyclovir. Fourteen days after stopping valgancyclovir, she presented with fevers, myalgias, and headache. Tacrolimus level was 6.6 ng/mL on admission. She was diagnosed with CMV disease (serology CMV PCR 2200 copies; CSF CMV PCR undetectable) and started on treatment-dose valgancyclovir. Ten days later, she returned with numbness of her hands and feet. CSF studies were notable for albuminocytologic dissociation. MRI brain and spine was normal. Electromyography showed diffuse sensory motor polyneuropathy consistent with GBS. She developed ascending motor weakness, sensory loss, and areflexia without progression to respiratory compromise, improving with IVIG therapy. She was discharged to rehabilitation.

**Results:** She returned 7 days later with compartment syndrome of her right arm due to deep venous thrombosis of her right subclavian, axillary, and brachial veins with associated hematoma requiring emergent fasciotomy and hematoma evacuation. This was attributed to recent IVIG therapy, as thromboses may occur even in the absence of other risk factors (US boxed warning). She was bridged to warfarin prior to discharge. Of note, she maintained excellent alloantibody function throughout this complicated course.

**Conclusions:** This vignette details a case of CMV-associated GBS after renal transplantation. The case is notable for the development of CMV disease shortly after cessation of valgancyclovir prophylaxis in a CMV donor positive/recipientseronegative renal transplant despite only being on only being on a two-drug immunosuppressive regimen. This may support a longer course of CMV prophylaxis in donor positive/recipientseronegative transplants.

**Funding:** Clinical Revenue Support
Mammalian Target of Rapamycin Inhibitors Withdrawal in Kidney Transplant Recipients: Risk Factors and Related Transplant Outcomes

Lee-Mooy Lim,1 Mei-Chuan Kuo,1,2 Hung-Tien Kuo,1,2 1Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; 2Faculty of Renal Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.

Background: With its antiproliferative and antineoplastic properties, Mammalian Target of Rapamycin Inhibitors (MTORI) potentially have important long-term therapeutic consideration in kidney transplantation. Treatment cessation frequently occurs following its unique adverse effects. The objective of this study was to investigate the risk factors for MTORI withdrawal and its impacts on transplant outcomes.

Methods: This retrospective observational study consisted of kidney transplant recipients followed up from January 1999 till May 2015. We examined the risk factor for MTORI withdrawal using multivariate logistic regression analysis. The impacts of MTORI withdrawal on transplant outcomes were analyzed using multivariate Cox regression and logistic regression. P<0.05 was considered as statistically significant.

Results: A total of 111 kidney transplant recipients who received MTORI treatments were included, with 46 patients withdrew (41.0%). The risk factors for MTORI withdrawal included initial proteinuria (adjusted OR=4.61, P<0.007), higher initial serum creatinine (per 1 mg/dl increment, adjusted OR=2.73, P=0.035), and glomerulonephritis as primary renal disease (adjusted OR=5.00, P=0.035). MTORI withdrawal was associated with an increased risk of graft failure (adjusted HR=3.79, P=0.027), but not with patient survival (adjusted HR=0.61, P=0.595).

Conclusions: MTORI withdrawal is a strong risk factor for renal graft failure. Proteinuria, poor initial graft function and primary renal disease of glomerulonephritis are predictors for MTORI withdrawal. Earlier identification of risk factors may assist physician to decide the best candidate for MTORI conversion in order to optimize transplantation outcomes.

Impact of Donor Age on Longterm Outcomes in Living Donor Kidney Transplants: A Propensity Score Matched Analysis Using Multicenter Transplant Recipients

Dong-Wan Chae,1 Yong-Soo Kim,2 Bum soon Choi.1 1Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary’s Hospital, The Catholic Univ of Korea, Seoul, Republic of Korea.

Background: The proportion of donor over 50 years was 21.2% (N=553). The mean age of donors was 45.9±4.3 years old. Despite of difference of donor age, mean recipient age was similar between the groups. Elderly donors were more likely to donate to unrelated recipients. The proportions of recipients with diabetes mellitus (22.8%), serum creatinine and BMI of donor were significantly higher in the elderly donor group than in the young donor-age group. In elderly donor group, recipients’ patient survival was worse than younger age group before PSM (p=0.014). After PSM, donor age did not affect the recipients’ survival (p=0.305) and allograft survival (p=0.077), however, BPAR was than younger age group before PSM (p=0.014). After PSM, donor age did not affect the recipients’ patient survival (p=0.305) and allograft survival (p=0.077), however, BPAR was than younger age group before PSM (p=0.014). After PSM, donor age did not affect the recipients’ patient survival (p=0.305) and allograft survival (p=0.077), however, BPAR was than younger age group before PSM (p=0.014). After PSM, donor age did not affect the recipients’ patient survival (p=0.305) and allograft survival (p=0.077), however, BPAR was than younger age group before PSM (p=0.014).

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Conclusions: MTORI withdrawal is a strong risk factor for renal graft failure. Proteinuria, poor initial graft function and primary renal disease of glomerulonephritis are predictors for MTORI withdrawal. Earlier identification of risk factors may assist physician to decide the best candidate for MTORI conversion in order to optimize transplantation outcomes.
Results: 10 CV events occurred in the overall group, and 7 events in the post KT balance group. The most affected CV events of this group were diabetes, high body mass index (BMI) and high baPWV. Overall arterial stiffness measured by baPWV after KT showed significant improvement (1417.5 ± 234.5 cm/s) compared to those of before KT (1503.5 ± 252.2 cm/s) (p=0.05 vs after KT).55 out of 79 patients (69.6%) showed improvement of baPWV after KT, but 24 patients did not. Between two groups, improvement group showed higher pre-transplant baPWV than no-improvement group (1561.0 ± 263.9 vs. 1371.6 ± 177.1), and multivariate analysis revealed that gender and BMI, degree of decrement of calcium level were an independent risk factor of change of baPWV.

Conclusions: We could expect CV event risk in KT recipients by diabetes, BMI and baPWV, and these were very strong prediction marker of CV event. Arterial stiffness in ESRD patients improves after transplantation, and lower BMI, the amount of calcium decreased, gender affected the improvement of baPWV.

PUB675
Left Ventricular Global Longitudinal Strain as Early Detection of Subclinical Myocardial Dysfunction in Renal Transplant Recipients
Secundino Cagigalan,Jose Lomban,Ana Maria Sanjurjo Amado,DiegoCoronel,SheilaCasas,JuanLatorre,Milagros Lopez hernandez,JesusCalvino.
Nephrology, Hospital Da Costa, Barela, Lago, Spain; Nephrology, Hospital Jesus Augusti, Lago, Spain; Cardiology, Hospital Da Costa, Barela, Lugo, Spain.
Background: Echocardiographic global longitudinal strain (GLS) is recognized as a technique to detect subtle changes in left ventricular function. As in CKD pts, kidney transplant recipients (TXKR) has an increased mortality risk by CV events. Early detection of CV risk is the utmost importance in the TXKR outcomes. The aim of this cross section study is to assess the grade of myocardial dysfunction in TXKR without previous CV events & normal left ventricular ejection fraction (LVEF).
Methods: 37 TXKR following >1 year were included. 44.4% F, 25.4% DM, age 55.4(±12.0) y.o, GFR-EPI 51.93±32.2 cm2/ml/min, No previous CV events & LVEF>55%. All of them were on stable treatment with ACE/ARB, CCBH, diuretics added to immunosuppressive drugs (TAC, CSA). Echocardiography 2D Vivid 9 (GE Vimed Ultrasound ,Horton, Norway), was performed;GLS;LAVI(ml/bsa),E/E’,A/LVEF following recommendations of American Society of Echocardiography. Body composition analysis were performed by BIVA and serum biomarkers of inflammation,anaemia,mineral bone disease, renal function (GFR-EPI) and CV risk markers.Normal GLS (-20%)LAVI 24 ml/m2 were considered as published for general population Rev Esp Cardiologia 2014;67:651-8.
Results: Mean GLS was -18.6 ± 3.78%, LVEF 70.8 ± 8.7%LAVI 30.16±20.4 ml/GFR correlated negatively with GLS (r=-0.338, P=0.016) and LAVI (r = 0.372, p = 0.14). GLS progression is a sensitive as GFR decline (P adjusted 0.025) E’ 13.06 ± 0.68; E/A 0.93 ± 0.28. Multivariate analysis was significant the relationship between GLS with ACR (P < -1.51, p = 0.43) E Ejection index (P< -0.377; p=0.14)LAVI correlated with age (b=0.467 p=0.004), No acid load (b=0.345; p=0.23) and AEGs (b=0.314; p=0.35). No other correlations were met. Conclusions: 66% TXKR showed GLS< -20%, and 41.6 % LAVI > 24 ml/m2.GLS & LAVI echocardiography derived are two valuable measures to assess early subclinical myocardial damage in TXKD. GLS appears more sensitive predictor than LVEF.Studies on TXKD pts are required.
Funding: Other NIH Support - SERGAS

PUB676
Seronegative Invasive Gas tro-Intestinal Cytomegalovirus Disease in Renal Allograft Recipients – A Diagnostic Dilemma! Tissue PCR the Saviour! Nirmal Kaur, Dharndra Bhaduria, Narayana Prasad, Anir Gupta, Raj K. Shankar, Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.
Background: CMV as opportunistic infection affecting the gastrointestinal tract is the most common cause for tissue invasive CMV disease occurring in 10-30% of organ transplant recipients. Gastrointestinal CMV disease can be diagnosed in presence of clinical suspicion along with histopathological findings (CMV inclusions) and presence of mucosal lesion(s) on endoscopic examination with collaborative evidences via molecular technique.
Methods: Few cases of CMV infection affecting the gastrointestinal tract show no evidences of dissemination despite use of highly sensitive molecular techniques.
Results: We encountered 6 cases where in despite strong clinical suspicion of Gastrointestinal CMV disease there were seronegative and endoscopic negative evidences for CMV ,blind tissue biopsy yielded positive results for CMV disease with excellent improvement with antiviral therapy.
Conclusions: Blind biopsy specimen for tissue PCR could serve as an invaluable companion diagnostic tool for strong clinical symptomatology for GL-CMV disease in absence of viremia ,normal endoscopy and histopathology ,so that the early therapeutic interventions could help in excellent patient and graft survival.

PUB677
Allograft Outcome After Desensitization with IV Ig: A Single Center Experience

Background: The presence of antibodies to donor human leukocyte antigens (HLA) is a significant barrier to transplantation. High dose intravenous Ig (IVIG) is widely used for desensitization. There is no general consensus on the best approach for desensitization, and there is no data on efficacy of IV Ig are unknown.
Methods: We reviewed kidney transplants done from Jan, 2010 to Dec, 2014 at Tufts. Sensitization was defined as PRA>20% and/or presence of donor specific antibody (DSA). Patients who were desensitized with IV Ig were identified as cases; those without desensitization served as controls. No attempt was made to desensitize patients with a long deceased donor kidneys. Baseline characteristics and follow up data were collected at months 3, 6, 12 and 24. A sensitivity analysis was done for patients who received a living donor kidney.
Results: There were 19 patients in the desensitized group and 37 patients in the control group. Mean age at transplant in two groups was 47±12 and 49±12 respectively. In the desensitized group, there were more patients with prior transplant (37% vs 22%), receipt of living donor (95% vs 54%) and positive DSA (89% vs 22%). One patient developed severe side effects from IV Ig, requiring discontinuation. Leukopenia and BK viremia were
seen more in non-desensitized patients at 3 months, but significance was not sustained after 3 months (Table). The leukopenia effect was not significant when adjusted for age. There was no difference in eGFR in either group, however mean eGFR was higher in those desensitized. Incidence of rejection was very low in both groups (5% vs 8%). When living donor recipients from both groups were compared, the eGFR and leukopenia effect was similar in both groups, and there was no significant difference in BK Viremia.

### Conclusions:
Desensitization with IVlg appears to be safe and effective. The lower incidence of leukopenia in desensitized group can be explained by greater use of steroids.

**PUB678**

**Results of Chinese Renal Transplant Recipients with Post-Transplantation Malignancies**

**LiHui Qu, Hong Jiang, Jianghua Chen. The Kidney Disease Center, The First Affiliated Hospital, Medical College, Zhejiang Univ, Hangzhou, Zhejiang, China.**

**Background:** Malignancies are a severe complication of immunosuppressive therapy among renal transplant recipients, representing an important cause of long-term morbidity and mortality.

**Methods:** A retrospective study of 2700 recipients who underwent renal transplantation between July 1977 and July 2013 was carried out. 51 patients developed the following malignancies at a mean of 55.2 months (range = 1-207) after kidney transplantation. According to the regimen of immunosuppressive agents, all the recipients occurred malignancies were divided into azathioprine group (Aza group, n=21) and mycophenolate mofetil group (MMF group, n=30). The recipient age, gender, interval from renal transplantation to tumor development, long term survival of patient and graft and the ratio of converting to rapamycin of patients were made a comparison in detail between two groups.

**Results:** 29 patients survived without a recurrence including 28 with graft function (Survival group, n=29), and 22 patients died of malignancies including 21 with graft function (Death group, n=22). In the survival group, only one patient lost the graft after 26 months after immunosuppressant adjustment due to chronic rejection. Renal graft function remained stable in all other patients from diagnosis throughout follow-up. Moreover, 10 patients in the survival group were switched from calcineurin inhibitor-based immunosuppression to rapamycin after the diagnoses of malignancy, otherwise no patient in death group switched to rapamycin. At a mean follow-up of 34.0 months (range = 4-74), all the 10 patients are cancer-free and survived with functional graft. The incidence of death was similar in the Aza group and MMF group.

**Conclusions:** Our results demonstrate that the incidence of malignancy in renal allograft recipients is much higher than normal population, closely related to the long term use of immunosuppressant. Treating cancer thoroughly and maintaining the function of the transplanted kidney can decrease the risk of death with functional graft. Rapamycin-based immunosuppression blocks the recurrence of nonmetastatic tumors.

**PUB679**

**Basiliximab Induction Therapy, Graft and Patient Survival**

**Sergio Santiago Pedroza-Orozco, Paloma Arleth Zavalza-Camberos, Benjamin Gomez-Navarro. Nephrology and Transplantation, Inst Mexicano del Seguro Social, CMNO, Guadalajara, Jalisco, Mexico.**

**Background:** Basiliximab is widely used in clinical practice for induction therapy of renal transplant recipients, expecting to reduce the incidence of acute rejection and improved graft function without increasing adverse events. We evaluate the impact of induction therapy using Basiliximab on relevant clinical outcomes: graft and patient survival, incidence of acute rejection (AR) and incidence of infectious or malignancy complications.

**Methods:** This retrospective study included all renal allograft recipients who were transplanted between January 2010 and April 2014 and who received Basiliximab as induction therapy. We collected the baseline characteristic of recipients, type of donor, donor’s age, HLA matches and immunosuppression at the time of transplantation. The clinical outcomes were evaluated at the first year of transplantation and include: AR incidence, infectious or malignancy complications, serum creatinine and estimated glomerular filtration rate (eGFR) using the 4-variable MDRD formula, as well as graft and recipient survivals.

**Results:** The demographic characteristics of recipients and donors are in Table 1. Among 662 renal transplant recipients including in this study, only 10.6% (n=70) experienced AR during the first year follow up. The incidence of infectious complications in the first year after transplantation was 32.3%, mostly urinary tract infection (82%). No episode of malignancy was reported. Graft and patient survival rates were 96.9% and 98.5% respectively.

**Conclusions:** In our hospital, 1 year mortality postkidney transplantation is low, but there are many individual patient factors that contribute to the risk of mortality increases significantly in them and there we could intervene.

**PUB681**

**Granzyme B Level and Acute Kidney Allograft Rejection: Impact on One Year Survival in Mexican Population**

**Perla Edith Simancas Ruiz,1 Caridad Aurea Leal,2 Benjamin Gomez-Navarro.1 1Nephrology and Transplant, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; 2Surgical Research, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.**

**Background:** Exposure to insufficient levels or discontinuation of immunosuppressants often increases the risk of rejection. Creatinine is the most useful test to monitor graft function. However, it is a poor predictor of rejection and often raises only after significant damages occurred to the graft. The Granzyme B is an enzyme that can mark acute rejection. Granzyme B has been tested as a marker of acute rejection, with high specificity and sensitivity in different types of sample and has also enabled the identification of subclinical
rejection. The elevation of both the mRNA and protein has been associated with a worse prognosis. Exploring the association between serum levels of Granzyme B and acute rejection after one year post-transplant.

Methods: Kidney recipients transplanted between January 2008 and March 2009. Donors (n=58) and healthy subjects (n=6) were also included. The relation of granzyme B levels determined by ELISA with graft function and rejection was studied.

Results:

<table>
<thead>
<tr>
<th>Receptor age (n=94)</th>
<th>26 ± 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy:</td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>46%</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>39%</td>
</tr>
<tr>
<td>Thymoglogulin</td>
<td>2%</td>
</tr>
<tr>
<td>CMV</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>21%</td>
</tr>
<tr>
<td>Moderate</td>
<td>72%</td>
</tr>
<tr>
<td>Low</td>
<td>7%</td>
</tr>
<tr>
<td>One year creatinine</td>
<td>1.66 mg/dl</td>
</tr>
<tr>
<td>Rejection:</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>46%</td>
</tr>
<tr>
<td>Banff IA</td>
<td>31%</td>
</tr>
<tr>
<td>Banff ≥1B</td>
<td>56%</td>
</tr>
<tr>
<td>Chronic nephropathy</td>
<td>14%</td>
</tr>
</tbody>
</table>
| Granzyme level in patients (n = 43) was 12.5 pg/ml while the reference group (n = 6) was 1.5 pg/ml (p<0.001). Comparison between patients with rejection (n = 14) and non-rejection (n = 20) was not statistically significant, nor the development of interstitial fibrosis year. The correlation between creatinine, GFT and granzyme level showed a trend to significance (n = 66, r = 0.30, p = 0.06).

Conclusions: The level of granzyme B was not associated with one year post-transplant rejection. However immune system activation is suggested by the higher level of granzyme in patients vs control group. Continuous analysis of patients.

PUB682
Epidemiological Analysis of Post Transplant Glomerulonephritis Prathak Das, Santosh Kumar, Rohit Rungta. Nephrology and Transplantation, Rabindranath Tagore International Inst of Cardiac Sciences, Kolkata, West Bengal, India.

Background: Post-transplant glomerulonephritis is an important cause of graft dysfunction and consequent graft loss. Aim of the study is to identify the incidence and outcome of glomerulonephritis in post-transplant patients.

Methods: We retrospectively evaluated all the patients who underwent renal allograft biopsy between January 2010 to January 2014, for graft dysfunction, proteinuria or active urinary sediments. All protocol biopsies were excluded from the study. Graft biopsies were evaluated by light microscopy and indirect immunofluorescence study. Out of 285 graft biopsies 242 biopsies were taken into study. Biopsies showing evidences of glomerulonephritis were further evaluated for incidence of individual types of glomerulonephritisand their outcome at the end of one year post diagnosis.

Results: Based on biopsy findings among 242 renal allograft biopsies taken in study 42(17.35%) had post-transplant glomerulonephritis. Further the incidence of individual glomerulonephritis were 14(33.3%) for focal segmental glomerulosclerosis, 13(31%) for IgA nephropathy, 8(19%) for mebranoproliferative glomerulonephritis, 4(9.6%) for pauci-immune crescentic GN, 2(4.8%) for anti-glomerular basement membrane disease and 2(2.3%) for membranous nephropathy. On follow up for one year 30(71.4%) patients lost their graft and became dialysis dependent irrespective of treatment. When compared to this outcome with other causes of graft dysfunction (rejection or infection) , results are inferior in terms of graft and patient loss.

Conclusions: We conclude that post-transplant glomerulonephritis is strongly associated with poor kidney allograft survival. Therefore, optimal management of recurrent or de novo glomerulonephritis should be the critical focus of post-transplant care.

PUB683
Impact of Hemoglobin Concentration on Mortality After Renal Transplantation Vitoria C. Vilela,1 Marcos A. Meniconi,1 J. Medina-Pestana,1 Miguel Cendoroglo Neto,1,2 Miguel A Goes,1,2 Nephrology Div, Federal Univ of Sao Paulo, Sao Paulo, Brazil; 1Nephrology Div, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.

Background: Kidney transplant recipients have chronic anemia, irrespective of the time from transplantation. Objective: To assess the impact of hemoglobin concentration on mortality after renal transplantation.

Methods: A total of 233 patients who underwent renal transplantation at one center (Hospital do Rim) were prospectively analyzed. Follow-up time was 6 years, from January 2008 through December 2014. Data on demographics, ESRD etiology, pre-transplant dialysis, transplant characteristics, and immunosuppression regimen. Two-sample t test were used to compare differences between two groups (mortality versus non-mortality groups) and X² to analyze categorical variables. Binary logistic regression was used to determine the impact of factors on outcome mortality.

Results: The main causes of ESRD were diabetes (35%) and hypertension (20%). Transplants from living donors occurred in 59%. During the entire follow-up period, there were 24 (10%) deaths within 3±1 yr after renal transplantation. 7 (29%) from cardiovascular disease and 17 (71%) died from infection. We observed that mortality group were older (p <0.01) and longer time on dialysis (4±2.5, 2.5±2.0 yr; p=0.006). Hemoglobin (Hb) concentration was lower in mortality (10.7 ±2.3) than non-mortality (12.0±2.4; p<0.01) group. Patients who used mycophenolate had lower mortality (p = 0.04). There is no correlation between Age and Hb (r=0.02; p=0.8). Age (p = 0.01) and Hb concentration (p <0.02) were independent predictors of mortality.

Conclusions: This study shows that a lower Hb concentration is an independent predictor of mortality in renal transplant patients.

PUB684
Prediction of Recipients Survival in Deceased Donor Kidney Transplant Using Korean Network for Organ Sharing Database Kyung Don Yoo,1 Junhyung Noh,1 Hajeong Lee,1 Dong Ki Kim,1 Chun Soo Lim,1 Young hoon Kim,1 Yon Su Kim,1 Gunhee Kim,1 Jung Pyo Lee.1 1Seoul National Univ College of Medicine; 2Seoul National Univ College of Engineering; 3Univ of Ulsan.

Background: The Korean Network for Organ Sharing (KONOS) was founded in 2000 for organ allocation in Korea. It has been allows medical doctors and researchers to fully access the national population-based raw data about KT recipients. We propose a novel prediction approach of recipient survival based on machine learning techniques using KONOS data.

Methods: Our dataset is collected from 2000 to 2014 by the KONOS. We design a novel prediction model that uses all of the follow-up recipients' data including censored ones, on which estimated death risks are weighted accordingly. We compare this approach with the baseline model that uses only uncensored data by the CART (Classification And Regression Trees) modeling.

Results: We analyze 5,430 recipients’ records with more than 15 attributes, among which we take the 15 independent attributes to learn our models. The proposed weighted algorithm leads a better performance when predicting survival rates of transplant recipients within 6 years, but fails to show any significant difference from the baseline for those more than 7 years after transplantation. Using the decision-tree models, we find that the inotropic agent usage of donor management is the most important predictor, which estimates in 51.3% of 10-year mortality. In the age ≥51.5 group, non-diabetes recipients, waiting period < 4years, and donor age < 23.5 years show significant associations with better 10YRS. The results are consistent with our hypothesis that poor donor status, recipients’ longer waiting time and advanced age are associated with poor prognosis.

Conclusions: In this study, we show that the proposed machine learning based models with weights of estimated-death risks can present more accurate and flexible than baseline models for predicting in long-term survival rates of kidney transplant recipients.

PUB685
Perforin Expression in Renal Allograft Biopsies Michele T. Rooney,1 Ping L. Zhang,2 Dilip Samarapungavan,3 Randolph Alexander Hennigar.1 1Incyte Diagnostics, Spokane, WA; 2Anatomic Pathology, William Beaumont Hospitals, Royal Oak, MI; 3Nephrology, William Beaumont Hospitals, Royal Oak, MI; 4Nephropathology Associates, Little Rock, AR.

Background: Perforin is a cytotoxic protein in effector lymphocytes that facilitates targeted cell killing and it has an established role in allograft rejection. A diagnostic value has not been delineated. We examined perforin expression in renal transplant biopsies by immunohistochemistry (IHC) and found that positive lymphocytes are confined largely to the microvasculature in cases of active cellular rejection (ACR). The goal of this study is to investigate whether perforin IHC is a useful metric in identifying and classifying acute rejection in renal transplant biopsies.

Methods: Renal transplant biopsies accessioned over a one-year period were selected to include cases showing no acute rejection, acute tubular injury, BK nephritis, ACR types 1 and 2, and C4d+ antibody-mediated rejection (AMR), according to the 2013 revised Banff Classification. IHC using a mouse monoclonal anti-perforin antibody was performed on each case. Perforin positive cells/10 high power (400X) fields (hpf) were counted from slides identified by number only.

Results: Most rejection-negative cases had <10 perforin-positive cells/hpf. Biopsies showing type 1A ACR, excluding one outlier, did not exhibit a significant increase in perforin-positive cells relative to rejection-negative cases. In contrast, cases of type 1B and 2 ACR, and C4d+ AMR displayed significantly increased perforin-positive cells (p = 0.0001) with most showing > 40/10 hpf. Cases of AMR contained the highest number of perforin-positive cells (p = 0.0352). Cases of BK nephritis varied widely from < 10 to > 500/10 hpf. 2 of 3 cases with > 50 had a recent history of ACR developing BK infection upon increasing immunosuppression, raising the possibility of coexisting BK and rejection.

Conclusions: Further study is needed, but our data suggests that increased numbers of perforin-positive lymphocytes correlate with more aggressive forms of rejection, and that perform IHC may be a useful ancillary test for acute allograft rejection of type 1B or higher.
due to TS were identified. Incidence rates and standardized incidence ratios (SIR) were computed using Poisson distribution and standardized using 2001-2002 as reference. Hazards ratios adjusting for age, sex, race and ethnicity (AHR) were calculated for outcomes.

**Results:** In 2001-2002, the overall incidence rate of ESRD due to TS was 1 per 10 million person years (PMPY) and the SIR remained largely unchanged over the observation period. Those with ESRD due to TS were more likely to be <40 years (23.2% vs. 9.2%), white ethnicity (81.5% vs. 65.5%), and lack diabetes (81.2% vs. 48.1%). Compared to those with ESRD due to other causes, odds ratios adjusted for age, sex, race and ethnicity (AOR) were highest for females (1.83) and those with eGFR > 15ml/min/1.73m2. Factors associated with AOR included age 40-64 years (0.29), age ≥ 65 years (0.25), and black race (0.33). Over the study period, 53.7% of TS patients died, 27.3% were listed and 10.6% were transplanted. The AHR for outcomes demonstrated those <40 years of age were more likely to be listed for renal transplant, receive renal transplant and survive.

**Conclusions:** The incidence of ESRD due to TS remained largely unchanged from 2001 through 2010. Our results indicated gender and racial differences in the odds of ESRD due to TS.

**PUB689**

The Impact of Hepatitis C Virus Infection on the Clinical Course, Short-Term and Long-Term Outcome in Renal Transplant Recipients – A Retrospective Study

Pratik Das, Rohit Rungta, Santosh Kumar. Nephrology and Transplantation, Rabindranath Tagore International Inst of Cardiac Sciences, Kolkata, West Bengal, India.

**Background:** Hepatitis C infection is common in patients of end stage renal disease with increased morbidity and mortality post-transplant. The aim of the study was to find out the impact of HCV infection on graft and patient outcome and compare it with the non-HCV infected post-transplant recipients.

**Methods:** We retrospectively analysed patient and graft survival of HCV infected (after virological remission) post renal transplant patients from 2008 to 2014 with a median follow up of 24 months and compared them with our HCV negative statistically matched cohort.

**Results:** Outcome analysis was done at 6, 12, 18 and 24 months in terms of liver dysfunction, acute rejections, infections, hospitalization and death. Results were further tabulated as shown.

**Conclusions:** HCV infected end stage renal disease patients may undergo renal transplantation safely after virological remission and outcome is not different from other renal transplant recipients.

**PUB690**

Patient and Graft Survival in Pediatric Kidney Transplantation: A Single-Center Experience According to Transplant Era

Juan Carlos Lopez; Gerardo Nyman; Liliana Briones. 1Nephrology Unit, Hospital JP Garrahan, Buenos Aires, CABA, Argentina; 2Urology Unit, Hospital JP Garrahan, Buenos Aires, CABA, Argentina.

**Background:** Improvements in the management of kidney transplantation has improved in the last 20 years. However the long term results in terms of graft survival and morbidity still require more research.

**Methods:** We evaluated 744 pediatric renal transplants (RTX), 551 with deceased donor (DD) and 222 with living-related donor (LRD), between 1988-2015. We divided this time in 2 periods: 1988-2000 and 2001-2015. Patient and graft survival were calculated for each period for LD and DD recipient. We analyzed causes of mortality, causes of graft failure and risk factors for graft loss. Mean age at RTX was 1.6y (r: 0.5-19.5). Median time of follow-up was 54.5 months (IQR: 22.4-90.1) months.

**Results:** Patient and graft survival for DD have significantly increased in the recent era (p=0.0002; p=0.0013 resp). Chronic rejection was the first cause of graft loss in both era (61.6% vs 52.1%), Vascular thrombosis decreased (14.9% vs 5.5%; p < 0.001), and also Death with a Functioning Graft (15.8% vs 8.3%; p = 0.001). Acute rejection during the first 30 days post RTX + relapse of the original disease increased (0% vs 9.7%). First cause of death in both eras was bacterial infection (77% vs 66%). No death due to PTD were seen in 2001-2015. Independent Risk factors for graft loss for DD recipients were: FSGS

**Variables**

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>HCV positive patients</th>
<th>hcv negative patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.Patient(s)</td>
<td>51</td>
<td>1381</td>
<td></td>
</tr>
<tr>
<td>2.Induction with ATG</td>
<td>26(50%)</td>
<td>700(50.68%)</td>
<td>NS</td>
</tr>
<tr>
<td>3.Tacrolimus</td>
<td>34(66.7%)</td>
<td>1196(86.9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4.Cyclosporin</td>
<td>17(33.3%)</td>
<td>185(13.1%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5.Infection</td>
<td>05(9.8%)</td>
<td>117(8.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>6.Anomal LFT</td>
<td>08(15.6%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>7.1 year patient survival</td>
<td>96.1%</td>
<td>97%</td>
<td>NS</td>
</tr>
<tr>
<td>8.2 year patient survival</td>
<td>92%</td>
<td>93.2%</td>
<td>NS</td>
</tr>
<tr>
<td>9.Hospitalization</td>
<td>24 episodes</td>
<td>621 episodes</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results were found not to be statistically different from non HCV infected renal allograft recipients.

**Conclusions:** HCV infected end stage renal disease patients may undergo renal transplantation safely after virological remission and outcome is not different from other renal transplant recipients.
as cause of ESRD (HR: 3.1; CI 95%: 2.4-3.8), DGF (HR: 2.8; CI 95%: 2.4) and Receiving no induction therapy (HR: 2.1; CI 95%: 3.3-5.3). For donor recipients: DGF (HR: 5.2; CI 2.9-9.3) and Age at RTX = 12y (HR: 2.2; CI95%: 1.2-3.9).

Conclusions: Patient and graft survival has significantly improved for DD in the recent era. Chronic rejection remains a major cause of graft failure. No death from malignancy were observed in the recent era.

### PUB691
Impact of Rituximab Induction on Short Term Outcome of Kidney Transplant Recipients

**Background:** Acute graft rejection remains a major problem in kidney transplant (KT) recipients. Induction with Thymoglobulin or Basiliximab is a KDIGO recommendation to minimize the risk of acute rejection. However, these induction agents do not eliminate the risk of antibody mediated rejection. Recent studies of ABO incompatible (ABO) transplant using Rituximab, in addition to standard induction and maintenance immunosuppression (IS) have shown better outcome than ABO compatible (Kohbi N, Tanabe K J Am Transplant Soc 2015; 15: 125-130). Transplantation. The aim of this study was to assess the outcomes and safety of Rituximab induction in addition to single dose Thymoglobulin induction in living donor (LD) KT patients.

The study included 53 adult LD KT recipients transplanted between 3/1/14 and 2/28/15 and followed for at least 3 months after KT. Of these, 39 were (ABOc) transplants and 14 were (ABO0) transplants. Rituximab 200 mg was given within a week before transplant. ABOc recipients received an additional 200 mg Rituximab on the day of transplant. Thymoglobulin 1 mg/kg was used only on the day of transplant. Maintenance immunosuppression included Tacrolimus, MMF and tapering doses of prednisolone in all patients. All recipients received valganciclovir and cotrimoxazole prophylaxis. The short-term outcomes of these patients (Ritusx group) was compared to that of 53 historic controls (control group) who received only thymoglobulin 1 mg/kg on the day of KT.

**Results:** There was no difference in characteristics (age, sex, etiology of CKD, donor characteristics, HLA mismatch) of patients in the 2 groups. Six patients in the Ritux group developed acute rejection (5, cellular and 1 antibody mediated). Six patients in the control group developed acute rejection (2 cellular and 4 antibody mediated). The patient and graft survival at 3 months was 100% in Ritux group. The patient survival was 100% in control group. One graft was lost from antibody mediated rejection in control group. Infections within 3 months after KT were similar in both groups.

**Conclusions:** Rituximab induction is safe in KT. It reduces the risk of antibody mediated rejection without increasing infectious complications in the early period after KT.

### PUB692
Epo Use in Pregnant Renopancreas Transplant Patients

**Background:** Renopancreas transplant improves life and reproductive function. Abnormalities in this population. Prenatal counselling addresses potential fetal complications; as well as worsening anaemia, hypertension, pre-eclampsia, proteinuria, gestational diabetes, acute rejection or graft loss. The aim of this study was to evaluate the use of Erythropoietin (HrEpo) during pregnancy in Tx recipients.

**Methods:** Four two-center (cadaveric donors) recipients underwent successful pregnancies after a complex medical history of diabetes in their childhood with retinopathy & polyneuropathy, two with hypothyroidism, and end stage renal disease. They were all normoglycemic, as compared to baseline (26.4 ± 3; 38; 76, 92) and 0.78 (0.4, 9.7), respectively. The estimated glomerular filtration rate levels by MDRD formula at 1 year (57.4 ± 12ml/min/1.73 m², P=0.0001) were significantly decreased as compared to baseline (82.2 ± 10 ml/min/1.73 m²). We did not find significantly differences in mean 24hs ABPM (84 ± 8 mmHg, P=0.940) and mean LVMV (96.6 ± 17 mm, P=0.727), mean AS (7.78 ± 2.3 m/s, P=0.210) and median EF (5.1% (0.8, 13.3), P=0.374) compared to baseline (85 ± 7 mmHg, 99.8 ± 3.16 g/m², 0.03 ± 2.3 m/s and 10% (-1.6, 36.4), respectively).

**Conclusions:** Our study demonstrated that after an year, reduced nephron mass because of kidney donation was not associated with changes in cardiovascular structure and endothelial function.

**Funding:** Government Support - Non-U.S.

### PUB695
A Rare Case of Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPPERS) After Kidney Transplantation

**Background:** Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPPERS) is a recently described inflammatory condition of the central nervous system. To date 50 cases have been reported in the literature, however none have been reported following renal transplantation.

**Methods:** A 47 year old Hispanic man, status post deceased donor kidney transplant in 2008, with history of hypertension and diabetes, presented to our clinic with several months of progressive dizziness, unsteady gait and right facial numbness that progressed to diplopia and right facial palsy. An MRI of the brain with gadolinium revealed a 1.3 cm mass with a ring-like target appearance in the right brachium pontis and dorsal pons. MR spectroscopy revealed mild elevation of choline, suggesting demyelinating disease versus lymphoma or other high-grade malignancy. Given his long term immunosuppression, malignancy or an infectious process were considered as the main diagnostic possibilities.

An extensive evaluation included serial lumbar punctures for cytology and a variety of tests.
viral, fungal and bacterial cultures. Cytologic and serologic studies were unremarkable. Flow cytometry analysis of the spinal fluid showed no evidence of lymphoma. A brain biopsy was performed revealing non-specific perivascular lymphoplasmocytic infiltrate with no evidence of lymphoma or infection. Additionally, myelin stain was positive ruling out demyelinating disease. Our patient was started on high-dose steroids with remarkable improvement of his symptoms. Diagnosis of CLIPPERS was made.

**Conclusions:** CLIPPERS is a rare and poorly recognized CNS inflammatory condition. To our knowledge, this is the first case reported after kidney transplantation. More studies are needed to determine the pathophysiology of CLIPPERS in immunosuppressed patients and whether it could represent a pre-malignant state. Duration of treatment and follow up is yet to be determined. In this case, treatment with steroids has led to symptomatic improvement over a month and close follow-up continues.

**PUB696**

The Impact of Post-Transplant Hemoglobin and Creatinine Level on Renal Allograft Survival

Luiz Fernando Christiani, Fernanda Paula Feres Rios Da Costa, Ana Flavia Baldoni, Alicja Imada, Kelly Rodrigues, Maria Izabel Neves de Holanda Barbosa, Gesísska Marcelo Gomes, Cláudia Fagundes.

**Nephrology, Hospital Federal de Bonnusco, Rio de Janeiro, Brazil.**

**Background:** Anemia is a common finding after kidney transplantation. The role and the prevalence of Posttransplantation anemia (PTA) in predicting renal allograft outcomes still vary between different studies. In this study, we aim to assess the prevalence of anemia at one and six months post transplant and its correlation with 1 year renal allograft survival.

**Methods:** Anemia was defined by an absolute level of hemoglobin less than 11 g/dL. Hemoglobin and creatinine level were assessed at one, six and twelve-months after transplantation.

**Results:** We included 261 consecutive patients who underwent renal transplant from January/2010 to June/2012. Mean recipient age was 42±10 years and 56% were male. Prevalence of anemia was 42% at 1 month, 16% at 6 months and 9% at 12 months. Mean hemoglobin and creatinine level at first month of transplantation were 11.2±2.1 and 4.8±3.4 for those who return to dialysis within 12 months (p<0.001 for both comparisons). Overall patient and graft survival was 8% and 10%, respectively. On multivariate analysis, creatinine and hemoglobin level were independently associated with poor graft survival at 12 months. The best cut-off selected by receiver operating characteristic curve analysis was 10.8 g/dL for Hemoglobin level, (AUROC 0.74 (0.63-0.86), p<0.001) and 2.25 mg/dL, for serum creatinine (AUROC 0.77 (0.62-0.91), p<0.001). Combining the best points of those two variables could identify patients at risk of graft loss. Patients who met both criteria (Hb < 10.8 g/dL and Creatinine > 2.25 mg/dL) had 59% graft survival at 1-year, whereas allograft survival was 98.5% for patients without any criteria (Hb > 10.8 g/dL and Creatinine < 2.25 mg/dL).

**Conclusions:** Prevalence of anemia was high in the first month after transplant and persisted in a substantial proportion of functioning kidney transplant recipients. Early (1-month) hemoglobin and creatinine level can predict 1-year graft survival.

**PUB697**

Examining Adverse Weight Gain After Kidney Transplantation

Birah Workneh, Linda W. Moore, William E. Mitch.

**Medicine/Nephrology, Baylor College of Medicine, Houston, TX; Transplant Medicine, Houston Methodist Hospital, Houston, TX.**

**Background:** Between 15,000-17,000 patients with end-stage renal disease (ESRD) receive a kidney transplant in the United States every year. Among the most consequential complications to these patients are adverse weight gain and the development of diabetes, commonly termed New-Onset Diabetes After Transplantation (NODAT) with consequent CV mortality. However, there is no consensus about the exact nature of the weight gain that routinely occurs after kidney transplantation (i.e., relative changes in fat vs. muscle vs. fluid volume) and how this relates to insulin resistance. We wish to test the hypothesis that weight gain is primarily due to an increase in fat mass.

**Methods:** We are conducting a longitudinal study in ESRD patients anticipating receiving a live donor kidney transplant. We are studying subjects before kidney transplant, at 12 weeks and 1 year after they have received living donor kidney transplant to measure changes body composition and other indices. Body composition was characterized by DEXA as well as total body potassium (a gold standard measure of muscle mass).

**Results:** Results from 5 subjects who completed baseline assessment and 3 months post-transplant reveals there is significant gain in adipose weight gain in all cases.

**Additional:** Additionally, we discovered there is significant loss in skeletal muscle mass (p=0.032) measured by total body potassium.

**Conclusions:** We have not studied enough to conclude whether changes in energy expenditure and diet contribute to adipose weight gain and whether there is acute nitrogen (muscle) loss perioperatively. Ultimately, methods to identify patients at high risk for adverse weight gain and related metabolic disorders before transplant are greatly needed.

**Funding:** Private Foundation Support

**PUB698**

Effect of Mycophenolate Mofetil Dose on BK Virus Infection in Kidney Transplant Recipients

Vedran Pasara, Danica Galesic Ljubanovic, Madlen Knotek, Dept of Medicine, Renal Div, Univ of Zagreb Medical School, Merkur Hospital, Zagreb, Croatia; Dept of Pathology, Univ of Zagreb Medical School, Dubrava Univ Hospital, Zagreb, Croatia.

**Background:** Intensity of immunosuppression is a risk factor for BK virus infection (BKVI). However, the exact impact of exposure to tacrolimus and mycophenolate mofetil (MMF) to BKVI is unclear. The aim of this study was to determine if BKVI in kidney transplant (KT) recipients is associated with drug exposure to MMF.

**Methods:** This prospective randomised controlled clinical trial (NCT01860183) included 36 KT who underwent KT from May 2013 to February 2015 at Clinical Hospital Merkur. Immunosuppression consisted of basiliximab induction, with tacrolimus, MMF±steroid maintenance. KT were randomized in two groups, with respect to MMF dose (2g or 3 g daily). Urine cytology for decoy cells was performed at prespecified time points posttransplant. KT were followed up to 12 months post KT. Graft biopsy was performed per protocol at 2, 6 and 12 months, or in case of graft dysfunction. Kaplan-Meier analysis with log-rank test was used to assess graft survival. A Cox regression was used to determine variables associated with graft survival.

**Results:** 13 (37.1%) KT had decoy cells in urine, 4 (11.4%) KT had biopsy-proven BK virus-associated nephropathy (BKVAN). The mean time-to-occurrence was 4.8 months for decoy cells and 4.3 months for BKVAN. Cumulative one-year overall graft survival was 93.5%. Incidence of decoy cells, BKVAN, or acute rejection was similar in the two MMF groups. Rejection was not a risk factor for decoy cell positivity or for BKVAN.

**Conclusions:** MMF dose may not increase risk for BKVI after kidney transplantation.

**Funding:** Government Support - Non-U.S.
Lipidapheresis in 3 Sisters with Familial Hypercholesterolemia
Chantal A. van de Waal,1 Andriez Schulte,2 Thomas Meissner,3 Lutz Thorsten Weber,3
1Pediatric Nephrology, Univ Hospital of Cologne, Cologne, Germany; 2Dept of Pediatrics, Neuroradiology and Cardiology, Univ Hospital of Duesseldorf, Duesseldorf, Germany.

Background: Familial hypercholesterolemia (FH) is the most common monogenic form of hypercholesterolemia. It carries the risk of premature coronary heart disease. As the atherosclerotic burden is dependent on the degree and duration of exposure to raised LDL-cholesterol levels, early diagnosis and effective treatment are imperative. Statins are the mainstay in the management of these patients. Lipoprotein-apoheresis becomes recently more established in patients with severe dyslipidemia. Together these treatments improve the prognosis of FH. Most children fail to attain targeted lipid goals owing to persistent shortcomings in diagnosis and treatment.

Methods: Three siblings with a LDLR mutation (p.Try577Arg) being on statins (20 mg/d Atorvastatin) and Ezetimib (10 mg/d) for 12 months with still LDL-C plasma concentrations of above 300-500 mg/dl started once a week a double filtration plasmapheresis (DFFP) with with a single plasma volume to be treated.

Results: After each LDL-apheresis LDL-C concentration of 100-150 mg/dl could be reached. (66-70% reduction). After 6 months plasma volume to treat was doubled because of a rebound within 7 days with LDL-C concentration up to 300-350 mg/dl. But though after each session LDL-C concentration decreased to 50-100 mg/dl the rebound was still evident after 7 days of therapy pause. With a treatment regime with twice plasma volume every 3-4 days the children finally attained a stable pre-treatment LDL-C concentration of 120-170 mg/dl. Another 2 months later statin therapy was stopped because of underlying mutation with assumed non receptor function. Neither the effectiveness of each apheraxis nor the LDL-C concentration after 4 days showed any change.

Conclusions: In pediatric FH patients with high levels of LDL-cholesterol plasma concentration it might be necessary to treat instead of conservative medication with apopheresis in high frequency and with high plasma volumes to reach a durable decrease in LDL-cholesterol plasma concentration. The use of cholesterol uptake-inhibitors should be considered.

Thrombomodulin Up-Regulation in Preeclamptic Nephropathy Is Associated with Parietal Cell Activation
Rosanne Jane Turner,1 Maria Elisabeth Penning,1 Malu Zandbergen,1 Elifuyeh V. Khankin,2 S. Ananth Karumanchi,3 Jan A. Bruijn,1 Kitty Bloemenkamp,1 Hans J. Baelde,1 Pathology, LUMC, Leiden, Netherlands; 2Howard Hughes Medical Inst and Dept of Medicine, Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA; 3Obstetrics, LUMC, Leiden, Netherlands.

Background: Preeclampsia is a pregnancy-specific syndrome characterized by angiogenic imbalance and endothelial dysfunction. This endothelial dysfunction leads to kidney injury, i.e. glomerular endotheliosis, increased podocyte turnover and proteinuria. Thrombomodulin (TM) facilitates maintenance of glomerular endothelium by inhibiting coagulation, inflammation and apoptosis. In preeclampsia, levels of soluble thrombomodulin in the circulation are increased. We hypothesize that glomerular thrombomodulin expression is increased in preeclampsia and set up to correlate thrombomodulin expression with endothelium and podocyte damage.

Methods: A nationwide, ethics committee-approved search of the Dutch Pathology Registry (PALGA) was conducted; this revealed renal autopsy material from 11 women with preeclampsia according to the ISSHP definition, from 22 normotensive pregnant controls. Registry (PALGA) was conducted; this revealed renal autopsy material from 11 women with preeclampsia according to the ISSHP definition, from 22 normotensive pregnant controls.

Results: TM expression was increased in glomeruli from preeclampsia patients (82%) compared to pregnant, (41%, P=0.03) and hypertensive controls (21%, P=0.004). In sFLT-1 transfected mice TM expression was the same as in controls. TM expression correlated with activation of parietal epithelial cells (P=0.023), but not with endothelium or endothelial fibronectin deposits (P=0.03).

Conclusions: TM expression in the kidney is increased in preeclampsia. This is associated with parietal cell activation and not with endothelial damage or fibronectin deposits. TM apparently exerts cytoprotective and not anticoagulant effects in the kidney in preeclampsia. Glomerular damage induced by sFLT-1 did not increase TM expression in a mouse model; this indicates that the increased TM expression in humans is probably not caused by this anti-angiogenic factor alone.

Cadmium Induces Matrix Metalloproteinase-9 Expression via NADPH Oxidase/ROS-Dependent EGFR Signals in Human Endothelial Cells
Nam ho Kim. Internal Medicine, Chonnam Natunial Univ Hospital, Gwangju, Korea.

Background: Cadmium, a widespread cumulative pollutant, is a known human carcinogen, associated with inflammation and tumor. Matrix metalloproteinase-9 (MMP-9) plays a pivotal role in inflammatory reaction and tumor metastasis, however, the mechanisms underlying MMP-9 expression induced by cadmium remains obscure in human endothelial cells.

Methods: Here, cadmium elevated MMP-9 expression and enzyme activity, as well as MMP-9 promoter-driven luciferase activity, in a dose and time dependent manner in ECV304 human endothelial cells. Moreover, cadmium activated phosphorylation of EGFR, Akt, Erk1/2, JNK1/2, P38MAPK and promoted NF-κB and AP-1 binding.

Results: Specific inhibition and mutation studies show that EGFR, Akt, Erk1/2, JNK1/2 and transcription factor NF-κB and AP-1 were related to cadmium-induced MMP-9 expression in ECV304 cells. Akt and MAPKs (Erk1/2 and JNK1/2) functioned as upstream signaling molecules in the activation of NF-κB and AP-1, respectively. Furthermore, Cadmium increased ROS production and the ROS-producing NADPH oxidase. Cadmium translocates p47phox, ayeyakutim, NADPHxidoase, to the cell membrane. The exogenous HO2 increased MMP-9 mRNA expression. And that, inhibition of ROS by ROS scavenger (NAC) or NADPH oxidase inhibitor (DPI) attenuated EGFR, Akt, MAPK (Erk1/2, JNK1/2, P38MAPK) activation, and MMP-9 expression. Likewise, inhibition of EGFR phosphorylation prevented the activation of AKT, MAPKs (Erk1/2, P38MAPK). Finally, ECV304 celllincited with cadmium displayed markedly invasiveness, which was partially abrogated by MMP-9 neutralizing antibodies.

Conclusions: These results demonstrated that cadmium induces MMP-9 expression via NADPH oxidase ROS-dependent EGFR Akt/NF-κ Band MAPKs Erk1/2,JNK1/2 signaling pathways and, in turn, stimulates invasiveness in human endothelial ECV304 cells. These findings provide further insight into the molecular mechanisms in the carcinogenesis effect of cadmium.

Exosomes from Activated Kidney Fibroblast Have Ambivalent Potential Effect on Atherosclerosis
Fumitoshi Nishio, Noritoshi Kato, Yoshio Funahashi, Takuji Ishimoto, Tomoki Kosugi, Naotake Tsuibo, Shoichi Maruyama, Seiichi Matsuo. Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi-Pref., Japan.

Background: Exosomes are small (50-140nm) membrane vesicles of endothelial origin that contain host cell’s proteins, mRNAs, and microRNAs (miRNAs). The body of exosomes is known that these particles were biologically active, and had roles in intracellular communication. Especially tumor-derived exosomes has been intensively explored and proven to be associated with distant metastasis. On the other hand, it is well known that CKD patients are at risk of cardiovascular diseases, but the mechanism of this distant organ crosstalk is not fully understood. Under the hypothesis that exosomes are involved in cardio-renal syndrome (CRS), the aim of this study is to explore the role of exosomes from kidney fibroblasts, which are activated in diseased kidney, on vascular endothelial cells.

Methods: We isolated Exosomes from culture media of TGF-β-stimulated rat kidney fibroblast cell line (RKF-49) by ultracentrifugation technique. Cultured vascular endothelial cells (RAOEC; Rat Aortic Endothelial Cells) were stimulated by these exosomes and cultured vascular endothelial cells (RAOEC; Rat Aortic Endothelial Cells) were stimulated by these exosomes or exosomes from unstimulated fibroblast. Then we evaluated the expression of genes, which associated with atherosclerosis by qPCR.

Results: RAOEC stimulated with exosomes form TGF-β activated kidney fibroblast (RAOEC-T) showed higher expression of PIGF and lower expression of FB-1, ABCA-1 than control (RAOEC-C). This expression pattern is compatible with atherosclerotic change. On the other hand, RAOEC-T showed reduced expression of adhesion molecules such as ICAM-1,VCAM-1 and E-selectin compare with RAOEC-C.

Conclusions: So far, CRS is supposed to cause by uremic factor, RAS system, chronic inflammation, and so on. From this study, we showed that exosomes from activated kidney fibroblasts have ambivalent roles in atherosclerosis by modulating the expression of adhesion molecules, metabolic factor, and VEGF system on endothelial cells. Further studies are needed to elucidate the contribution level of exosomes on CRS.

Prevalence of Metabolic Syndrome in Patients with End Stage Renal Disease: Relevance of Biomarkers, Vinod K. Bansal1, Jennifer Saluk,2 Debra Bongiovi,2 Danuyeal Syed1, Schubhataz Abd,1 Jawed Fareed.1 Nephrology, Loyola Univ Medical Center, Maywood, IL; 2Pathology, Loyola Univ Medical Center, Maywood, IL.

Background: Since the metabolic syndrome (MetS) and chronic kidney disease (CKD) share many of the same risk factors and similar inflammatory pathogenesis, many studies have suggested a correlation between CKD and MetS, and shown that patients with MetS are more likely to develop CKD. The purpose is to investigate metabolic biomarker levels in ESRD patients to evaluate their relevance to ESRD and to prevent CRFs and to elucidate the pathogenic ESRD processes and the development of associated comorbidities.

Methods: Plasma samples were retrospectively collected from 89 ESRD patients prior to maintenance hemodialysis. Normal human plasma samples (female & male, 18-35 years old) were purchased from George King Biomedical Inc. (Overland Park, KS). Samples

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Underline represents presenting author.

1050A
were stored at -80°C. Biochips were purchased from RANDOX (Co. Antrim, Northern Ireland) to test C peptide, ferritin, IL-6, resistin, insulin, TNFs, IL-1α, leptin, PAI-1. These biomarkers were tested on 82 ESRD and 17 normal samples.

Results: All biomarkers, except insulin, were significantly elevated in Patients with ESRD compared to normal (p values are 0.05 - 0.0001). MetS patients with ESRD, as compared to non-MetS Patients with ESRD, had significantly elevated Leptin (P=0.002), and the correlation between MetS and Leptin levels was significant (P=0.0001; r=0.43). All other biomarkers showed no significant difference between ESRD+MetS and ESRD-MetS patients. Furthermore, when leptin levels for Patients with ESRD were broken down into ESRD+MetS and ESRD-MetS, ESRD+MetS vs. normal was significant (P=0.003), but ESRD-MetS vs. normal was not (P=0.6).

Conclusions: Elevated biomarkers suggest an ongoing inflammatory process in ESRD patients. Insulin levels were not significantly elevated in ESRD patients, possibly attributed to the high Leptin levels, which can interfere with insulin secretion and signaling. ESRD-MetS and ESRD-MetS populations are not statistically different for all other biomarkers. This suggests that biomarker elevation is due to ESRD pathogenesis, rather than due to MetS as a comorbidity.

**PUB706**

Decreased Mitochondrial Membrane Potential in Monocyte Subsets from Patients with Chronic Kidney Disease

Ying Wang,1 Eric Joseph Lai,2 Annie Febus,1 Yuan Zhang,2 Linda Vernocchi,3 Anjali Ganda1,2

1 Div of Nephrology, Dept of Medicine, Columbia Univ Medical Center, New York, NY; 2 Div of Biostatistics, Mailman School of Public Health, Columbia Univ, New York, NY;

Methods: Monocyte subsets from 18 adult CKD patients (eGFR=30 ml/min/1.73 m²) and 26 matched controls (eGFR ≥60 ml/min/1.73 m²) were freshly analyzed by flow cytometry. Mitochondrial membrane potential (DYM), as a measure of mitochondrial functionality, was determined by the mean fluorescence intensity (MFI) of TMRM (tetramethylrhodamine methyl ester).

Results: DYM was significantly reduced by 10% in patients with CKD vs. controls in total monocytes (P<0.05). Interestingly, the intermediate monocyte subset (CD14+CD16–) which has the highest DYM among all the monocyte subsets and has been shown to predict future cardiovascular events in CKD patients, had the most pronounced reduction in DYM (14% lower, P<0.01) in patients with CKD vs. controls.

Conclusions: Patients with CKD demonstrate mitochondrial dysfunction in total monocytes and monocyte subsets. Mechanistic and prospective studies are needed to examine the relationship between monocyte mitochondrial dysfunction, atherosclerosis, and future cardiovascular events in CKD patients.

**Funding:** NIDDK Support, Private Foundation Support

**PUB707**

Paricalcitol Upregulates Renal Klotho and Restores Uremia-Induced Endothelial Integrity Disruption

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Background: Klotho deficiency in chronic kidney disease (CKD) is associated with the disruption of the endothelial integrity. Active vitamin D induces klotho expression. Hence, active vitamin D may limit endothelial layer disruption.

Methods: Male wistar rats were assigned into one of four groups: Control; Vitamin D deficiency, induced with Vitamin D deficient diet; Uremic, + Vitamin D deficiency. Animals were treated with Paricalcitol or vehicle control during 7 weeks. Serum samples were analyzed for 25D and 1,25D. Evans Blue was injected for estimation of the endothelial thoracic aorta and lung permeability and quantified using spectrophotometry. To determine the levels of Klotho, qPCR and WesternBlot was performed in kidney tissue.

Results: Average 25D levels were 9.83 nmol/L while 1,25D levels were below the detection levels (20pmol/L) after the induction Vitamin D deficiency. mRNA and protein levels of Klotho in the kidney were decreased in Vitamin D deficient and uremic rats and restored after Paricalcitol treatment. Aortic Evans blue leakage increased in all uremic rats regardless of vitamin D level, compared with the control group and restored after Paricalcitol treatment (p<0.03). Uremia did not induce pulmonary leakage, but paricalcitol lowered it compared to control and uremic condition (p<0.04). Figure shows uremic without D-deficiency together.

Conclusions: CKD induces aortic endothelial leakage, while the deficit of vitamin D on its own did not. Paricalcitol completely rescued endothelial leakage induced by CKD. In parallel, Klotho expression increased upon this treatment and may mediate the beneficial effect on the endothelium. To explain the difference between aortic and pulmonary tissue, additional studies are required.

**Funding:** Pharmaceutical Company Support - Abbvie

**PUB708**

Uregulation of Microparticles, Tissue Factor, Adhesion Molecules, Nitric Oxide and Adiponectin in End Stage Renal Disease

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Background: End stage renal disease (ESRD) represents the final stage of chronic kidney disease characterized by kidney failure (GFR <15 ml/min/1.73 m²). To understand the pathophysiology of ESRD, we measured the circulating levels of microparticles (MP), tissue factor (TF), adhesion molecules, such as p-selectin (P-Sel), soluble ICAM (s-ICAM), nitric oxide (NO) and adiponectin (AD).

Methods: Plasma samples were collected from 119 ESRD patients undergoing maintenance hemodialysis to profile various inflammatory biomarkers. 100 normal plasma samples were collected from healthy individuals. MP levels were measured using an annexin

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Coronary Artery Calcification and All-Cause Mortality in RRT Patients with Diabetes: 5 Year Survival Analysis

**Background:** Vascular calcification is a significant sequela of ESRD. A Coronary Artery Calcification (CAC) Agatston score ≥ 300 has been associated with adverse cardiovascular events & increased mortality. The purpose was to evaluate all-cause mortality rates in ESRD with diabetes.

**Methods:** 113 diabetic pts undergoing RRT had CAC scoring by sub-second gated helical CT standard Agatston scoring system, slice thickness 3mm. Patients were categorized into 3 groups according to CAC score: 0, 1-299, ≥ 300 (Low, Medium, High Risk). Survival of 3 groups was calculated using Kaplan-Meier curves for all-cause mortality for 5 year period after CAC. Unadjusted and risk-factor adjusted for age & length of time on dialysis Cox proportional hazard modeling was used to estimate time to all-cause mortality.

**Results:** 5 year survival was 92%, 60%, 46% for Low, Medium, High Risk CAC groups.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Months on Dialysis</th>
<th>CACS 0</th>
<th>CACS 1-299</th>
<th>CACS ≥300</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 ±11</td>
<td>40 ±33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57 ±11</td>
<td>23 ±20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61 ±9*</td>
<td>46 ±15</td>
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</tr>
</tbody>
</table>

**Conclusions:** These studies suggest that MP, TF, NO, p-selectin and s-ICAM levels are increased in the ESRD patient. It is of interest to note that despite that a significant number of ESRD patients were diabetic; the AD levels were increased. These results also suggest that while ESRD represents a pro-inflammatory/hypercoagulable state, the repeated administration of heparin and other drugs may contribute to the regulation of the hemostatic process and inflammatory balance.

PUB710

**Elevated Toll Like Receptor 4 Expression and Macrophage Infiltration Is Found in High Dose Vitamin D-Induced Non-Uremic Vascular Calcification**

**Background:** Vascular calcification is strongly associated with cardiovascular morbidity and mortality. Several studies have suggested that monocytes/macrophages are involved in arterial vascular calcification, while the involvement of the TLR4 pathway in vascular calcification has also been proposed.

**Methods:** Male C57BL/6 mice aged 8 weeks were injected with a high dose of vitamin D (50000IU/kg/day) subcutaneously for 3 days at 0, 24 and 48 hours. All mice were sacrificed 3 days after the final administration of vitamin D. Kidneys were assessed histologically. Whole aortas were dissected. Macrophage infiltration and TLR4 expression was assessed by immunohistochemistry and histology and vascular calcification by Von Kossa staining.

**Results:** High dose vitamin D treatment did not induce kidney fibrosis or injury in C57BL/6 mice within the short time frame, as assessed by GT lisiboscore and PAS tubular damage score. High dose vitamin D treated mice demonstrated significantly higher calcium deposition in the aortic arteries (17.45% of vessel area) compared to controls (1.2% p<0.05). This was accompanied by a greater level of macrophage infiltration and TLR4 expression in these arteries compared to controls.

**Conclusions:** Accelerated vascular calcification was induced in mice with high dose vitamin D treatment. These data also identify a potential role for macrophages and the TLR4 pathway in vascular calcification.

PUB711

**Lack of Correlation of Pyrophosphate Levels with Survival and Coronary Artery Calcification in Hemodialysis Patients**

**Background:** Vascular calcification is an important predictor of cardiovascular mortality in ESRD. Decreased levels of inorganic pyrophosphate (PPi) are thought to increase vascular calcification. The purpose of this study was to evaluate the association of PPi & coronary calcification scores in maintenance HD patients and all-cause mortality over 5 years.

**Methods:** 98 maintenance HD patients were studied (mean ±SD): Age (yrs) 57 ±10.7, HD vintage (month) 36 ±37.6. Platelet free plasma PPi was measured by radiometric, enzymatic method as described by Tolouian. Coronary arterial calcification score (CACS) was measured by sub-second gated helical computed tomography with an Imatron C-150 XL ultra fast CT scanner using a standard protocol for vascular calcification. Patients were categorized into 3 groups according to their CAC score: 0, 1-300, and ≥ 300.

**Results:**

<table>
<thead>
<tr>
<th>CACS 0 (n=17)</th>
<th>CACS 1-299 (n=40)</th>
<th>CACS ≥300 (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPi (μM)</td>
<td>1.49 ±0.37</td>
<td>1.60 ±0.56</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>51 ±11.0</td>
<td>58 ±11.3</td>
</tr>
<tr>
<td>Months on HD</td>
<td>32 ±27.2</td>
<td>25 ±21.5</td>
</tr>
</tbody>
</table>

*p<0.05 Low vs High, **Medium vs High ANOVA, Dunnet T3*

The covariate PPi had no significant effect on the hazard rate, log rank p=0.61. After adjusting for covariates of PPi, age, length of time on HD at time of measurement the log rank statistic for the survival curves is not great enough to exclude the possibility that the difference is due to random sampling variability; there is not a statistically significant difference (P = 0.614).

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

Underline represents presenting author.
Conclusions: The difference in 5 year survival rate in dialysis patients based on the severity of vascular calcification is not influenced by pyrophosphate levels. This supports the multi-factorial nature of vascular calcification.

**PUB712**

Aortic Artery Calcification and Cardiac Valve Calcification Is Associated with Mortality in Chinese Haemodialysis Patients: A 3.5 Year Follow-Up

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Background: Aim to investigate the relationship among aortic artery calcification (AAC), cardiac valve calcification (CVC) and mortality in maintenance haemodialysis (MHD) patients.

Methods: The study included 110 MHD patients. All MHD patients were treated in Shanghai Ruijin Hospital in July 2011. Follow-up these patients for 42 months.

Results: Totally 110 MHD patients were involved in this study. 64 (58.2%) patients were male, and the mean age was 55.2 ± 15.0 years old, the mean dialysis duration was 41.7 ± 38.1 months. 25.5% patients had cardiac valve calcification, while 61.8% had visible calcification. After 42 months follow-up, 26 (22.7%) patients died, including 16 cases death from cardiovascular events, 5 cases respiratory failure, 3 cases tumor metastasis, 1 case deep venous thrombosis and 1 case abandon treatment. Kaplan-Meier analysis showed that patients with AAC or CVC had a significant greater number of all-cause and cardiovascular deaths than those without. In multivariate analyses, the presence of AAC was a significant factor associated with all-cause mortality (HR 3.149, P = 0.025) in addition to lower albumin level and lower 25(OH)D level. The presence of CVC was a significant factor associated with cardiovascular mortality (HR 3.800, P = 0.029) in addition to lower albumin level and lower 25(OH)D level.

Conclusions: The presence of AAC and CVC were independently associated with mortality in MHD patients. Regular follow-up by X-ray and echocardiography could be useful method to stratify mortality risk in MHD patients.

Funding: Government Support - Non-U.S.

**PUB713**

Beneficial Effect of the Vasopressin AV1a and AV2 Receptor Blocker Conivaptan (C) on the Renal Alterations Resulting from Mild Heat-Induced Dehydration (MHID) and Rehydration with a 10% Fructose (F) Beverage

Gabriela Sanchez-Lozada,1 Fernando E. Garcia-arroyo,1 Monica Gabriela Bias-Marron,1 Jose Pedraza-chaverri,2 Cecilia Zazueta,2 Magdalena Cristobal,1 Edilia Tapia.1 1Renal Physiopathology, INCICh, Mexico City, DF, Mexico; 2Biology, UNAM, Mexico City, DF, Mexico; 3Cardiovasc BioMed, INCICh, Mexico City, DF, Mexico.

Background: The aims of this study were: 1. To define a possible synergistic effect between fructose and vasopressin during MHID, and 2. To evaluate the potential therapeutic benefit of C (3mg/kg BW) on this condition.

Methods: Six groups of male Wistar rats were MHID (37°C/1 h/day) and rehydrated with the selected beverage during 30 days: Water (W)+Veh, W+C, F+Veh, F+C, Stevia (S)+Veh and S+C. A group of normal control (NC) rats was studied as reference. After 30 days plasma and urine parameters were evaluated, renal cortex mitochondria were isolated and respiratory control rate (RRC) was evaluated with malate/glutamate (M/G) and succinate/rotenone (S/R) substrates.

Conclusions: The presence of AAC and CVC were independently associated with mortality in MHD patients. Regular follow-up by X-ray and echocardiography could be useful method to stratify mortality risk in MHD patients.

Funding: Government Support - Non-U.S.
Results:

<table>
<thead>
<tr>
<th>Group/parameter</th>
<th>POsm (mOsm/kg)</th>
<th>PCr (mg/dL)</th>
<th>PCr-pept (mg/mL)</th>
<th>Renal Osm-Prot (mOsm/kg prot)</th>
<th>Urine NaG</th>
<th>RCR MgG</th>
<th>RCR S/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>295±4</td>
<td>0.7±0.3</td>
<td>0.03±0.01</td>
<td>5±4</td>
<td>0</td>
<td>4.4±0.2</td>
<td>3.4±0.2</td>
</tr>
<tr>
<td>W+V</td>
<td>303±4</td>
<td>0.8±0.1</td>
<td>24±3</td>
<td>61±3</td>
<td>0.5±0.03</td>
<td>3.9±0.3</td>
<td>3.2±0.1</td>
</tr>
<tr>
<td>W+C</td>
<td>301±4</td>
<td>0.8±0.1</td>
<td>24±2</td>
<td>14±1</td>
<td>0.4±0.02</td>
<td>3.9±0.2</td>
<td>3.4±0.2</td>
</tr>
<tr>
<td>F+V</td>
<td>317±4</td>
<td>1.1±0.1</td>
<td>9±7</td>
<td>49±3</td>
<td>1.1±0.1</td>
<td>3.6±0.2</td>
<td>2.5±0.2</td>
</tr>
</tbody>
</table>

Conclusions: These data suggest a crosstalk between F and vasopressin on this particular condition. In addition, treatment prevented renal and mitochondrial alterations induced by rehydration with F.

Funding: Pharmaceutical Company Support - Danone Nutricia Research

PUB716
Low Osmolar Diet and Adjusted Water Intake for Vasopressin Suppression in ADPKD

Objective: To identify a novel dietary approach that can reduce vasopressin levels in patients with ADPKD.

Materials and Methods: This randomized controlled trial examined the effect of a novel approach of combining low osmolar diet and adjusted water intake on vasopressin, measured by change in urinary osmolality and serum sodium.

Results: Baseline characteristics of the two groups were similar. Compared with baseline, the mean urine osmolality significantly declined from 426 (±193) to 258 (±110) mOsm/kg (P=0.007) but not in the control group. At 2 weeks, levels significantly differed between groups (P=0.04).

Conclusions: A low osmolar diet was effective in reducing vasopressin levels, which may be useful in the management of ADPKD.

Funding: NIDDK Support

PUB715
Urinary Excretion Pattern of Exosomal Aquaporin-2 in Nephronphthisis

Objective: To investigate the urinary excretion pattern of exosomal aquaporin-2 (AQP2) in patients with nephronphthisis.

Materials and Methods: Urine samples were collected from patients with nephronphthisis and healthy controls. Exosomal AQP2 was analyzed by immunoblotting.

Results: The level of urinary exosomal AQP2 was significantly increased in patients with nephronphthisis compared to controls.

Conclusions: Urinary exosomal AQP2 may be a potential biomarker for nephronphthisis.

Funding: Tufts Medical Center; Tufts University School of Medicine
CRISPR-Cas9-Mediated Deletion of Myosin Light Chain Kinase in Cultured Collecting Duct Cells Kiyoshi Isobe, Viswanathan Raghuram, Pablo Sandoval, Chin-Rang Yang, Chung-Lin Chou, Mark A. Knepper. Systems Biology Center, NHLBI, NIH.

Background: Regulation of osmotic water transport in the renal cortical collecting duct by vasopressin is in part dependent on membrane trafficking of aquaporin-2 (AQP2) to the apical plasma membrane of the principal cells. It is known that trafficking of AQP2 is in part dependent on changes in AQP2 phosphorylation. We previously proposed that AQP2 trafficking is dependent on the protein kinase Myosin Light Chain Kinase (MLCK; gene symbol: Mylk). Here, we test the role of MLCK in AQP2 phosphorylation and trafficking, utilizing CRISPR-Cas9-mediated mutations in the cultured mouse mpkCCD cells.

Methods: We used CRISPR-Cas9 genome-editing to mutate the catalytic region of the Mylk gene. Clones were generated with 4 different guide RNAs and were characterized by genomic sequencing and immunoblotting. Effects of the deletions were assessed by immunoblotting and immunofluorescence immunocytochemistry of AQP2.

Results: Multiple clones with mutations in the catalytic domain of MLCK were generated. Western blots showed absence of MLCK protein in MLCK-deleted clones. Controls were clones that express MLCK without mutations in the catalytic domain, but may contain off-target modifications. AQP2 protein abundance varied over a broad range, among all MLCK-deleted (n=4) and control (n=4) lines, but, on average, was not affected by the deletion. Immunocytochemistry showed that vasopressin stimulates redistribution of AQP2 to the apical plasma membrane in both control cells and MLCK-deleted cells. Vasopressin-dependent phosphorylation of AQP2 at Ser256 and Ser269 was not significantly reduced in MLCK-deleted cells.

Conclusions: The results demonstrate the feasibility of CRISPR-Cas9-mediated genome editing in mouse mpkCCD cells. Our experiments in mouse cultured collecting duct cells provide evidence that vasopressin-induced phosphorylation of AQP2 and redistribution of AQP2 to the apical plasma membrane can occur independently of myosin light chain kinase.

Funding: Other NIH Support - NHLBI Intramural

The PDZ Domain-Containing Protein Harmonin Is a Binding Partner of Sodium-Coupled Monocarboxylate Transporter 2 Nobuyuki Onizawa,1,2 Naoyuki Otani,1 Promsku Jutabha,1 Motoshi Ouchi,1 Hajime Hasegawa,2 Naohiko Anzai.1 1Dept of Pharmacology and Toxicology, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan; 2Dept of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical Univ, Kawagoe, Saitama, Japan.

Background: Lactate is freely filtered and extensively reabsorbed in the proximal tubule to prevent the loss of this valuable metabolite from the body. Sodium-coupled monocarboxylate transporter SMCT2 (SLC5A12) mediates the transport of pyruvate, lactate, and acetate from the extracellular compartment to the cytoplasm of the renal epithelial cells. As the terminal PDZ motif abolished the interaction with harmonin in the yeast two-hybrid assay, we tested whether harmonin interacts with SMCT2.

Methods: We used the yeast two-hybrid screening to investigate the putative SMCT2-associated proteins that modulate its transport function. Using the SMCT2 C-terminal tail (SMCT2-CT) as bait, we performed a yeast two-hybrid screen of a cDNA library constructed from mouse kidney and identified the interaction with harmonin in the yeast two-hybrid system. Furthermore, co-immunoprecipitation studies revealed that the SMCT2 interacted directly with harmonin.

Conclusions: Harmonin was identified as the binding partner for SMCT2. The elucidation of these interactions may further our understanding of the function and regulation of monocarboxylate (e.g., lactate) transport in the human kidney.

Stimulation of V1a Receptor Increases Renal Uric Acid Clearance via ABCG2 Transporter - Insight into Hypouricemia in SIADH Kei Taniguchi, Yoshihiro Tamura, Shigeru Shibata, Shunyu Uchida. Dept of Internal Medicine, Teikyo Univ School of Medicine, Itabashi, Tokyo, Japan.

Background: Hypouricemia seen in the subjects with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is pathogenicomic but the mechanism of hypouricemia remains to be clarified. V2 receptor agonist ‘desmopressin’ induced hypouricemia but not hypouricemia in human unlike SIADH (G Deicas, JASN, 1996). Therefore, we hypothesized that V1 receptor but not V2 receptor may play a role in inducing hypouricemia. In the present study, we examined the changes in serum uric acid, urinary uric acid excretion and expression of uric acid transporters in response to V1a receptor agonist ‘terlipressin’.

Methods: Terlipressin was subcutaneously infused by osmotic mini pump to 7-weeks-old male Wistar rats (n = 9). Control rats were infused with normal saline (n = 9). The rats were sacrificed to obtain renal cortical tissues at 3 days.

Results: Serum uric acid significantly decreased and the excretion of urinary uric acid significantly increased in the terlipressin group. Thus, fractional excretion of uric acid increased from 1.20 ± 0.28 % to 3.10 ± 0.56 % (P < 0.001). The expression of ATP-binding cassette transporter, sub-family G, member 2 (ABCG2) significantly increased in the terlipressin group. Other uric acid transporters did not significantly change.

Conclusions: These results suggest that stimulation of V1a receptor increases renal uric acid clearance probably via upregulation of ABCG2, leading to hypouricemia seen in SIADH patients.


Background: Fluorescein angiography (FA) is an indispensable tool for diagnosis and management of diabetic retinopathy (DR). However, safety of fluorescein sodium on renal functions is not fully understood.

Methods: 100 type 2 diabetic patients presenting to the ophthalmology outpatient clinic at Alexandria main university hospital were included in our study. Serum creatinine and cystatin-C were measured before and 2 days after FA. Urinary NGAL as a tubular biomarker was measured before and 4 hours after FA. Renal injury was defined as 25 % increase in serum creatinine or cystatin-C.

Results: The mean of serum creatinine was 0.99 ± 0.36 mg/dl and 1.0 ± 0.36 mg/dl before and after FA respectively with no statistically significant change (P=0.061). Only one patient (out of 100) experienced more than 25 % rise in serum creatinine from baseline. Cystatin-C and urinary NGAL increased significantly after FA (P<0.001). Mean of serum Cystatin-C was 0.89 ± 0.34 mg/l and 0.95 ± 0.36 mg/l before and after FA respectively. 11 patients experienced more than 25% rise in serum cystatin-C from baseline. Mean of urinary NGAL was 21.78 ± 23.90 ng/ml and 27.15 ± 28.17 ng/ml before and after FA respectively.

Conclusions: Using ordinary renal biomarkers as serum creatinine, FA was thought to be kidney friendly. Nevertheless, using more sensitive early biomarkers as serum cystatin-C and urinary NGAL, FA is not as innocent as previously thought. A creatinine negative, biomarker positive change may implicate a form of subclinical AKI.
Hemodialysis was required in 9.3% of cases. The recovered AKI was observed in 75.9% at the time of hospital discharge. The length of hospital stay (9.9 ± 7.6 days; p < 0.05) and mortality (18.5 ± 7.2%; p < 0.02) were greater in patients with AKI compared with patients without. Patients with H-AKI had a longer hospital stay (15±12 vs. 8±8; p < 0.05) and a statistical trend to higher mortality (36.4% vs 14%; p < 0.08) in relation to patients with C-AKI.

### Table 1. Clinical and prognostic differences between C-AKI vs H-AKI

<table>
<thead>
<tr>
<th>AKI severity</th>
<th>C-AKI</th>
<th>H-AKI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>17</td>
<td>39.5%</td>
<td>2</td>
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<tr>
<td>Stage 2</td>
<td>5</td>
<td>11.6%</td>
<td>5</td>
</tr>
<tr>
<td>Stage 3</td>
<td>21</td>
<td>48.8%</td>
<td>4</td>
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</table>

### Etiology of AKI

#### Prerenal

- Parenal plots: 15
- Renal: 25

#### Postrenal

- 3
- 0%
- 0.0%

#### Oliguria

- G4
- 5
- 6

#### Hemodialysis

- G4
- 5
- 6

#### Discharged with recovered AKI

- G4
- 33
- 76.7%
- 8

### Pub724

**Drug Utilization Patterns and Factors Associated with Acute Kidney Injury in an Intensive Care Unit at a Brazilian Public Hospital – A Prospective Cohort Study**

**Authors:** Danielly Botelho Soares, Gabriela Rebouças Botelho, Flávia Fialho Girundi, Fernando Antonio Botoni, Maria Auxiliadora Parreiras Martins, School of Pharmacy, Univ Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; School of Medicine, Univ Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

**Background:** Acute kidney injury (AKI) is associated with a significant increase in morbidity, mortality and health care costs. In intensive care units (ICU), the cause of AKI is commonly associated with multiple factors, among which the use of potentially nephrotoxic drugs is often neglected as a preventable cause of AKI.

**Methods:** This is a prospective cohort study that evaluated the AKI as a primary outcome in ICU patients at a teaching hospital in Belo Horizonte, Brazil. Length of stay greater than 24 hours and hospital stay lower or equal to 7 days were evaluated for potential eligibility. To be enrolled, patients should not present kidney dysfunction at the time of ICU admission.

**Results:** Data collection was performed from October 2014 to February 2015, including 122 patients, mostly originated from the surgical department (46.7%). An average of 22.0 ± 9.4 drugs was prescribed and 2-24 potentially nephrotoxic drugs were used per patient. Mechanical ventilation was required for 67.2% of patients and at least one vasoactive drug was used in 68.0% of cases. An incidence of AKI was observed in 23.8% of patients, among them 34.5% required dialysis, 24.1% reached the third stage of AKI and 31.8% were referred to additional treatment after ICU discharge. Eleven (9%) patients died and 63.6% of them developed AKI. The bivariate analysis showed that (p = 0.06) and APACHE II score (p = 0.0013) had higher median among patients who developed AKI compared with those who did not develop AKI. In the logistic regression, the number of medications (OR: 1.15; 95% CI: 1.05 to 1.26) presented a statistically significant correlation with the development of AKI.

**Conclusions:** These results demonstrate that the identification of factors associated with AKI in ICU patients is very important for the early identification of renal dysfunction induced by drugs, providing conditions for appropriate prevention and treatment of the extent of kidney damage.

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

**Underline represents presenting author.**
Clinical, Dialytic and Laboratorial Factors Associated with Poor Health Related Quality of Life in Mexicans Hemodialysis Patients

Edgar Dehesa Lopez,1 David Olvera,2 Carlos Gonzalez parra,2 Rafael Baizabal.4 

1Dept of Nephrology, Research and Teaching Center in Health Sciences (CIDOCS), Culiacan, Sinaloa, Mexico; 2Dept of Nephrology, Hospital ISSSTE, Ciudad Valles, San Luis Potosi, Mexico; 3Dept of Nephrology, IMSS, Puebla, Mexico; 4Department of Nephrology, Hospital ISSSTE, Xalapa, Veracruz, Mexico.

Background: The evaluation of health related quality of life (HRQOL) in hemodialysis patients has recently gained great importance because it has proven to be an independent predictor of clinical outcomes.

Methods: Cross-sectional study. The validated Mexican version of the KDQOL-SF36 v1.3 questionnaire were applied to 194 adult patients with ESRD on hemodialysis in different regions of Mexico. According to the global score of questionnaire, patients were grouped in: patients with poor HRQOL (global score below the median) and patients with good HRQOL (global score greater than the median). Logistic regression was used to investigate the effects of clinical, dialytic and laboratorial factors on HRQOL.

Results: The average age was 54+16 with 54.6.1% male. Comorbidities were: hypertension in 86.6%, diabetes mellitus 2 in 57.2% and dyslipidemia in 7.2%. The vascular access was a catheter in 55.2% and fistula in 44.8% of the cases. Diabetes mellitus and the use of catheters as vascular access were more frequent in patients with poor quality of life. On the other hand, phosphorus >5.5 mg/dl and albumin >4g/dl were more frequent in patients with good quality of life. There were no differences in age, Kt/V, hemoglobin and calcium between groups. Table 1 shown the clinical, dialytic and laboratorial factors studied in the multivariate logistic analysis.

Conclusions: The associated factors with poor HRQOL in Mexicans hemodialysis patients were: the time spent in hemodialysis, serum albumin <4 g/dl and use of catheter for vascular access.

Table 1-Multivariate logistic regression analysis of clinical, dialytic and laboratorial factors associated with poor HRQOL.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.02</td>
<td>0.99</td>
<td>1.05</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>0.87</td>
<td>0.40</td>
<td>1.89</td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>1.35</td>
<td>0.56</td>
<td>3.24</td>
</tr>
<tr>
<td>Vascular access (catheter vs fistula)</td>
<td>3.03</td>
<td>1.30</td>
<td>7.09</td>
</tr>
<tr>
<td>Hemoglobin (&lt;9 g/dl vs &gt;9 g/dl)</td>
<td>1.23</td>
<td>0.46</td>
<td>3.26</td>
</tr>
<tr>
<td>Albumin (&lt;4 g/dl vs &gt;4 g/dl)</td>
<td>3.30</td>
<td>1.37</td>
<td>7.98</td>
</tr>
<tr>
<td>Kt/V (&lt;1.4 vs &gt;1.4)</td>
<td>1.02</td>
<td>0.40</td>
<td>2.60</td>
</tr>
<tr>
<td>Calcium (&lt;8.5 mg/dl reference)</td>
<td>1.56</td>
<td>0.65</td>
<td>3.78</td>
</tr>
<tr>
<td>Calcium (&gt;10 mg/dl)</td>
<td>0.55</td>
<td>0.18</td>
<td>1.65</td>
</tr>
<tr>
<td>Phosphorus (&lt;4.5 mg/dl reference)</td>
<td>2.45</td>
<td>0.30</td>
<td>19.77</td>
</tr>
<tr>
<td>Phosphorus (≥5.5 mg/dl)</td>
<td>1.15</td>
<td>0.14</td>
<td>9.28</td>
</tr>
<tr>
<td>Hemodialysis stay (months)</td>
<td>1.02</td>
<td>1.00</td>
<td>1.04</td>
</tr>
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Later part of the text includes various references and molecules, but the main focus is on renal diseases such as;

- **Gitelman syndrome**
- **glomerular disease**
- **glomerular disease (continued)**
- **glomerular disease (continued)**
- **glomerular hyperfiltration**

Additionally, the text touches on various topics like gene transcription, renal diseases, and hyperfiltration. The references and keywords are spread throughout the text, indicating a comprehensive discussion of nephrology topics.
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  SA-PO722, SA-PO783, SA-PO850, PUB364,
  PUB688, SA-PO893, SA-PO942, PUB140,
  PUB176, PUB200, PUB252, PUB328,
  PUB707
vascular disease.........................TH-OR060, TH-PO378,
  TH-PO385, TH-PO397, TH-PO400,
  TH-PO402, TH-PO403, TH-PO413,
  TH-PO459, TH-PO901, TH-PO907,
  TH-PO909, FR-OR025, FR-PO211,
  FR-PO212, SA-PO054, SA-PO222,
  SA-PO314, SA-PO585, SA-PO596,
  SA-PO601, SA-PO610, SA-PO786,
  SA-PO896, PUB140, PUB176, PUB200,
  PUB252, PUB328, PUB707
vascular endothelial growth factor...............TH-PO315, TH-PO375,
  TH-PO419, TH-PO421, FR-OR084,
  FR-PO348
vasculitis.................................TH-OR024, TH-OR025,
  TH-OR026, TH-PO126, TH-PO135,
  TH-PO145, TH-PO1076, TH-PO1085,
  TH-PO1121, FR-PO006, FR-PO055,
  FR-PO404, FR-PO405, FR-PO411,
  FR-PO412, FR-PO413, FR-PO415,
  FR-PO417, FR-PO979, SA-PO031,
  SA-PO033, SA-PO467, SA-PO052,
  SA-PO078, SA-PO106, SA-PO106,°
  SA-PO127, SA-PO555, PUB218, PUB224,
  PUB228, PUB424
vasopressin........................... TH-PO213, TH-PO795,
   TH-PO1056, FR-PO028, FR-PO031,
   FR-PO095, FR-PO097, FR-PO100,
   FR-PO106, FR-PO108, SA-OR111,
   SA-OR112, SA-OR113, SA-OR114,
   SA-OR115, SA-OR116, SA-PO010,
   SA-PO379, SA-PO852, SA-PO853,
   SA-PO857, SA-PO863, SA-PO880,
   SA-PO916, PUB095, PUB713, PUB717,
   PUB719

VEGF ........... TH-PO016, TH-PO241, FR-PO148,
   FR-PO350, FR-PO831, SA-PO116,
   SA-PO215, SA-PO317

vesico-ureteral reflux .... TH-PO462, TH-PO737,
   FR-PO018, FR-PO455

virology ....... TH-PO1031, FR-PO052, FR-PO332,
   FR-PO778, SA-PO106, SA-PO181,
   SA-PO1058, SA-PO1062, SA-PO1063,
   SA-PO1064, SA-PO1065, SA-PO1069,
   PUB689

vitamin Bl ................................ FR-PO596

vitamin C .... TH-PO1095, FR-PO890, SA-PO807

vitamin D .... TH-PO394, TH-PO485, TH-PO488,
   TH-PO505, TH-PO506, TH-PO507,
   TH-PO508, TH-PO510, TH-PO511,
   TH-PO512, TH-PO513, TH-PO514,
   TH-PO515, TH-PO522, TH-PO523,
   TH-PO524, TH-PO601, TH-PO623,
   TH-PO641, TH-PO645, TH-PO822,
   TH-PO914, TH-PO1019, FR-PO029,
   FR-PO034, FR-PO229, FR-PO311,
   FR-PO615, FR-PO696, FR-PO800,
   FR-PO815, FR-PO841, FR-PO926,
   FR-PO943, FR-PO944, FR-PO1009,
   SA-OR028, SA-PO016, SA-PO065,
   SA-PO365, SA-PO398, SA-PO558,
   SA-PO580, SA-PO597, SA-PO611,
   SA-PO633, SA-PO655, SA-PO660,
   SA-PO743, SA-PO1067, PUB073, PUB525,
   PUB528, PUB531, PUB540, PUB542,
   PUB544, PUB547, PUB548, PUB646,
   PUB647, PUB667

water channels ........... FR-OR038, FR-PO096,
   FR-PO098, FR-PO099, FR-PO100,
   FR-PO101, FR-PO102, FR-PO104,
   FR-PO105, FR-PO109, FR-PO140,
   FR-PO611, FR-PO945, SA-OR115,
   SA-OR117, SA-OR118, SA-PO285,
   SA-PO928, SA-PO972, PUB268,
   PUB715, PUB717

water transport ........... FR-OR004, FR-OR038,
   FR-PO095, FR-PO107, FR-PO109,
   FR-PO808, SA-OR118, PUB714

water-electrolyte balance .......... TH-OR082,
   TH-OR084, TH-PO120, TH-PO423,
   TH-PO428, TH-PO832, TH-PO1056,
   FR-OR004, FR-OR009, FR-PO007,
   FR-PO026, FR-PO050, FR-PO097,
   FR-PO099, FR-PO100, FR-PO106,
   FR-PO118, FR-PO122, FR-PO506,
   FR-PO923, SA-OR110, SA-OR111,
   SA-OR112, SA-PO257, SA-PO417,
   SA-PO657, SA-PO902, SA-PO903,
   SA-PO906, SA-PO907, SA-PO909,
   SA-PO913, SA-PO916, SA-PO932, PUB362,
   PUB431, PUB446, PUB600
Empagliflozin and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Chronic Kidney Disease

Christoph Waninger,1 John M. Lachin,2 David H. Fitchett,3 Silvio E. Inzucchi,4 Maximilian von Eynatten,4 Michaela Matteus,5 Odd Erik Johansen,6 Hans-Juergen Woerle,7 Ulric Christian Broedl,8 Bernard Zinnan,9 1Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; 2Biostatistics Center, The George Washington Univ, Rockville, MD; 3St Michael’s Hospital, Div of Cardiology, Univ of Toronto, Toronto, Canada; 4Section of Endocrinology, Yale Univ School of Medicine, New Haven, CT; 5Boehringer Ingelheim Pharma Gmbh & Co. KG, Ingelheim, Germany; 6Boehringer Ingelheim Norway KS, Asker, Norway; 7Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, Canada; 8Div of Endocrinology, Univ of Toronto, Toronto, Canada.

Background: Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) are at high risk of cardiovascular (CV) events and premature death. Empagliflozin is a sodium-glucose co-transporter (SGLT)-2 inhibitor used in the treatment of T2D.

Methods: In EMPA-REG OUTCOME10, we explored long-term CV outcomes with empagliflozin vs placebo when added to standard of care in 7020 T2D patients with established CV disease. Inclusion criteria included ≤eGFR 30/min/1.73m². Patients (mean age 63 years, mean HbA1c 8.1%) were randomized 1:1:1 to empagliflozin 10 mg, or mg placebo. Selected Results: Most patients had impaired kidney function (52.2% stage 2, 17.8% stage 3a, 7.7% stage 3b CKD) while 28.7% and 11.0%, respectively, had moderately (30-300mg/g) or severely (>300mg/g) increased urine albumin to creatinine excretion. After a median follow-up of 3.1 years, the primary outcome (first occurrence of non-fatal myocardial infarction, non-fatal stroke, or CV death) occurred in a lower percentage of patients on empagliflozin (10.5%) than placebo (12.1%) (HR 0.86 [0.74-0.99]; p=0.04). This result was driven by a 38% reduction in CV death vs placebo (HR 0.62 [0.49-0.77]; p<0.001), with no difference in the risk of heart attack or stroke. Empagliflozin reduced hospitalization for heart failure by 35% (HR 0.65 [0.50-0.85]; p=0.0017). Pre-defined subgroup analyses on CV outcomes in patients with T2D and CKD will be presented.

Conclusions: Empagliflozin reduces CV morbidity and mortality in patients with T2D and various degrees of CKD.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim and Eli Lilly and Company.

High-Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery

Frederic Tremaine Billings, Chad E. Wagner, Patty Hendricks, Yaping Shi, Michael R. Petracek, Nancy J. Brown. Vanderbilt Univ, Nashville, TN.

Background: Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins) affect several mechanisms underlying acute kidney injury (AKI), a common and dangerous complication after cardiac surgery. We hypothesized that short-term high-dose perioperative atorvastatin would reduce AKI following cardiac surgery.

Methods: We randomized elective cardiac surgery patients, stratified by chronic kidney disease (CKD), to atorvastatin or matching-placebo starting the day prior to surgery until hospital discharge in pre-study statin-naïve subjects or until the day after surgery in pre-study statin-using subjects. Our primary endpoint was AKI by AKIN criteria.

Results: The study was stopped on recommendations of the DSMB after 653 of 820 subjects completed the study due to futility and an increased incidence of AKI among statin-naïve subjects with CKD randomized to atorvastatin. AKI occurred in 20.8% of subjects randomized to atorvastatin versus 21.6% randomized to placebo (P=0.70). Among statin-naïve subjects (n=199), however, AKI occurred in 21.6% randomized to atorvastatin versus 13.4% randomized to placebo (P=0.14), and 52.9% vs. 15.8%, P=0.03, in patients with CKD (n=36). Serum creatinine concentrations increased a median of 0.11 (-0.11 – 0.56) versus 0.05 (-0.12 – 0.33) mg/dl in statin-naïve patients randomized to atorvastatin versus placebo (P=0.007), and this effect was magnified among those with CKD, whereas serum creatinine concentrations increased by 0.26 (0.22 – 0.94) versus -0.06 mg/dl (-0.16 – 0.41), P=0.04.

Conclusions: Empagliflozin reduces CV morbidity and mortality in patients with T2D and various degrees of CKD.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim and Eli Lilly and Company.

Effect of Methylprednisolone on Acute Kidney Injury in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Amit X. Gang,1 Richard P. Whitlock,2 1Western Univ, London, Canada; 2McMaster Univ, Hamilton, Canada and the Population Health Research Inst; for the SIRS Investigators.

Background: Acute kidney injury is a common complication of the 20 million cardiac surgeries performed worldwide each year. We conducted a substudy of the Steroids In Cardiac Surgery (SIRS) trial to determine whether methylprednisolone alters the risk of acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass (substudy protocol BMJ Open 2014 Mar 5;4(3):e004842).

Methods: This was a randomized clinical trial of 7,286 high-risk patients undergoing cardiac surgery with cardiopulmonary bypass from 79 centres in 18 countries between June 2007 and December 2013. Patients were assigned to take intravenous methylprednisolone (250 mg at anesthetic induction and 250 mg at initiation of cardiopulmonary bypass) or placebo. Patients, care givers and outcome-assessors were blinded to allocation. Acute kidney injury was defined as ≥25% or ≥ 26.5 mmol/L (≥ 0.3 mg/dL) increase in the postoperative serum creatinine concentration from the preoperative concentration in the 14 days following surgery, or new dialysis in the 30 days following surgery.

Results: Methylprednisolone (n=3,647) versus placebo (n=3,639) did not alter the risk of acute kidney injury (40.9% versus 39.5%, respectively; relative risk 1.03 [95% CI, 0.96 to 1.11]). Results were consistent with multiple alternate continuous and categorical definitions of acute kidney injury, and in the subgroup with baseline chronic kidney disease.

Conclusions: Amongst patients undergoing cardiac surgery with cardiopulmonary bypass the use of corticosteroids in the perioperative period did not alter the risk of acute kidney injury. Trial Registration: NCT00427388.

Funding: Government Support - Non-U.S.

High-Impact Clinical Trials Oral/Saturday

The NEFNIAN Trial: NEFCON, a Targeted Released Formulation of Budesonide, Reduces Proteinuria and Stabilizes eGFR in IgA Nephropathy Patients at Risk of ESRD

Benet C. Feliu,1 Rosanna Coppo,1 John Fech alley,1 Jürgen Floege,1 Johan W. De Fijter,2 Alan G. Jardine,3 Francesco Locatelli,2 Bart D. Maes,1 Alex Merce,2 Fernanda Ortiz,1 Manuel Praga,4 Soren Schwartz Soerensen,5 Vladimir Tesar,6 Uppsala Univ Hospital;7 Univ Turin;8 Univ Leicester;9 RWTH Univ Aachen;10 Leiden Univ Medical Center;11 Univ Glasgow;12 Ospedale A Manzoni, Lecco;13 AZ Delta Roeselaare;14 Pharmalink;15 Helsinky Univ Hospital;16 Hospital 12 de Octubre, Madrid;17 Rigshospitalet, Copenhagen;18 Charles Univ, Prague.

Background: IgA nephropathy (IgAN) is the most prevalent primary chronic glomerular disease. Despite RAS blockade, >25% of patients progress to ESRD within 20 years. This study evaluated a novel budesonide formulation (NEFCON) targeted for release in the distal ileum, where Peyer’s patches reside, in patients at risk of ESRD despite optimized RAS blockade.

Methods: Double-blind, placebo-controlled study in 150 patients (62 sites, 10 EU countries) with primary IgAN, proteinuria (UPCR >0.5 g/G or urine protein >0.75 g/d) and eGFR >50 mL/min/1.73m² randomised to EPE=45 mL/m/min/1.73m² randomisation to 8 or 16.73m² randomisation to 1:1:1; after 6 mo run-in phase to optimize RAS blockade. Primary endpoint: reduction in UPCR at 9 mo of treatment; secondary: mean change in eGFR.

Results: Baseline data were similar across groups; BP was 127-128/78-80 mmHg, UPCR 0.76-0.83 g/d, and eGFR 72-78 mL/min/1.73m². Primary endpoint was met at the pre-specified interim analysis. Mean UPCR decreased by 24% (NEFCON 8+16 mg/d) vs 3% increase (placebo) at 9 mo (p=0.007); reduction in the 16 mg/d group was 27% (p=0.003). Adverse event rates were higher in NEFCON groups (88–94%) than placebo (84%). Two serious adverse events were assessed as possibly related to NEFCON; deteriorated renal function (in follow-up) and deep vein thrombosis.

Conclusions: NEFCON reduced UPCR and maintained eGFR in patients with primary IgAN at risk of progression to ESRD despite optimized RAS blockade. Treatment was generally well-tolerated.

Funding: Pharmaceutical Company Support - Pharmalink AB.
**HI-OR05**

**Randomized Trial on Efficacy of Mycophenolate Mofetil versus Tacrolimus in Maintaining Remission in Children with Steroid Resistant Nephrotic Syndrome Aditi Sinha, Arvind Bagga. *All India Inst of Medical Sciences, New Delhi, India.*

**Background:** Since prolonged therapy with tacrolimus (Tac) causes nephrotoxicity, this RCT examined non-inferiority of mycophenolate mofetil (MMF) to Tac in maintaining remission in patients with steroid resistant nephrotic syndrome (SRNS).

**Methods:** Following approvals, 84 patients with SRNS (1-18 yr; minimal change 48, FSGS 36) & eGFR >60 ml/min/1.73m² received Tac (0.15 mg/kg/d; trough 4-8 ng/ml) for 6-months. Stratifying for histology & type of response, patients with complete (Up/Uc 36) & eGFR >60 ml/min/1.73m² were randomized to continue Tac or receive MMF (0.75-1 g/m²/d), prednisone & enalapril. Primary outcome, at 12-mo, was proportion with remission or infrequent relapses. Therapy failure was recurrent SRNS, frequent relapses or >1 SAE. Enrolment was closed after interim intention-to-treat analysis of outcome in 1/3 sample.

**Results:** Baseline features were similar. Therapy with MMF led to significantly higher treatment failure, prednisone dose & SAE; eGFR change was similar. On multivariate analysis of outcome in 1/3 sample.

**Conclusions:** Therapy with MMF is inferior to Tac in maintaining Tac induced remission in patients with SRNS.

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**HI-OR06**

**Prevention of Bone Mineral Density Loss in De Novo Kidney Transplant Recipients with Twice-Yearly Denosumab: A Randomized Controlled Trial (ClinicalTrials.gov number NCT01377467) Rudolf P. Wuthrich,1 Diana P. Frey,2 Jens Günther Brockmann,3 Thomas Feith,4 Thomas F. Mueller,5 Lanja Salde,6 Arnold von Eckardstein,7 Nicole Graf,8 Marco Bonani.1 1Div of Nephropathology; 2Div of Visceral and Transplantation Surgery; 3Inst of Clinical Chemistry, Univ Hospital, Zurich, Switzerland; 4Graf Bio-statistics, Winterthur, Switzerland.

**Background:** Kidney transplantation is associated with bone loss and an increased risk of fracture. Since current therapeutic options to prevent bone loss are limited we assessed the efficacy and safety of Receptor Activator of Nuclear Factor kB Ligand (RANKL) inhibition with denosumab to improve bone mineralization in the first year after kidney transplantation.

**Methods:** We enrolled 108 kidney transplant recipients and randomized 90 patients two weeks after surgery in a 1:1 ratio to receive denosumab (subcutaneous injections of 60 mg denosumab at baseline and after 6 months) or no treatment. The primary endpoint was the percentage change in bone mineral density (BMD) measured by DDXA at the lumbar spine at 12 months.

**Results:** After 12 months, the primary outcome of total lumbar spine BMD increased by 4.6% (95% CI 3.3-5.9%) in 46 patients in the denosumab group and decreased by -0.5% (95% CI -1.8-0.3%) in 44 patients in the control group (between-group difference 5.1%, 95% CI 1.7-8.0%, p=0.0001). Denosumab also significantly increased BMD at the total hip by 1.9% (95% CI 1.0 to 3.7%; p=0.035) over that in the control group at 12 months. HR-pQCT in a subgroup of 24 patients showed that denosumab also significantly increased BMD and cortical thickness at the distal tibia and radius (p<0.05). Biomarkers of bone resorption (β-CTX, urine deoxypyridinoline) and bone formation (P1NP, BSAP) markedly decreased with denosumab (p<0.0001). Episodes of cystitis and asymptomatic hypocalemia occurred more often with denosumab, whereas graft function, rate of rejections and incidence of opportunistic infections were similar.

**Conclusions:** Antagonizing RANKL with denosumab effectively increased BMD in de novo kidney transplant recipients, but was associated with more frequent episodes of urinary tract infection and decreased calcium.

**Funding:** Government Support - Non-U.S.

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**HI-OR07**

**Randomized, Double-Blind, Placebo-Controlled, Parallel, 3-Arm Study of Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Hemodialysis Patients with Uremic Pruritus Vandana S. Mathur,1 Jayant Kumar,2 Paul W. Crawford,1 Howard Halt,3 Thomas Sciascia.3 1Mathur Consulting; 2Trevi Therapeutics; 3Research by Design; 4Edenridge Consulting; 5Renal Medical Associates.

**Background:** Uremic pruritus (UP) is associated with decrements in quality of life and sleep and higher mortality. UP pathogenesis may involve endogenous α/δ opioid ligand ratio imbalance. Nalbuphine ER tablets (NAL) are an α-σ opioid agonist/α-δ opioid antagonist being developed for chronic pruritic conditions.

**Methods:** 373 hemodialysis patients (HDP) with mean baseline numerical rating scale score (NRS) ≥ 4.5 for worst itching (0: no itching to 10: worst possible itching) were randomized 1:1:1 to NAL 60 mg (n = 128), NAL 120 mg (n = 120), or placebo (n = 125) and treated for 8 weeks.

**Results:** Demographics, dialysis adequacy and vintage, phosphorus, parathyroid hormone, pruritus duration, and antihistamine use were similar in the 3 arms at baseline. The primary efficacy endpoint was the change from Baseline to the Evaluation Period (Weeks 7 and 8) in the NRS for each dose of NAL, with pre-specified hierarchical ordering – the most common adverse events were nausea, vomiting, dizziness and somnolence with incidence rates of these events quickly approaching that of placebo. The most common adverse events were nausea, vomiting, dizziness and somnolence with incidence rates of these events quickly approaching that of placebo. The most common adverse events were nausea, vomiting, dizziness and somnolence with incidence rates of these events quickly approaching that of placebo. The most common adverse events were nausea, vomiting, dizziness and somnolence with incidence rates of these events quickly approaching that of placebo.

**Conclusions:** Nalbuphine ER tablets at a dose of 120 mg BID were safe and significantly reduced itching intensity.

**Funding:** Pharmaceutical Company Support - Trevi Therapeutics

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**HI-OR08**

**The Omega-3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Controlled Trial** Ashley B. Irish,1,2 1Nephrology, Fiona Stanley Hospital, Perth, Western Australia, Australia; 2Australasian Kidney Trials Network, Univ of Queensland, Brisbane, Queensland, Australia.

**Background:** Patients with end-stage renal disease require haemodialysis to remove waste products and excess fluid. Platelet aggregation is an important cause of vascular access failure; platelet aggregation can be reduced by antiplatelet drugs such as aspirin and/or omega-3 polyunsaturated fatty acids (w3FA) may prevent these complications by inhibition of platelet aggregation, vasoconstriction, intimal hyperplasia and inflammation.

**Methods:** The Omega-3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease (FAVoured) Trial: A Randomised Placebo-Controlled Trial

**Results:** Omega-3 polyunsaturated fatty acids (w3FA) may prevent these complications by inhibition of platelet aggregation, vasoconstriction, intimal hyperplasia and inflammation.

**Funding:** Pharmaceutical Company Support - Trevi Therapeutics

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**Underline represents presenting author/disclosure.**
Methods: This international, randomised, double-blind, placebo-controlled trial examined whether 3 months therapy with w3FA (4g/day) reduced primary AVF failure at 12 months after AVF creation. AVF failure was defined as AVF thrombosis and/or abandonment and/or cannulation failure. A subset of patients received aspirin (100mg/day) or matching placebo in addition to w3FA or placebo in a factorial design (n=388).

Results: The 567 randomised participants had a mean age of 55 years, 63% were male and 46% diabetic. AVF failure occurred in 128/270 (47%) participants assigned to w3FA compared with 125/266 (47%) assigned to placebo (relative risk adjusted for aspirin use 95% CI 0.72-1.34, p=0.90). AVF abandonment (19% vs 22%, RR 0.87, CI 0.62-1.22, p=0.43) or cannulation failure (40% vs 39%, RR 1.03, 0.83-1.26, p=0.81) was not significantly different between groups. Other markers of kidney and myocardial injury were also examined.

Conclusions: These results fail to provide proof-of-concept that RIPC may impact clinically important endpoints.

Funding: Other NIH Support - NHMRC Project Grant, Pharmaceutical Company Support - AMGEN Australia

SA-PO1091

The Remote Ischemic Preconditioning in Cardiac Surgery Trial (Remote IMPACT) Michael Walsh,1,2 Michael C. Rydzak,1,2 McMaster Univ;1 Population Health Research Institut.

Background: Cardiac surgery is frequently complicated by ischemia-reperfusion injury which can lead to kidney and myocardial injury. Preoperative Remote Ischemic Preconditioning (RIPC), cycles of brief ischemia to a limb alternating with reperfusion, may reduce the frequency or severity of organ injury after cardiac surgery.

Methods: We randomly allocated 258 patients at high risk for death after cardiac surgery to receive either RIPC or a sham procedure immediately after induction of anesthesia. RIPC consisted of 3 cycles of thigh tourniquet inflation to 300 mmHg for 5 minutes followed by 5 minutes reperfusion. The sham group tourniquets were inflated to 15 mmHg. Patients and care providers were blinded. The main clinical outcomes were change in creatinine over the first 4 postoperative days and the peak CK-MB within 24 hours of surgery.

Other outcomes assessed were 30 days after randomization. Analyses were performed according to the intention-to-treat principle.

Results: We randomized 128 patients to RIPC and 130 to sham. No patients were lost to follow-up. There were no significant between group differences in postoperative change in creatinine (p=0.79) or peak CK-MB (p=0.18) (Figure 1). We found no significant differences in the frequency of acute kidney injury (34% vs 31%), myocardial injury (24% vs 19%), stroke (4% vs 3%) or mortality (6% vs 5%) at 30 days.

Figure 1. Mean and 95% confidence intervals of creatinine over time for the RIPC (green diamonds) and sham (blue circles) groups.

Conclusions: In this trial RIPC did not affect markers of kidney and myocardial injury. These results fail to provide proof-of-concept that RIPC may impact clinically important outcomes in the cardiac surgery setting.

SA-PO1092

Nephrotoxicity of Invasive and Noninvasive Coronary Angiography: Randomized Controlled Study of Intracoronary and Intravenous Contrast Agent Administration Eva Schönberger,1 Patricia D. Bady,2 Peter Martus,3 Elke Zimmermann,1 Michael Laule,3 Marc Dewey,3 Anesthesiology, Charité, Berlin, Germany;4 Radiology, Charité, Berlin, Germany;1 Inst for Clinical Epidemiology and Applied Biostatistics, Eberhard Karls Univ, Tübingen, Germany;2 Cardiology, Charité, Berlin, Germany.

Background: Intracoronary contrast agent administration may reduce the frequency or severity of organ injury after cardiac surgery.

Methods: We randomly assigned patients with suspected coronary disease to either intracoronary contrast agent for invasive coronary angiography (ICA) or intravenous administration for coronary computed tomography angiography (CTA). The sham group received intravenous contrast agent administration.

Results: There was no difference in any serious adverse event (AE), 9.2% vs 13.0%, p=0.14; bleeding, 2.2% vs 2.5%, p=0.61; hypertension, 23.6% vs 25.8%, p=0.47; diabetes mellitus, 17.7% vs 17.3%, p=0.63; and atrial fibrillation, 14% vs 14.9%, p=0.71. Of 134 patients in the ICA group (13%) and 6 of the 139 patients in the CTA group (4%; RR 0.87, CI 0.62-1.22, p=0.43) the group randomised to aspirin or placebo-aspirin as part of the factorial design. There was no difference in any serious adverse event (AE), 9.2% vs 13.0%, p=0.14; bleeding, 2.2% vs 2.5%, p=0.61; hypertension, 23.6% vs 25.8%, p=0.47; diabetes mellitus, 17.7% vs 17.3%, p=0.63; and atrial fibrillation, 14% vs 14.9%, p=0.71. Of 134 patients in the ICA group (13%) and 6 of the 139 patients in the CTA group (4%; RR 0.87, CI 0.62-1.22, p=0.43) the group randomised to aspirin or placebo-aspirin as part of the factorial design.

Conclusions: These results fail to provide proof-of-concept that RIPC may impact clinically important endpoints.

Funding: Other NIH Support - NHMRC Project Grant, Pharmaceutical Company Support - AMGEN Australia

SA-PO1093

Efficacy and Safety of Bosutinib in Autosomal Dominant Polycystic Kidney Disease: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Karl-Heinz Eichner,1 W. I. W. I. X. I. C. E. S. I. E. N. A. K. O. F. I. O. M. O. N. P. S. O. M. O. N. 1,1,2,3,4,5,6 Andreas L. Serra,1 Pomeranian Medical Univ, Szczecin, Poland;1 Charles Univ, Prague, Czech Republic;1 Univ Health Network, Toronto, Ontario, Canada;1 Icahn School of Medicine at Mount Sinai, New York, NY;1 Pfizer Inc, San Diego, CA;1 Pfizer Inc, Cambridge, MA;1 Sanofi US, Bridgewater, NJ;4 Roche Pharma Research and Development, Basel, Switzerland;1 Inst for Allgemeine Innere Medizin und Nephrologie, Suisse ADPKD Hirslanden, Zurich, Switzerland.

Background: Src overactivation has been linked to the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). We assessed efficacy and safety of bosutinib (BOS), an oral dual Src/Abi tyrosine kinase inhibitor, in ADPKD patients (pts).

Methods: In this phase 2, multicenter study (NCT01233869), ADPKD pts with estimated glomerular filtration rate ≥60 mL/min/1.73 m² and magnetic resonance image (MRI)-confirmed total kidney volume (TKV) >750 cc were randomized 1:1:1 to placebo (PBO), 200 mg/d or 400 mg/d of oral BOS for 24 mo. The primary endpoint was normalized TKV % change. Pts treated for 2 wk who had an MRI after a 30-d washout period were in the modified intent-to-treat (mITT) analysis.

Results: 169 of 172 enrolled pts received ≥1 dose of treatment. 24 pts who initially received 400 mg/d BOS were later reduced to 200 mg/d BOS per protocol. 88 pts (52%) were in the mITT population (200 mg/d, n=27; 400 mg/d, n=7; 400 to 200 mg/d, n=21; PBO, n=33) after discontinuations (unrelated to study drug, 27%; study drug-related adverse events, 17%; consent withdrawal, 14%). Annual rate of kidney enlargement was significantly reduced for pooled BOS vs PBO (0.84% vs 4.74%, respectively, 95% CI for difference in annualized rates [2.02-5.74]; p<.0001) and was 65.2% lower for BOS 200 mg/d vs PBO (1.63% vs 4.74%, respectively, 95% CI [0.93 to 5.23]; p<.005). Gastrointestinal (GI) effects were dose-dependent for BOS, the overall safety profile, including GI toxicities, was consistent with the known profile of BOS.

Conclusions: BOS reduced the annual rate of kidney enlargement vs PBO in ADPKD pts, and the safety profile was consistent with the BOS label.

Funding: Pharmaceutical Company Support - Pfizer Inc

SA-PO1094

Low Osmolar Diet and Adjusted Water Intake for Vasopressin Suppression in ADPKD: A Randomized Controlled Trial Osama W. Amro,1,2 Jessica K. Paulus,1 Farzad Noubary,1 Ronald D. Perrone,1 Nephrology, Tufts Medical Center, Boston, MA;1 Tufts Univ School of Medicine.

Background: Autosomal dominant polycystic kidney disease (ADPKD) affects 12.5 million people worldwide. Vasopressin promotes disease progression.

Methods: This randomized trial examined the effect of combining a low osmolar diet and adjusted water intake on vasopressin as measured by change in plasma copeptin, and
SA-PO1095

A Phase 2, Double-Blind, Randomized Study of Fresolimumab or Placebo in Patients with Steroid-Resistant Primary Focal Segmental Glomerulosclerosis

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Background: Steroid-resistant primary FSGS confers substantial risk of morbidity & progressive kidney failure. Fresolimumab (freso), a neutralizing mAb to all 3 isoforms of TGF-β, is a potential new treatment.

Methods: 36 pts with biopsy-proven nephrotic-range FSGS randomized to freso 1mg/kg (n=14) v 4 mg/kg (n=12) v placebo (PL) (n=10) for D112, allowed immunosuppressives after D112 & followed up double-blind for D252. 1° outcome: proteinuria remission; 2° outcomes included changes in Up/c & eGFR.

Results: Pts: 53% male; median age 47 y; 78% Black, 31% Hispanic. Baseline (BL) median Up/c 6.19 mg/kg; eGFR, 63 ml/min/1.73 m². 72% pts received prior CNL. Durable partial remission ≥50% Up/c decrease from BL to <3 mg/kg: 3 pts, 1mg/kg; 2 pts, 4 mg/kg; 1 pt, PL; 1 additional pt on 1mg/kg had steep & consistent Up/c decline from 17-4 mg/kg. All 7 freso responders were Black/Hispanic. Mean Up/c changes at D112: -18.5% (1mg/kg, P=0.008), +10.5% (4 mg/kg, P=0.52), +9.0% (PL, P=0.91). eGFR showed nonsignificant trend for stability in freso v decline in PL. Freso was generally well tolerated with no significant difference in AEs in low v high doses.

SA-PO1096

Effects of Sustained-Release Beraprost Sodium in Patients with Primary Glomerular Disease or Nephrosclerosis: The CASSIOPEIR Study

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Background: No single treatment, except RAS inhibitors, can delay progression of CKD. TRK-100STP, a sustained-release tablet of an orally-active prostacyclin analoge, beraprost sodium, is suggested to suppress worsening of renal filtration function. We aimed to demonstrate superiority of TRK-100STP over placebo in patients with CKD, either as primary glomerular disease or nephrosclerosis; determine the recommended dose of TRK-100STP, and evaluate its safety profile.

Methods: We performed a randomized, double-blind, placebo-controlled, parallel-group comparative study at 160 sites in seven Asian-Pacific countries and regions (CASSIOPEIR: CRF Asian Study with Oral PG); Derivative for Evaluating Improvement of Renal Function). Patients entered a run-in period with oral administration of placebo twice daily for two to eight weeks. Patients meeting the inclusion/exclusion criteria at the end of the run-in period (n=892) were randomized to TRK-100STP 120 mg, TRK-100STP 240 mg, or placebo for a treatment period of two to four years. The primary efficacy endpoint was the time to first occurrence of a renal composite endpoint: doubling of SCr or occurrence of end-stage renal disease. ClinicalTrials.gov identifier: NCT01090037.

Results: No significant differences were evident in renal composite endpoints between TRK-100STP and placebo (2-sided 5% significance level, P=0.5674). The overall incidence of adverse events and adverse drug reactions was comparable between the treatment arms.

Conclusions: TRK-100STP did not demonstrate superiority over placebo, and the recommended therapeutic dose for patients with CKD either primary glomerular disease or nephrosclerosis was not determined. However, no findings raised safety concerns in the comparison between TRK-100STP and placebo.


SA-PO1097

Corticosteroid Monotherapy versus Combined Immunosuppression in IgA Nephropathy: Insights from the STOP-IgAN Trial

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Background: In high-risk IgA nephropathy (IgAN) the value of immunosuppression is controversial.

Methods: We recently reported a randomized, controlled trial in IgAN patients (STOP-IgAN trial). Following 6 months of optimized supportive treatment 162 trial participants, who still displayed a proteinuria >0.75 g/d, entered a 3 year study phase and were randomized to continue on supportive therapy (SUP) or to receive additional immunosuppression (IMM). IMM-patients with an eGFR <60 ml/min/1.73 m² received a 6-month corticosteroid monotherapy (“Pozzi-protocol”). Patients with an eGFR of 30 to
59 ml/min/1.73m² received cyclophosphamide for 3 months, followed by azathioprine, plus oral prednisolone (“Ballardie protocol”). Primary endpoints were (i) full clinical remission (proteinuria < 0.2 g/day and eGFR loss of < 5 ml/min) and (ii) eGFR loss > 15 ml/min from baseline to trial end.

Results: Here we report a secondary analysis of the two IMM subgroups versus corresponding SUP patients matched for eGFR. The intention-to-treat (ITT) analysis assuming a worst-case scenario at 3 years is shown in the table.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GFR &gt;60 ml/min/1.73m²</th>
<th>GFR 30-60 ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMM vs. SUP (n = 55 vs. 54)</td>
<td>GFR &gt;60 ml/min/1.73m²</td>
<td>GFR 30-60 ml/min/1.73m²</td>
</tr>
<tr>
<td>Full clinical remission</td>
<td>OR 5.23 (95%-CI 1.29-21.15), p=0.020</td>
<td>OR 2.77 (95%-CI 0.38-22.29), p=0.319</td>
</tr>
<tr>
<td>eGFR loss &gt;15 ml/min</td>
<td>OR 0.65 (95%-CI 0.27-1.56), p=0.333</td>
<td>OR 1.62 (95%-CI 0.49-5.61), p=0.428</td>
</tr>
</tbody>
</table>

Patients treated with the Pozzi protocol had a transient decrease in proteinuria after 12 months and significantly less microhematuria at trial end compared to matched SUP patients. In the group with the low eGFR range, there were no significant differences between both arms. Compared to supportive care, more patients receiving immunosuppression developed severe infections, impaired glucose tolerance and weight gain in year one.

Conclusions: Our secondary analyses provide little evidence for a stabilization of renal function with immunosuppression in the group with an eGFR >60 ml/min and no evidence for a benefit in patients with a lower eGFR.

Funding: Government Support - Non-U.S.

SA-PO1098

A Randomized Trial of Rituximab in Advanced IgA Nephropathy

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Background: IgA nephropathy (IgAN) frequently leads to progressive renal dysfunction. Present immunosuppressive treatment remains uncertain in terms of benefit and risks side effects. B cells are an attractive target in IgAN so we performed a pilot trial of rituximab in subjects at high risk of progression.

Methods: Patients with biopsy proven IgAN, more than 1 g/day of proteinuria despite RAASi (or >0.5 g/day if on dual RAASi), well controlled blood pressure (BP) and eGFR >90ml/min were randomized to 1 year of rituximab therapy (4g total) vs ongoing BP control, fish oil and use of RAASi. They were followed for B cell depletion, effects on proteinuria and changes in eGFR. Safety signals were also followed.

Results: 34 patients were randomized. Baseline serum creatinine was 1.5±0.5 mg/dl and proteinuria was 2.1, 0.6-5.5 g/day. There was no change in BP during the study. Treatment with rituximab resulted in significant B cell depletion and was generally well tolerated. There was no change in renal function during the study in either group. Rituximab treatment had no significant effect on proteinuria compared to baseline or control patients, and 3/17 patients in each group experienced ≥ 50% reduction in proteinuria during the study.

Figure 1: Proteinuria in (A) Control vs. (B) Rituximab Groups. The heavy weight red line represents median data.

Conclusions: In this small study, rituximab therapy had no influence on renal function or proteinuria in subjects with advanced disease due to IgA nephropathy. There were numerically greater reductions in proteinuria, but this did not reach significance. Few patients had substantial responses in either group. These results do not support the use of rituximab as treatment for patients with IgA nephropathy.

Funding: Pharmaceutical Company Support - Roche, Inc.

SA-PO1100

Establishing Endpoints for Lupus Nephritis Clinical Trials: Progress by the Kidney Health Initiative/Lupus Nephritis Trials Network Collaboration

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Background: There are no universally accepted endpoints for lupus nephritis (LN) clinical drug trials. To obtain approval of new therapies a uniform endpoint that can be applied to future LN trials is needed. The optimal endpoint is a short-term measurement that accurately reflects long-term kidney survival. The present work was undertaken to define LN trial end points.

Methods: Clinical data at LN flare (baseline) and during serial follow-up (minimum 22 months) from 751 patients were analyzed. Clinical variables at baseline and after 6 and 12 months were tested as predictors of adverse long-term renal outcomes, in this case time to new chronic kidney disease (CKD), defined as a sustained increase in serum creatinine (SCr) ≥30%. Multivariable Cox regression analysis was used to model time to CKD.

Results: After accounting for missing data 507 patients were included in the final analysis. This cohort was 89% female, 56% White, 20% Asian and 14% Black. The average baseline eGFR was 61.2±20.7 ml/min, proteinuria was 4.1±3.4 g/day, and eGFR by CKD-EPI was 81.35 ml/min. Median follow-up was 42 months (range: 22-147 months). By univariate analysis urine RBCs, race, complement C3, SCr, eGFR and proteinuria were potential significant predictors of time to CKD. By multivariate modeling the significant predictors of future CKD were: SCr at 12 months (p=0.0005, Hazard Ratio (HR) 1.8 (95%-CI 1.3-2.5)), proteinuria at 12 months (p=0.0001; HR 1.6 (1.3-1.8)); and an increase in eGFR>10% from baseline to 12 months compared to no change in eGFR (p=0.0001; HR 0.4 (0.3-0.6)).

Conclusions: We have identified 3 highly significant predictors of time to CKD in LN patients that can be measured during the first 12 months of treatment for flare. These can be developed into a composite endpoint for future LN therapeutic trials. Unexpectedly, small improvements in eGFR appear to predict renal survival. Also, because urine RBCs do not appear to predict time to CKD, it may be possible to exclude urinalysis as an endpoint component in future clinical trials.

Funding: Private Foundation Support

SA-PO1103

Grazoprevir (GZR)/Elbasvir (EBR) Treatment of Hepatitis C Virus (HCV) Infection in Patients with Chronic Kidney Disease Stage 4/5: Final Results of the C-SURFER Phase 3 Study

David Roth,1 Annette Bruchfeld,2 Paul Martin,3 David R. Nelson,4 Marcelo Silva,5 Howard Monsour,1 Laurent Alric,4 Shuyan Wan,1 Beth Jackson,1 Bach-Yen Nguyen,1 Janice Wahl,4 Elia1,2 Wayne L. Greaves,7 Univ of Miami, Miami, FL; Karolinska Inst, Stockholm, Sweden; 3Univ of Florida, Gainesville, FL; Hospital Univ Austral, Pilar, Buenos Aires, Argentina; 4Houston Methodist Hospital, Houston, TX; 5Hôpital de Purpan, Toulouse, France; 6Merck & Co., Inc., Kenilworth, NJ.

Background: Limited options are available for treating HCV infection in patients with advanced kidney disease. C-SURFER is the first randomized, placebo-controlled phase 3 study to evaluate an all-oral, ribavirin-free regimen in CKD 4/5 patients.

Methods: 224 patients with HCV genotype (G)1 and CKD 4/5 ± hemodialysis (HD) were randomized to GZR/EBR 100/50mg (Immediate Treatment Group, ITG; n=111) or placebo for 12 weeks. Placebo subjects (deferred treatment group, DTG; n=113) received GZR/EBR after placebo therapy. 11 additional subjects received GZR/EBR with intensive pharmacokinetic (PK) sampling. The primary safety comparison was GZR/EBR vs. placebo. The primary efficacy endpoint, sustained virologic response (SVR) 12 weeks post-therapy in the ITG+PK group, was reported previously. Here we report the final results, including data from subjects who received GZR/EBR after placebo.

Results: In the placebo-controlled phase, serious adverse events (AES) occurred in 16 (14%) GZR/EBR and 17 (15%) placebo subjects; discontinuation due to an AE in GZR/EBR and placebo subjects was 0% and 4%, respectively. SVR12 in GZR/EBR and placebo subjects was 96.0% (ITG+PK; 94.3% [95%CI 91.8-96.9], DTG after placebo. 95.0% [96.0%]). 12 subjects failed to attain SVR12: virologic relapse, n=3; discontinuation for AE, n=1; admin reason, n=8. Excluding subjects who discontinued for reasons unrelated to study drug, overall SVR12 was 98.6% (211/214). PK data indicate no need for dose adjustment in HD patients (geometric mean ratio [HD/ND] ranged from 0.67-0.85 for GZR and 1.43-1.67 for EBR).

Conclusions: Once-daily GZR/EBR for 12 weeks was highly effective with a low rate of adverse events in patients with advanced kidney disease and HCV G1 infection.

Funding: Pharmaceutical Company Support - Merck Sharpe & Dohme Corp.
SA-PO1101

Long-Term (52-Week) Efficacy and Safety of ZS-9 in the Treatment of Hyperkaemia: Interim Results From a Phase 3 Open-Label, Multi-Center, Multi-Dose Maintenance Study

James A. Tumin,1 Mikhail Kosiorobod,2 Pablo E. Pergola,3 Wajeh Y. Qunibi,3 David K. Packham,3 Simon D. Roger,3 Edgar V. Lerna,4 Steven Fishbane,5 Henrik S. Rasmussen,2 Bruce S. Spinowitz,6 1U of Texas Medical College of Dallas, Dallas, TX; 2Mayo Lakeview Health, Chicago, IL; 3Multi-Institution, ongoing, open-label study evaluating ZS-9 treatment for 52wks in ambulatory pts with HK (K+ ≥ 5.1 mEq/L) with or without concurrent RAASi therapy. In the acute phase (AP), pts with HK received 10g ZS-9 TID over a 24-72hr period until NK (K+ 3.5-5.0 mEq/L) was achieved. Pts achieving NK were enrolled in a 52wk maintenance phase (MP) starting at 5g ZS-9 QD. There were no restrictions on diet and ZS-9 could be titrated to maintain NK. Primary outcomes were proportion of pts with mean K+ ≤5.1 mEq/L during MP and safety of ZS-9.

Results: To date, 583 pts with a mean baseline K+ of 6.4 mEq/L (15% ≥6.0 mEq/L) entered the study. Overall, 575 (99%) normalized K+ in AP and transitioned to the MP. To date, K+ was maintained at ≤5.1 and ≤5.5 mEq/L in 87% and 99% of patients, respectively. The incidence and severity of adverse events were similar to that of previous studies.

Conclusions: ZS-9 acutely reduced K+ levels in pts with HK and maintained NK for up to 52wks irrespective of RAASi use. ZS-9 may control HK, both emergent and long-term, while allowing continued use of cardio- and renoprotective RAASi.

Funding: Pharmaceutical Company Support - ZS Pharma, Inc.

SA-PO1102

Interleukin-1 Inhibition and Vascular Function in Patients with Chronic Kidney Disease (CKD): A Randomized Controlled Trial

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Background: Vascular endothelial dysfunction and increased arterial stiffness contribute to increased cardiovascular risk in CKD patients who exhibit chronic systemic inflammation. As chronic inflammation is a key mechanism contributing to vascular dysfunction, blocking inflammation may reduce cardiovascular risk in CKD.

Methods: In a two-site, double-blind trial, n=42 patients with stage 3-4 CKD were randomized to receive either the interleukin-1 (IL-1) trap rilonacept (subcutaneous injection; loading dose of 320 mg followed by 160 mg/wk) or placebo for 12 weeks. All patients were receiving optimal treatment of hypertension, diabetes, and/or hypercholesterolemia, with 64% and 62% receiving a statin and an ACE inhibitor or ARB, respectively. The co-primary endpoints were change in brachial artery flow-mediated dilation (FMD) and aortic pulse-wave velocity (aPWV) after 4, 8 and 12 weeks using mixed effects models. Secondary endpoints were change in high-sensitivity C-reactive protein (hsCRP), AFMDa, following an acute infusion of ascorbic acid known to inhibit superoxide production, and interleukin-6).

Results: Participants were 63±11 (mean±SD) years of age, 24% female and 24% Black, with eGFR 38±13 ml/min/1.73m2. Rilonacept improved FMDa (baseline: 3.8±3.1%, 12 wks: 4.9±3.2%) compared to placebo (baseline: 3.4±2.1%, 12 wks: 2.5±2.3% p<0.01), without changing aPWV (p=0.52). Rilonacept also reduced hsCRP levels (baseline: 4.6 (1.9, 8.22) median (interquartile range)); 12 wks: 2.16 (0.96, 7.38) mg/L; p<0.01), and endothelial cell NADPH oxidase expression (p=0.05). Acute infusion of ascorbic acid tended to improve FMDa in the placebo (p=0.07) but not the rilonacept group (p=0.56), indicating reduced vascular oxidative stress. Overall, rilonacept was well tolerated.

Conclusions: 12 weeks of treatment with an IL-1 trap improved FMDa without changing aPWV in patients with stage 3-4 CKD. This was associated with a reduction in systemic inflammation and vascular oxidative stress.

Funding: Veterans Administration Support, Pharmaceutical Company Support - Regeneron Pharmaceuticals, Inc, Private Foundation Support

SA-PO1103

Abstract Withdrawn

SA-PO1104

Impact of Vitamin D Supplementation on Endothelial and Vascular Function in Patients with Chronic Kidney Disease: A Randomized, Double Blind, Placebo-Controlled Trial

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Background: Vitamin D deficiency is associated with mortality in CKD patients. We investigated the effect of Vitamin D supplementation on endothelial and vascular function in patients with non-diabetic CKD stage 3-4.

Methods: In a prospective, randomized, double blind, placebo-controlled trial, 120 patients with non-diabetic CKD stage 3-4 and vitamin D deficiency [serum 25(OH)D <20ng/ml] aged 18-70 years were randomized (1:1) to receive either two directly observed oral doses of 3000 IU of cholecalciferol at 0 and 8 weeks or matching placebo. The pre-specified primary outcome was 40% change in endothelium dependent brachial artery flow mediated dilatation (FMD) at 16 weeks. Secondary outcome measures included changes in pulse wave velocity (PWV), augmentation index (AI), and serum biomarkers.

Results: Baseline FMD was identical in both arms (7.6±2.24% vs 7.8±2.34%). Intervention arm showed a 21.8±20.6% increase in serum 25(OH)D (+ 24.9 mg/ml, 95% CI: 21.8±28.06, p=0.0001), and the number of subjects meeting the primary endpoint (70% vs 5%, p<0.0001). FMD change was 5.42% (95% CI: 4.44 to 6.40%) in the intervention arm and -0.07% (95% CI, -0.70 to 0.58%) in placebo arm. Intervention led to favorable changes in PWV (-0.94 m/s, 95% CI: -1.30 to -0.58, p<0.0001), E-selectin (-3.68 mg/ml, 95% CI: -8.1 to 0.7 p<0.002), IL-6 (-2.96 to -0.8 p=0.001), FGF-23 (-14.7 pg/ml, 95% CI: -28.5 to -1.9 p=0.036) and 1,25(OH)D3 (+15.5 pg/ml, 95% CI: 5.4 to 25.5, p<0.003). These did not change significantly in the control group. No changes were observed in AI, s-WF and s-CRP in either group.

Conclusions: In non-diabetic patients with stage 3-4 CKD and vitamin D deficiency, vitamin D supplementation leads to improvement in endothelial function, markers of inflammation and arterial stiffness.

Funding: Government Support - Non-U.S.

SA-PO1105

Effect of Cholecalciferol versus Calcitriol on Vascular Endothelial Function in CKD: A Randomized Active-Controlled Trial

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Background: Epidemiological studies have shown that vitamin D is associated with decreased vascular morbidity and mortality, but direct evidence supporting vitamin D supplementation on patient outcomes in chronic kidney disease (CKD) are lacking. We conducted a prospective, double-blind, randomized trial to determine the effects of oral cholecalciferol vs. calcitriol on vascular endothelial function over 24 weeks in patients with CKD stage 3-4.

Methods: 128 patients with CKD stage 3-4 (estimated GFR 15-44 ml/min/1.73m2) with vitamin D deficiency, defined as serum 25-hydroxyvitamin D level (25(OH)D) <30 ng/ml, were randomly assigned to receive either cholecalciferol (4000 IU daily x 4 weeks then 2000 IU daily x 20 weeks) or calcitriol (0.25 mcg daily x 4 weeks then 0.5 mcg daily x 20 weeks). The primary endpoint was change in brachial artery flow mediated dilatation (FMDa) over 24 weeks. Secondary endpoints included changes in parameters of mineral bone disease and plasma concentrations of inflammatory cytokines (C-reactive protein and interleukin-6).

Results: 115 patients completed the study. The mean (SD) age and eGFR was 58.1±12.4 years and 33.1±10.2 ml/min/1.73m2, respectively. In the cholecalciferol group, mean 25(OH)D levels increased from 22.7±7.5 ng/ml to 33.5±7.9 ng/ml. There was no change in 25(OH)D levels in the calcitriol group. Parathyroid hormone levels decreased significantly in the calcitriol group compared to the cholecalciferol group (p=0.001). At 24 weeks, the change in FMDa did not differ significantly between treatment groups (cholecalciferol group -0.72%, 95% CI -1.97 to 0.54 vs calcitriol group 0.29%, 95% CI -0.72 to 1.29, p=0.44). There was no significant change in C-reactive protein or interleukin-6 concentrations between the two groups. Episodes of hypercalcemia were more frequent in the calcitriol group (n=4) compared with the cholecalciferol group (n=1).

Conclusions: Twenty-four week therapy with calcitriol or cholecalciferol did not improve vascular endothelial function or reduce inflammation in patients with CKD.

Funding: NIDDK Support
SA-PO1106

Vitamin D Receptor Activation and Dietary Sodium Restriction to Reduce Residual Albuminuria in Chronic Kidney Disease  
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Background: Reduction of residual albuminuria during single-agent RAAS-blockade is associated with improved cardioireal outcomes in CKD. Both vitamin D receptor activators (VDRA) and dietary sodium restriction reduce residual albuminuria. Previous data suggested that sodium restriction is not required for optimal albuminuria reduction by VDRA. We studied the individual and combined effects of paricalcitol and sodium restriction on residual albuminuria during optimally dosed ACEi in CKD.

Methods: In a multi-center, randomized, placebo-controlled cross-over trial, 45 patients with non-diabetic CKD stage 1-3 and residual albuminuria >300 mg/24h despite ramipril 10 mg/d and BP <140/90 mmHg were treated during four 8-week periods with paricalcitol (PARI, 2 µg/day) or placebo (PLAC), each combined with a low (LS, 2.5 gr Na+/-d) or regular sodium (RS, 4 gr Na+)/d diet, in random order. Linear mixed-effect models for repeated measurements were used to determine treatment effect.

Results: In the intention-to-treat analysis, albuminuria was 1.060 [778 to 1.443] (geometric mean [95% CI]) mg/24h during RS+PLAC. During RS+PARI, albuminuria was 990 [755 to 1.299] mg/24h [-12.5% [-26.0% to 26.3%] vs. RS+PLAC, P<0.2]. LS+PLAC reduced albuminuria to 717 [512 to 1.005] mg/24h [-25.4% [-52.6% to -2.3%] vs. RS+PLAC, P<0.001]. LS+PARI provided the strongest albuminuria reduction to 683 [502 to 929] mg/24h [-31.7% [-55.0% to -9.9%], P<0.001 vs. RS+PLAC], although the additional reduction by PARI beyond the effect of LS was non-significant (P=0.6). However, in a per-protocol analysis (≥95% compliance, N=34) PARI did reduce residual albuminuria beyond the effect of LS (P=0.04).

Conclusions: The combination of paricalcitol and moderate dietary sodium restriction provided the strongest reduction of residual albuminuria during optimal ACEi; the effect was mainly driven by sodium restriction. Our findings underline the relevance of sodium restriction, possibly combined with paricalcitol, to optimize albuminuria reduction.

SA-PO1107

Vascular Function and Uric Acid Lowering via Allopurinol in Stage III CKD: Results of a Double-Blinked Randomized Placebo-Controlled Study  
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Background: Observational studies suggest that asymptomatic hyperuricemia associates with vascular disease in chronic kidney disease (CKD). A recent study suggested that lowering serum urate with allopurinol improves endothelial function in elderly adults with stage III CKD. It remains unknown if lowering serum urate improves endothelial function in adult subjects with stage III CKD. Methods: 80 adult subjects (18-70 years of age with stage III CKD and asymptomatic hyperuricemia (>7 mg/dL in men and ≥6 mg/dL in women) were randomized to receive placebo or allopurinol (100 mg) tablets for 12 weeks. The study was double-blinded and subjects were instructed to take 1 tablet for 1 week, 2 tablets for another week, and 3 tablets thereafter. Changes (from baseline) between both groups were compared by Wilcoxon rank-sum test.

Results: No significant differences existed between both groups at baseline. After 12 weeks, allopurinol lowered serum urate significantly. FMD increased in the allopurinol group compared to placebo; but this was not statistically significant. NMD increased with allopurinol but decreased with placebo; p value = 0.14. These data are shown in Table 1. There were no significant differences between allopurinol and placebo for systolic or diastolic blood pressure, markers of inflammation, or markers of oxidative stress. 10 subjects withdrew from the study. A few adverse events were noted in both groups including 1 gout attack in each group. 1 subject died during the study due to a cardiac event.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Urate(mg/dL)</td>
<td>0.051 (1.54)</td>
<td>-3.24 (1.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FMD (% change)</td>
<td>0.16 (4.05)</td>
<td>0.93 (3.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>NMD (% change)</td>
<td>-1.29 (5.33)</td>
<td>0.93 (6.05)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Conclusions: Allopurinol effectively and safely lowered serum urate in adult subjects with stage III CKD and asymptomatic hyperuricemia but this did not improve endothelial function significantly. There was tendency towards improved NMD suggesting that hyperuricemia may negatively impact vascular smooth muscle function in stage III CKD.

Funding: NIDDK Support
SA-PO1110

Vadadustat, a Novel Oral Treatment for Anemia of Chronic Kidney Disease, Maintains Stable Hemoglobin Levels in Dialysis Patients Converting from Erythropoiesis-Stimulating Agents

Methods: A multi-center, open-label, 16-week trial was designed to assess Hb response, safety, and tolerability of vadadustat. The trial enrolled 94 hemodialysis patients (Hb 9 - 12 g/dL), who were maintained on erythropoiesis-stimulating agents (ESAs) prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily (QD); 450 mg QD, or 450 mg three times weekly (TIW). The primary efficacy analysis was to evaluate mean Hb changes from baseline at weeks 7/8, and weeks 15/16. From week 8, dose could be adjusted as needed to maintain Hb. All patients were maintained on stable hemoglobin levels in dialysis patients across the 3 cohorts. Serious adverse events have been reported.

Results: Vadadustat safely and effectively maintained Hb levels in dialysis patients who were converted from injectable ESAs.

Conclusions: Vadadustat, a novel, oral agent that stimulates erthropoiesis by stabilizing hypoxia-inducible factor (HIF). Prior studies in patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) have shown that vadadustat results in controlled, dose-dependent increases in hemoglobin (Hb) and enhances iron mobilization and utilization. Here we present data from a Phase 2 trial of vadadustat in hemodialysis patients.

Mean Hb levels (g/dL) in Modified Intent-To-Treat (MITT) population

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>Baseline</th>
<th>Week 7/8</th>
<th>Week 15/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg QD</td>
<td>10.4</td>
<td>10.4</td>
<td>10.3</td>
</tr>
<tr>
<td>450mg QD</td>
<td>10.6</td>
<td>10.3</td>
<td>10.5</td>
</tr>
<tr>
<td>450mg TIW</td>
<td>10.5</td>
<td>10.2</td>
<td>10.4</td>
</tr>
</tbody>
</table>

One subject in the 300mg QD cohort had a single Hb excursion to 13.1 g/dL. Adverse events were balanced across the 3 cohorts. Serious adverse events (SAEs) were reported in 13 subjects (13.8%), which was within the expected range (13 - 17 subjects). No drug-related SAEs, nor deaths, were reported.

Funding: Pharmaceutical Company Support - Akebia Therapeutics Inc., Cambridge, MA; United States

SA-PO1111

Autologous Erythropoietin Production by the TARGT Gene Therapy Platform Maintains Stable Hb for 6-12 Month in ESRD Patients without the Need for ESA Administration

Background: Recombinant human erythropoietin (rHuEPO) administration to iron replete patients corrects anemia in most patients with ESRD, but doses result in supra-physiological peak serum concentration (Cmax) of EPO that may cause thromboembolic complications. The Transduced Autologous Restorative Gene Therapy system (TARGT™) is an ex-vivo gene therapy, providing autologous, continuous protein therapies at physiological ranges that was used encoding for the human erythropoietin gene (TARGT™) for these studies. Patient dermal tissue biopsies (MOs) are transduced with a Helper-Dependent Adenoviral Vector containing the EPO gene and then re-implemented subcutaneously to deliver the required EPO dose.

Methods: We present initial data from 2 ongoing open label ascending dose studies of TARGT™ in patients with anemia due to CKD undergoing either Hemo or Peritoneal Dialysis.

Results: Thus far 14 patients were enrolled in all protocols. Follow up is ongoing with the first implanted patient being followed with stable EPO secretion and stable Hb for over 14 months from a single implantation without the need for rHuEPO or blood transfusion. Results obtained suggest that treatment with TARGT™ stabilize serum EPO levels at the physiological range of 20 mIU/ml resulting in Hb levels between 9-12 g/dL. Comparative analysis of serum EPO levels revealed significantly lower Cmax with TARGT™ compared to rHuEPO and an order of magnitude less overall EPO exposure as calculated by Area Under the Curve which may confer significant clinical benefit. No treatment related serious adverse events have been reported.

Conclusions: TARGT™ is a promising novel therapy for the treatment of anemia of CKD and potentially for other protein deficient diseases.

Funding: Pharmaceutical Company Support - Medgenics Inc.

SA-PO1112

Monitoring in Dialysis (Mid) Study: Exploring the Timeline and Etiology of Increased Arrhythmias in Hemodialysis (HD) Patients

Background: Sudden cardiac death (SCD), likely due to cardiac arrhythmias (CA) is the most important cause of mortality in the HD population. We herein present data on the timeline and potential etiology of CA in HD patients (pts).

Methods: The Mid study (n=66) characterized the type and frequency of CA in 3x/wk HD pts over 6 mths, using an implanted loop recorder (Medtronic Reveal). Reviewer confirmed arrhythmias (RCA;all documented CA) and clinically significant arrhythmias (CSA;brady/asystole/VT/symptomatic), were linked to the dialysis cycle, pt wt and pre/post-session electrolytes, using negative binomial mixed effects regression analyses.

Results: Mean age was 56.3±12.2; 64% diabetic; 70% male; HD vintage 4.3±5.1 yrs. 97% and 67% of pts had a RCA/CSA. Most CA occurred during the intradialytic period of the first weekly HD and then decreased in subsequent sessions. Univariate analyses identified increased pre and post wt, high pre HD potassium (K) and drop in K as risk factors for RCA. Multivariate analyses (adjusted for DM, yrs on HD, pre-wt), identified higher pre HD K levels as a predictor for increased RCA. The highest risk of arrhythmia occurred in pts with high K drops AND substantial volume removal (p=0.03).

Funding: Pharmaceutical Company Support - Akebia Therapeutics Inc., Cambridge, MA, United States
Conclusions: These data establish linkages between intra-diabetic CSA and the long interdialytic period, and also identify a unique interaction between fluid removal and K in the generation of RCA. This suggests for the first time, that future data driving targets of these parameters might reduce CA and potentially SCD in HD pts.

Funding: Pharmaceutical Company Support - Medtronic

SA-PO1113

The Occurrence of Cardiac Arrhythmias in Hemodialysis Patients is Linked to the Hemodialysis Procedure and to Electrolyte Abnormalities as Recorded by Implantable Loop Recorders

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Background: Sudden cardiac death (SCD) is the commonest mode of death among hemodialysis (HD) patients. Little is known about the terminal arrhythmic events in these pts. Our objective was to identify mechanisms which may lead to SCD in HD pts using an implantable loop recorder (ILR, Reveal XT®, Medtronic).

Methods: Pts from 9 HD centers have been included in the study. Continuous monitoring of the cardiac rhythm has been performed using the remote monitoring capability of the ILR device (CardiOlink®). Clinical, biological, and technical HD parameters and medications have been recorded for at least 1 year. General joint frailty model for recurrent event data were used to analyze associations between these parameters and the occurrence of cardiac rhythm events.

Results: 72 pts (65 ±8.6 yrs, 52M) have been included. Causes of ESRD were diabetes (n=32) and hypertension (n=19). 22 pts had an ischemic cardiomyopathy. In 8 pts (11%), SCD was recorded (death (n=5), ventricular fibrillation (n=2), and pulseless electrical activity (n=1)). In 7 pts, the event was preceded by a short-lasting (3-10 s) atrial fibrillation (Abbott, Minneapolis, MN; Boston Scientific, Natick, MA; Medtronic, Minneapolis, MN).

Conclusions: Our data show that the various types of arrhythmias and conduction abnormalities occurring in HD pts are linked to different pathophysiological mechanisms. Compared with a central role of serum K+ levels, lower levels (<4 mEq/l or >5 mEq/l) were associated with patient-dependent and HD-dependent variables. In 6 SCD patients, ILR tracings demonstrated progressive bradycardia followed by asystole.

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

SA-PO1114

Abstract Withdrawn

SA-PO1115

Comparison of the Efficacy and Safety of Intravenous (IV) Etecloceide (AMG 416) and Oral Cinacalcet (CIN) in Patients on Hemodialysis (HD) with Secondary Hyperparathyroidism (sHPT)

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Background: This is a randomized, active controlled, double-blind, double dummy study comparing the efficacy and safety of a novel IV calcimimetic, AMG 416, with CIN. Patients receiving HD with PTH >500 pg/ml, albumin-corrected calcium (cCa) >8.3 mg/dl, and no CIN use for 3 months were randomized 1:1 to AMG 416 IV/oral placebo or oral CIN/IV placebo for 26 weeks (wks). Doses were titrated at wks 5, 9, 13, 17 based on the prior wk’s PTH and cCa. AMG 416 was started at 3mg and titrated by 2.5mg or 5mg up to 15mg 3 times weekly with HD. CIN was started at 30mg and titrated up to 180mg daily target. PTH 100 was 100 mg/dl. Primary endpoint was noninferiority on >30% reduction in PTH during wks 20-26. Secondary endpoints were >50% reduction in PTH (utility analysis), >50% reduction in PTH, mean days of nausea or vomiting (n/v) (patient reported outcome) per wk in the first 8 wks.

Results: 683 subjects were randomized (340 AMG 416, 343 CIN), 553 completed the trial (84% AMG 416, 86% CIN). AMG 416 was noninferior to CIN on the primary endpoint. AMG 416 was superior on >30% reduction in PTH (68% AMG 416, 58% CIN, p=0.004) and >50% reduction in PTH (52% AMG 416, 40% CIN, p=0.001). Mean days of n/v in the first 8 wks did not differ (0.4 AMG 416, 0.3 CIN, NS). The most common adverse event (AE) in either group was blood calcium decreased (69% AMG 416, 60% CIN), mostly mild to moderate severity. Heart failure related AEs were reported in 10 (3.0%) AMG 416 subjects and 0 (0.6%) CIN subjects, of which 5 and 1, respectively, were serious. 9 (3%) subjects receiving AMG 416 and 8 (2%) receiving CIN had fatal treatment-emergent AEs – all unrelated to study drug.

Conclusions: AMG 416 achieved a >50% and a >30% reduction in PTH in more subjects compared to CIN. Hypocalcemia was seen more often with AMG 416. Nausea and vomiting did not differ. IV AMG 416 is more efficacious than oral CIN for the treatment of sHPT in patients on HD.

Funding: Pharmaceutical Company Support - Amgen

SA-PO1116

A Trial Assessing Use of a Wearable Artificial Kidney (WAK) in Patients Undergoing Maintenance Hemodialysis

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Background: Current stationary dialysis machines hinder mobility and limit activities of daily life during dialysis treatments. There is a critical need for new technologies to increase patient autonomy, enhance quality of life, and allow for increased patient rehabilitation.

Methods: This is the first FDA-approved human trial of the WAK, a miniaturized, wearable artificial kidney machine based on dialysate-regenerating sorbent technology (NCT02280005). We aimed to determine the safety and efficacy of the WAK in maintaining euolemia and achieving solute clearance and electrolyte homeostasis over 24 hours.

Results: All patients remained hemodynamically stable, and there were no serious adverse events. Serum electrolytes and hemoglobin remained stable over the treatment period for all subjects. Six out of seven patients ambulated while receiving WAK treatment. Fluid removal was consistent with prescribed ultrafiltration rates. Mean blood flow was 42 ±24 and dialysate flow was 43:±20 ml/min with no laboratory evidence of hemolysis. Mean BUN, creatinine, and phosphorus clearances were 21 ± 13, 20 ± 11, and 22 ± 12 ml/min respectively during the first hour of treatment. In one subject, treatment was discontinued due to clotting after 4 hours. In a second subject, treatment was discontinued due to discoloration of dialysate observed after 10 hours. The trial was stopped after the 7th subject due to device-related malfunctions. These included excessive CO2 bubbles in the dialysate, variable blood and dialysate flows, and tubing leaks during the priming phase. Redesign and re-manufacturing of the WAK prototype will be required prior to additional human studies.

Conclusions: Treatment with the WAK was well tolerated, resulted in effective uremic solute clearance and maintenance of electrolyte and fluid homeostasis. These results serve as proof-of-concept of the WAK as a viable novel dialysis technology.

Funding: Private Foundation Support

SA-PO1117

CR845, A Novel Kappa Opioid Receptor Agonist Reduces Moderate-to-Severe Pruritus and Improves Quality of Life in Chronic Kidney Disease Patients Undergoing Hemodialysis

Robert Spencer,1 Vandana S. Mathur,2 James A. Tumlin,1 Joseph W. Stauffer,3 Frederique Menzaghi,1 1Cara Therapeutics, Inc., Shelton, CT; 2Mather Consulting, San Francisco, CA; 3Univ of Tennessee, Chattanooga, TN.

Background: Approximately 40% of US hemodialysis (HD) patients experience moderate-to-severe itching, which negatively affect their mental and physical health (e.g., sleep loss, depression, higher antibiotic and erythropoietin use and increased mortality). The etiology of this condition is likely multi-factorial, including immune system dysfunction and imbalance of mu/kappa endogenous opioids. CR845 is a novel and well-tolerated kappa opioid receptor (KOR) agonist with limited central nervous system entry, thereby preferentially activating KOR on peripheral neurons and immune cells.

Methods: In this Phase 2 double-blind, randomized (1:1:1), placebo-controlled clinical study, 65 prevalent US HD patients with persistent (≥ 5 months) moderate-to-severe pruritus (baseline VAS ~68 mm, 0=no itch; 100 mm =worst itch) were treated with 1 mcg/kg intravenous CR845 or placebo following each HD session for 2 weeks. Antihistamines were discontinued 1 week prior to the study.

Results: The primary endpoint was VAS (change in worst itch intensity from Baseline to Days 12-15), with a significant difference in itch intensity between placebo and CR845-treated patients (p=0.016). CR845-treated patients had a 50% mean reduction in itch intensity from baseline. The 1st secondary endpoint was also met with a significant improvement in Skindex-10, a validated patient-reported outcome measure of pruritus-related quality of life (p <0.031). Furthermore, a trend for a sleep improvement was observed (SLEEP).

Conclusions: Short-term treatment with CR845 significantly reduced itch intensity and improved quality of life in HD patients with moderate-to-severe pruritus. Thus, CR845 appears to have substantial potential to alleviate the symptoms and consequences of this frequently incapacitating condition for which existing treatments have often provided little or no relief. These data also support the opioid/immune etiology of this condition.

Funding: Pharmaceutical Company Support - Cara Therapeutics, Inc.
SA-PO1118

The ASSertID Study: Feasibility Randomised Controlled Trial of Drug Treatment for Depression in Patients on Haemodialysis
Ayan Guirguis,1,2,3 Michael K. Almond,4 Joseph Chilcot,5 Andrew Davenport,5 Clara Day,6 Naomi Finchett,2,3 Karin Friedli,7 Benjamin Spencer,8 David Wellsted,2 Ken Farrington,1,2 1East & North Hertfordshire NHS Trust, United Kingdom; 2University of Hertfordshire, United Kingdom; 3Herfordshire Partnership University NHS Trust, United Kingdom; 4Southend Univ Hospitals NHS Trust, United Kingdom; 5King’s College London, United Kingdom; 6Royal free London NHS Trust, United Kingdom; 7Univ Hospitals Birmingham NHS Trust, United Kingdom.

Background: Major Depressive Disorder (MDD) is common in patients on Haemodialysis (HD) but there is little evidence of benefit from antidepressants. Hence we undertook a multicentre feasibility Randomised Controlled Trial (RCT) of sertraline versus placebo.

Methods: A screening phase identified patients with Beck Depression Inventory (BDI-II) score >16.Those meeting eligibility criteria, underwent psychiatric assessment (MIni International Neuropsychiatric Interview). Consenting patients with mild to moderate MDD and Montgomery-Åsberg Depression Rating Scale (MADRS) score >18 were randomised to sertraline or placebo. Follow-up by study psychiatrist: week 2, month 2, 4 and 6 and monthly by study nurses. Initial dose was 50 mg with titration to 100 mg if required.

Results: Of 1355 patients approached, 715 consented for screening. BDI-II ‘16 was present in 231(32%), 58 (25.1%) were ineligible due to current treatment for MDD. Sixty-three underwent psychiatric assessment. MDD was diagnosed in 37; 30 consented to the RCT (mean age 61 ± 15; 71% male; 60% white). Twenty-one (70%) completed the trial, 8(of 15) on sertraline and 13(of 15) on placebo. Over 6 months, BDI-II and MADRS scores decreased (-17.6 ± 3.3, p <0.01 and -20(11.3 ± 3.1, p <0.01 respectively). There was no reliable difference between the sertraline and placebo groups. Fewer on sertraline completed 6 withdrawals and one death versus 2 withdrawals on placebo [C2=3.97, p=0.046]. There was a trend towards a greater fall in MADRS scores by month 2 on sertraline (effect size 0.37; lower bound >0).

Conclusions: This feasibility study is the largest RCT investigating the use of anti-depressants in HD patients with MDD. Similar significant improvement in MDD occurred over 6 months in both groups. Recovery may have been quicker on sertraline.

SA-PO1119

Randomised Controlled Trial to Determine the Appropriate Time to Initiate Peritoneal Dialysis after Insertion of Catheter to Minimise Complications
Thin M. Han,7 Lakshmanan Jeyaseelan,3 Kavitha Ramanathan,2 Dwarakanath Ranganathan,1 1Renal Dept, Royal Brisbane & Women’s Hospital, Brisbane, Queensland, Australia; 2Renal Dept, Rockhampton Hospital, Rockhampton, Queensland, Australia; 3Dept of Statistics, Christian Medical College, Vellore, India.

Background: The optimal time for the commencement of peritoneal dialysis (PD) after catheter insertion is not well known. If dialysis is started too soon after insertion, dialysate leaks and infection may occur. However by starting PD earlier, morbidity and costs can be reduced through less need for haemodialysis. This is the first randomised controlled trial to determine the safest and shortest interval to commence PD after catheter insertion.

Methods: All consecutive patients undergoing PD catheter insertion at the Royal Brisbane and Women’s Hospital and Rockhampton Hospital from 1st March 2008 to 31st May 2013, and who met the inclusion and exclusion criteria were invited to participate in the study. Participants were randomised to one of three groups. Group 1 (G1) commenced PD within 24h of catheter insertion, group 2 (G2) at two weeks and group 3 (G3) at four weeks after Tenckhoff catheter insertion. The groups were stratified by hospital and the presence of diabetes.

Primary outcomes were the incidence of peritoneal fluid leaks or PD related infection. Secondary outcomes were acid base disturbances; delayed graft function and hospital length of stay.

Results: Forty-nine patients were randomised: 25 to NS and 24 to PL. Baseline characteristics were similar in both groups. The median [IQR] total volume of fluid administered was 6446ml [4807,8075] for NS and 7776ml [5140,9080] for PL (p=0.3). The incidence of hyperkalemia in the first 48 hours postoperatively was higher in the NS group: 20 patients (80%) vs. 12 patients (50%) in the PL group (p=0.04). Sixteen patients (64%) in the NS group required treatment for hyperkalemia compared to 5 patients (21%) in the PL group (p=0.003). The peak serum potassium in the 48 h postoperative period was higher in the NS group (6.1±0.8 vs. 5.4±0.9 mmol, p=0.009). Patients receiving NS were more acidic (pH: 7.32 ±0.06, vs. 7.39 ±0.05, p=0.001) and had higher serum chloride (107 mM vs. 101 mM, p<0.001) at the end of surgery. There were no significant differences in delayed graft function or hospital length of stay.

Conclusions: Deceased donor renal transplant patients that received NS developed hyperchloremic metabolic acidosis with an increased incidence of hyperkalemia when compared to PL. This study supports the use of acetate buffered crystalloid solutions for peroperative fluid management in patients undergoing deceased donor renal transplantation.

Funding: Pharmaceutical Company Support - Baxter Healthcare Pty Ltd

SA-PO1121

Abstract Withdrawn

SA-PO1122

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Background: Complement activation by preformedDSA is the major mechanism of acute antibody-mediated rejection (aAMR) in sensitized, kidney transplant recipients (SKTR). In a previous interim study report, the CS inhibitor eculizumab (Ec) appeared effective in preventing aAMR in deceased donor (DD) SKTR compared to historical controls. We now report 12-mo efficacy and safety data from a Sept 2015 update of this ongoing, open-label, single-centre trial.

Methods: SKTR defined as current DSA>3000MFI detected by SAB; or B- or T-cell flow cytometric crossmatch >/=300 and </=500 mean channel shift; or historical positive complement-dependent cytotoxicity crossmatch to donor HLA. All recipients received Ec 1200mg postoperative day (POD) 0 prior to reperfusion. 900mg on POD 1, 7, 14, and 28, and 1200mg at wks 5, 7, and 9. Recipients received Rabbit ATG for induction and corticosteroids, tacrolimus, and mycophenolate for maintenance immunosuppression. Plasmapheresis was not allowed through Post-transplant week 9. The primary composite endpoint was clinically significant, biopsy-proven aAMR grade IIIB (Banff 2007, based on centrally read bx), graft loss, death, or loss to follow-up at 9wks. Graft and patient (pt) survival were estimated by K-M.

Results: 80 pts were transplanted (48 F, 32 M); median age 52y (range, 24–70). 7 of 80 SKTR had aAMR (8.8%) compared to 30% expected for historical controls. 11.80 SKTR met the 9wk composite primary endpoint based on local bx (13.8% [95% CI 7.1–23.3]). Graft survival at 6 and 12mo was 93.7% and 88.7%, respectively; pt survival at 6 and 12mo was 97.4%. SCR levels (mg/dL) at baseline, 1 and 12mo were 7.43 (±2.51), n=79; 1.63 (±0.97), n=76. No safety concerns.

Conclusions: Ec appeared to be effective in reducing aAMR in SKTR. Pt and graft survival and kidney function at 12mo were similar to those expected for non-sensitized KTR. Ec was well tolerated.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

SA-PO1123

Impact of De Novo Donor Specific Antibodies on Graft Outcomes in Kidney Transplant Recipients following Early Switch from Calcineurin Inhibitor to Everolimus: Analysis of the ELEVATE Trial
Johan W. De Fijter, Hallvard Holaas, Patricia M. Lopez, Peter Bernhardt, Zailong Wang, Frans Claas, Wolfgang Arns, Josep M. Cruzado, Markus van der Giet. For the ELEVATE Study Group.

Background: Development of de novo donor specific HLA-antibodies (dnDSA) after kidney transplantation (KTx) is associated with an increased risk of antibody-mediated rejection (AMR) and graft failure. The ELEVATE study evaluated the impact of early conversion from CNIs to everolimus (EVIR) after KTx and prospectively explored the status and development of DNAs.

Methods: In this 24 month (M), multicentre study KTx recipients were randomized at 10–14 weeks post-Tx to convert from CNI to EVIR (n=360; C0 6–10 ng/mL) or continue CNI (n=373; C0, tacrolimus 5–10 ng/mL; ciclosporin 100–250 ng/mL); all received enteric-coated mycophenolate sodium (MPS) ≥ corticosteroids. Blood samples were collected at

Underline represents presenting author/disclosure.

B10
baseline, randomization (RND), M12 and M24 or at time of rejection episodes and analysed by Luminex/SAB assay in one central lab. dnDSA was defined by a MFI value ≥500 any time post-RND in patients with MFI <500 at RND. 

Results: Baseline characteristics were comparable between groups. Incidence of preformed DSA (MFI ≥500 at baseline) against HLA class-I or -II was low (table A). Overall, incidence of dnDSA HLA class-I was higher with EVR/MPS treatment vs CNI/ MPS at M12 and M24. The incidence of dnHLA Class-II antibodies was dominated by anti-DQ in the CsA/MPS [lrm]group (table B). No association between de novo (either HLA class-I or -II) antibodies and a diagnosis of AMR or tBPAR was evident in this population up to M24 (table C, D).

Conclusions: Early conversion to EVR at 3M post-Tx did not increase the risk of dnDSA formation vs CNI continuation. Moreover, no association was observed between development of dnDSA and AMR or tBPAR, even with the lowest detection thresholds.

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Funding: Pharmaceutical Company Support - Novartis

Donor-Derived Cell-Free DNA in Plasma Increases with Rejection and Decreases after Treatment in Kidney Transplant Recipients

Donor-Derived Cell-Free DNA (dd-cfDNA) is an emerging biomarker of acute cellular rejection in organ transplant recipients. The utility of determining plasma levels of dd-cfDNA aimed at diagnosing rejection and evaluating treatment response was assessed in kidney transplant recipients in a longitudinal observational trial.

Methods: Clinical status, biopsy grade (performed in response to elevated serum creatinine) and plasma were collected at 326 routine surveillance visits from 101 patients. Samples from nine patients assigned a biopsy grade I, II or III (NIH criteria) were classified as rejection (R). Samples from seventeen patients assigned a biopsy grade 0 were classified as quiescent (Q). cfDNA extracted from plasma was amplified at targeted SNPs and analyzed using a sensitive and accurate Next Generation Sequencing assay to quantify dd-cfDNA levels without the need to separately genotype the donor. Standard statistical measures of significance were used.

Results: dd-cfDNA levels were significantly higher (p=0.029) in patients with biopsy-confirmed rejection (R, mean 4.23%) compared to quiescent patients (Q, mean 0.96%). Creatinine levels were not significantly different between R and Q patients (p=0.69; mean 4 and 3.1 mg/dL, respectively). Longitudinal sample analysis from 15 patients showed increased dd-cfDNA levels following transplant (mean 2.8%) with reduction to levels below 1% by two weeks post transplantation. In 3 cases with clinically treated biopsy-confirmed rejection and 2 serial samples following the rejection, levels of dd-cfDNA decreased following rejection treatment.

Conclusions: dd-cfDNA shows promise as a biomarker of rejection that may be used for non-invasive surveillance of kidney allograft status and treatment response. The ongoing measurement of cfDNA may allow clinicians to better personalize care and improve patient outcomes.

Funding: Pharmaceutical Company Support - CareDx, Inc.

Funding: Pharmaceutical Company Support - Novartis

Donor-Derived Cell-Free DNA in Plasma Increases with Rejection and Decreases after Treatment in Kidney Transplant Recipients

Marica Grskovic,1 Brian Christie,1 David Hiller,1 Robert Woodward,1 Jim Yee,1 Flavio Vincenti.2 1CareDx, Inc., Brisbane, CA; 2UCSF, San Francisco, CA.

Background: Donor-derived cell-free DNA (dd-cfDNA) is an emerging biomarker of acute cellular rejection in organ transplant recipients. The utility of determining plasma levels of dd-cfDNA aimed at diagnosing rejection and evaluating treatment response was assessed in kidney transplant recipients in a longitudinal observational trial.

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Funding: Pharmaceutical Company Support - CareDx, Inc.